FDA Briefing Document

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

November 15, 2018

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought background information related to assessment of opioid analgesic sparing outcomes in clinical trials of acute pain and the need to focus on the development of opioid sparing and opioid replacement drugs, which have potential to reduce the need for and use of opioid analgesics, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered. The final determination may be affected by issues not discussed at the advisory committee meeting.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

November 15, 2018

Table of Contents

DIVISION DIRECTOR MEMO

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: October 17, 2018

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

RE: November 15, 2018 AADPAC Meeting to Discuss Opioid Sparing Outcomes for Analgesics

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At this meeting of the AADPAC, we will be discussing the assessment of opioid analgesic sparing outcomes in clinical trials of acute pain. Opioid analgesic sparing is a topic that has become an area of interest as an avenue to reduce exposure to opioids for concurrent patient benefit and as a way to reduce the amount of opioid analgesics prescribed for acute pain, and as a result, available in the community where individuals may seek out the opioid analgesic for abuse.

Prescription opioid analgesics are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. To address what has become a public health crisis, FDA has announced a multi-year action plan that focuses on new and existing policies to help curb abuse, addiction, and overdose of these drugs, while continuing to make them available to patients in need of effective pain relief.

The priorities announced by our commissioner, Dr. Scott Gottlieb, include cutting the rate of new addiction by decreasing inappropriate exposure to opioids, supporting the treatment of those with opioid use disorder, fostering development of novel pain treatment therapies, improving our enforcement role for diverted and illegal drugs, and ensuring that the benefit and risk assessment

of drug approval and removal decisions takes into account the outcomes of opioids when used as prescribed and the public health effects of inappropriate use of these drugs.[1]

This meeting will address the topic of opioid sparing, including defining the term opioid sparing. Opioid sparing has been used to refer to a reduction in the amount of opioid analgesic medication used by a patient.

Draft Points to Consider:

- Is any amount of opioid reduction meaningful? Or is there a need to associate the reduction in opioid analgesic with a clinical benefit to the patient? How should this be measured?

- Is there clinical value to a reduction in the amount of opioid analgesic for a period of time, for instance, while hospitalized following surgery, even if it is followed by use of an opioid analgesic after hospital discharge?

- The term opioid-sparing has also been used to refer to a medication that completely replaces an opioid analgesic. Is this opioid-sparing or is this a novel non-opioid analgesic?

- What are the study requirements to determine that a novel analgesic provides adequate analgesia in a setting where opioid analgesics are generally used?

- For a novel analgesic with abuse liability sufficient to warrant scheduling under the Controlled Substances Act (CSA), is it enough to show that it works against placebo?

These are clearly difficult questions for which there are no easy answers. We are asking that you provide your expertise, your experience and your best insights in order to help us find a reasonable and responsible path forward. Your advice and recommendations will be essential in assisting us with addressing this complex and critical public health concern. We are grateful that you have agreed to join us for this important discussion and look forward to seeing you at the meeting.

[1] https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066 htm

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: October 17, 2018

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

RE: Background information for Opioid Sparing Advisory Committee

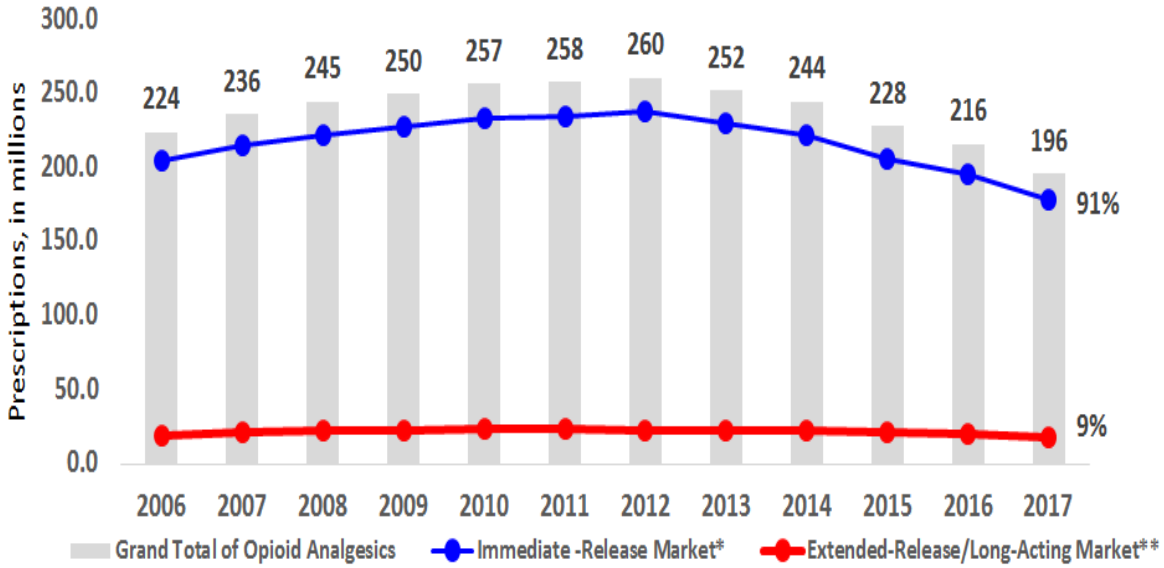
Executive Summary: Opioid analgesics are used by tens of millions of Americans each year to manage acute and chronic pain. Due to their potency relative to other classes of analgesics, opioids are an essential component of the pharmaceutical armamentarium. The US is in the midst of a public health crisis of misuse, abuse, addiction, and overdose of prescription and illicit opioids. The risks associated with opioid analgesics, including the risks of addiction, overdose, and death could be expected to decrease if the overall use of opioid analgesic drugs were reduced; however, the need remains for effective analgesics for pain severe enough to warrant the use of an opioid. Opioid-sparing and novel non-opioid drugs, if proved to be safe and effective, have the potential to reduce the need for and use of opioid analgesics and thereby help mitigate this public health crisis. This advisory committee meeting will focus on the development of these drugs for acute pain.

1 Background

Opioid analgesics are commonly used to manage both acute and chronic pain. The National Quality Forum [1] reported that more than 50 million surgical procedures are performed annually in the United States, a large proportion of which require the use of opioid analgesia. There are over 100 million Emergency Department (ED) visits per year in the US [2], and about half are for a chief complaint of pain [3], often receiving opioid analgesics [4]. Opioid analgesics are used in the perioperative and ED settings and are commonly used to treat acute and chronic pain in the outpatient setting. In 2017, approximately 58 million patients received a dispensed prescription for an opioid analgesic from U.S. outpatient retail pharmacies, and about 41 million patients were administered an opioid analgesic from U.S. non-federal hospitals.[2,3]

[2] Patients may receive an opioid analgesic from hospital and retail settings within the timeframe assessed. Therefore, summing of these patient estimates will result in double counting as there is overlap and the estimates are not mutually exclusive.
[3] Sources: IQVIA, Total Patient Tracker (TPT) and IQVIA, Hospital Visit Analyzer (HVA), Data Extracted

The United States is in the midst of a public health crisis related to prescription opioid analgesic misuse, abuse, addiction, and overdose as well as to an increasing amount of use of illicit opioids [5-8]. As shown in the following figure, over the period from 2012 to 2017, the number of prescriptions for opioid analgesics dispensed at retail pharmacies has declined from 260 to 196 million. This trend suggests that prescribing practices are becoming more conservative.



Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2011.
Static data extracted March 2017, 2012-2017 data extracted February 2018
**Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal
***Extended-Release/Long-Acting formulations include oral solids and transdermal patches
Note: Includes opioid analgesics only, excludes injectable formulations as well as opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products

However, the opportunity to further refine prescribing practices remains—a growing body of literature suggests that many patients, particularly in the post-surgical setting, continue to receive a larger quantity of opioid analgesics than needed to treat their post-surgical acute pain, resulting in leftover medications that are often stored in unsecured locations [9 - 15].

An analysis conducted by FDA's Office of Surveillance and Epidemiology within Sentinel, based upon a statistical model accounting for initial days supplied and patient demographics, also suggested that for certain surgical procedures, such as laparoscopic cholecystectomy, appendectomy, or hysterectomy, one day or less of opioid therapy may be adequate to cover the analgesic needs of the majority of patients, which is lower than the observed average prescribing for these procedures [16]. This mismatch between the amount of opioid analgesic filled and actual need increases the quantity of leftover medications, with the potential for subsequent misuse, abuse, addiction and overdose by patients themselves, or by friends and family members. A national survey of the non-institutionalized population ages 12 years and older found that the most recent source of prescription pain relievers among people who reported misusing or abusing opioids in the past year was from a friend or relative (53.1%), and the

friend or relative usually obtained the prescription pain reliever from a healthcare provider (85.9%) [17].

Analgesics with potency similar to opioids remain and will continue to remain a medical imperative for adequate medical care. Given the large numbers of Americans treated with opioid analgesics, any strategy that could reduce opioid use while achieving adequate analgesia has the potential to result in benefit to patients and the public at large. One potential strategy to reduce the need for opioid analgesics is opioid-sparing and novel non-opioid drugs.

There is no consensus around the meaning of "opioid-sparing." For the purpose of focusing the discussion at this Advisory Committee, an opioid-sparing drug will refer to a drug or combination of drugs (none containing an opioid) that, when used in combination with opioid analgesics, reduces the use of opioid analgesics. Novel non-opioid drug will be used to describe a drug product or drug-drug combination of non-opioid drug products that can be substituted for use of an opioid analgesic.

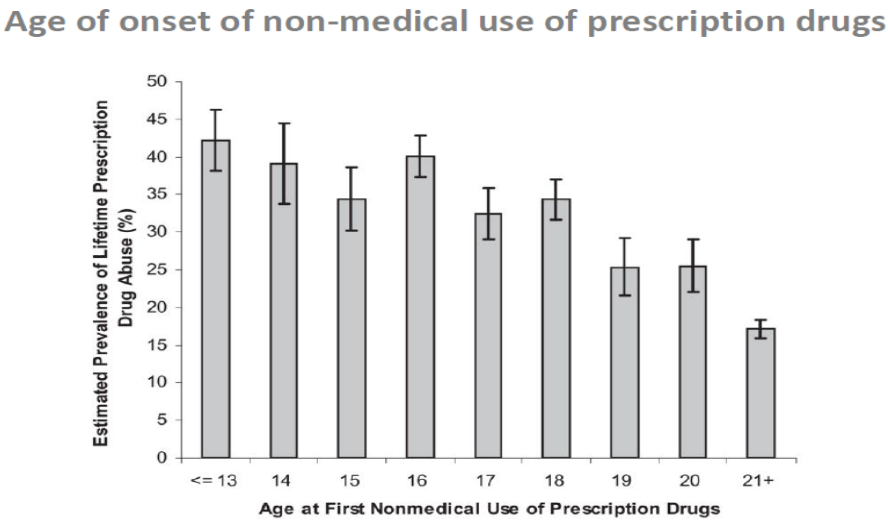
2 Potential Benefits

Potential benefits of drugs that reduce or eliminate the use of opioid analgesics can be conceptualized to those directly related to patients legitimately prescribed opioid analgesics and societal or public health benefits.

In patients, the risks of opioid analgesics include misuse, abuse, addiction, and respiratory depression and death, particularly when co-administered with other CNS depressants. In the setting of acute pain, common symptomatic adverse reactions associated with opioid analgesic use include respiratory depression, nausea, vomiting, constipation, dizziness, sedation, urinary retention, and pruritus.

Patient populations that could particularly benefit from reduction or elimination of opioid analgesic use include those with an active substance use disorder or a history of substance abuse, a history of post-operative nausea and vomiting, chronic obstructive pulmonary disease, obstructive sleep apnea, obesity, the elderly, or those who require concomitant sedative administration.

The pediatric and adolescent brain may be particularly sensitive to the effects of opioid exposure. Sharon Levy, MD, MPH from Boston Children's Hospital, summarized the findings in a presentation at an FDA Pediatric Advisory Committee meeting in September 2017 [18]. Among other important data, Dr. Levy summarized findings from relevant research [19]. The figure below, reproduced from Dr. Levy's presentation, shows that risk of prescription drug abuse is inversely related to the age at first use or misuse of the drug. These patterns imply that avoiding or minimizing opioid analgesic use in the pediatric population may prevent this increase in risk for substance use disorder later in life.

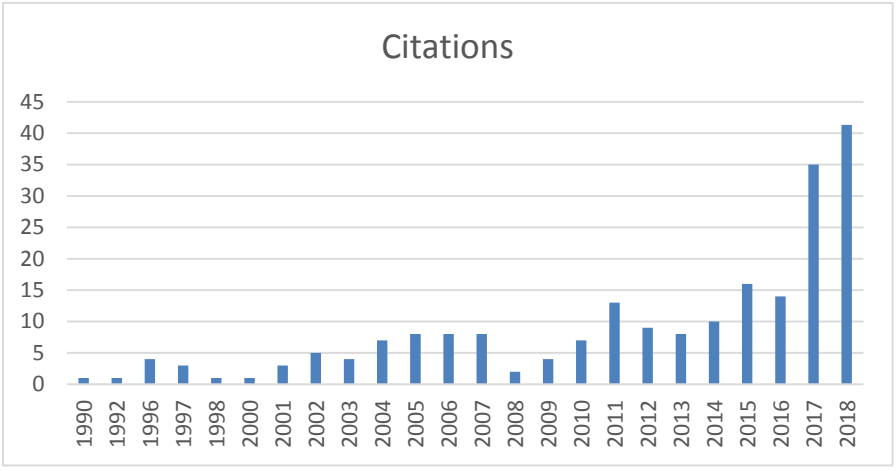


3 Potential Unintended Consequences

One concern is that as attempts are made to reduce opioid analgesic use, patients may be undertreated for pain. There are already data describing inadequate management of acute pain and that poorly controlled acute postoperative pain, for example, is associated with increased morbidity, functional and quality-of-life impairment, delayed recovery time, prolonged duration of opioid use, and higher health-care costs [20, 21]. During the development of products that reduce the use of concurrent opioid analgesics or are substituted for opioid analgesics, it is important to consider whether the degree of pain management is the same or at least adequate.

4. Literature Review

A search of PubMed conducted in September 2018 using the search terms “opioid sparing” AND “review” yielded 203 citations, not all of which were pertinent to this document. The following histogram of matching publications by year shows a marked increase in research activity in this area over the past 29 years (2018 normalized for partial year).



Review of relevant journal titles and abstracts indicates that activity in this area included retrospective, chart-review studies, review articles, systematic reviews and meta-analyses. No prospective randomized clinical trials appeared in the search results. The vast majority of relevant articles pertained to post-operative analgesia. The surgical subspecialties involved in research in this area are broad and included orthopedic, general (abdominal/tonsillectomy), hepatic, colo-rectal, pediatric, obstetric-gynecology, oncology, and bariatric surgeons. The search results also included articles from the specialty of Emergency Medicine, including pediatric Emergency Medicine.

A search of PubMed also conducted in September 2018 using the search term “randomized clinical trial opioid sparing” returned 341 citations. When limited to the years 2016-2018, 12 relevant journal articles [22-33] were identified and summarized below.

First Author/Year	Design*	Population/Study Drug	Endpoint(s)
Purdy/2018	P, R, OL	Midline laparotomy No rectus sheath block vs. single-dose, repeat-dose, or continuous rectus sheath block	PCA[b] oxycodone over 48 hours
Reagan/2017	P, R, OL	Pelvic reconstructive surgery Multimodal analgesia vs "usual care"	Narcotics used in the operating room, while in the hospital, and after discharge
Argoff/2016	P, R, DB	Bunionectomy Diclofenac vs. celecoxib vs placebo	Proportion of patients requiring opioid rescue during hours 0-24 and 24-48. Number of opioid rescue tablets used.
Bang/2016	P, R, OL	Hemiarthroplasty for femoral neck fracture Block with local anesthetic vs. no block	PCA fentanyl over 24 and 48 hours
Zhao/2016	P, R, DB, PC	Open reduction, internal fixation Dexmedetomidine vs. placebo	PCA morphine over 24 hours
Cai/2016	P, R, DB, PC	Thoracic surgery in highly nicotine dependent men Dexmedetomidine vs. placebo	PCA sufentanil over 24 hours
Sousa/2016	P, R, DB, PC	Gynecologic oncology surgery Magnesium sulfate + ketorolac vs. placebo + ketorolac	Opioid consumption, nausea, vomiting, pruritus
Ahn/2016	P, R, DB, PC	Arthroscopic shoulder surgery Pregabalin vs. placebo	Cumulative fentanyl consumption over 48 hours, adverse effects related to analgesic regimen
Li/2016	P, R, DB, PC	Pediatric patients undergoing tonsillectomy Parecoxib vs. placebo	Proportion requiring morphine, number of morphine doses, time to first morphine rescue, adverse effects
Chan/2016	P, R, DB, PC	Total knee arthroplasty Dexmedetomidine vs. placebo	PCA morphine used in 24 hours after surgery
Bakshi/2016	P, R, DB, PC	Midline laparotomy for gynecologic surgery Bupivacaine vs. placebo via rectus sheath catheter x 48 hours	24- and 48-hour morphine requirements
Jin/2016	P, R, DB, PC	Open laparotomy Nefopam + fentanyl vs. fentanyl	PCA fentanyl over 24 hours

*P=prospective, R = Randomized, DB = double-blind, OL = open-label, PC = placebo-controlled
[b] PCA = patient controlled analgesia

Eleven of 12 studies were conducted by academic researchers and one was industry sponsored. Most studies were randomized, double-blinded, and placebo-controlled. Except for Reagan et al. and Li et al, the key opioid-sparing outcome measure was an assessment of the amount of opioid analgesic consumed within 24 or 48 hours of surgery. Reagan et al. was the only study that assessed the proportion of patients who did not require an opioid analgesic after hospital discharge.

In these 12 studies, the reduction in opioid analgesic used varied from no difference to 68% depending on the type of comparison made. The study that reported the largest percentage

reduction [332], reported mean morphine use of 8.8 mg over 24 hours in patients treated with bupivacaine via a catheter in the rectus sheath vs. 27.3 mg for those who received saline. This group also reported opioid-related side effects at 48 hours. The researchers reported three episodes of vomiting in patients treated with saline and none in those treated with bupivacaine. Flatus was passed in 92% of patients treated with active compared to 17% of patients treated with saline.

4. Drugs with relevant labeling

Sponsors have sought and continue to seek opioid-sparing claims. While the Agency has approved drugs with labeling that describes the amount of opioid analgesic used by patients in comparator groups in clinical trials of non-opioid analgesics, none have gotten labeling that clearly describes a clinically meaningful reduction in the use of opioid analgesic. This language can be found in the labeling of six drugs which were approved from 2009 to 2018. In some of the labels, the amount of opioid analgesic used was part of the assessment of efficacy. All studies described in labeling were of a randomized, double-blind, placebo-controlled design. Studies for four drugs were conducted in the post-operative setting. These studies reported a difference in opioid rescue analgesia consumed, generally over 24 to 48 hours. Of the remaining two drugs, one drug, elagolix, (NDA 210450) is indicated for endometriosis pain and was conducted in premenopausal women with endometriosis. The package insert for elagolix contains data for opioid rescue analgesic use. Finally, abiraterone acetate (NDA 202379) is approved for the treatment of prostate cancer. As an oncology study, the primary endpoints in the Phase 3 studies for abiraterone related to survival. However, to be eligible for enrollment in one of the studies, patients were not to have moderate to severe pain or be using opioids at baseline. In this long-term study (median follow-up was 49 months), the sponsor was able to demonstrate a longer median time to opioid use (not reached in active vs. 23.7 months for placebo) for prostate cancer pain, which was included in labeling. Additional detail on these approved drugs appears in the following table. The product labels are provided in Appendix 1.

Table 1. Approved drugs with opioid-sparing labeling

New Drug Application (NDA) #	Product	Indication	Study Design	Pertinent Endpoints	Excerpts of Pertinent Labeling in Section 14
22450	Ofirmev, acetaminophen injection	Mild to moderate pain and moderate to severe pain with adjunctive opioid analgesics	R, DB, PC total hip or knee replacement	SPID 24 with rescue medication data capture	"There was an attendant decrease in opioid consumption, the clinical benefit of which was not demonstrated."
22496	Exparel, bupivacaine liposome injectable suspension	Post-surgical local analgesia via infiltration or block	R, DB, PC hemorrhoidectomy, total shoulder arthroplasty or rotator cuff repair	PI with rescue medication data capture	"There were statistically significant, but small differences in the amount of opioid rescue analgesia used across the treatment groups, the clinical benefit of which has not been established. The median time to rescue analgesic use was 15 hours for patients treated with EXPAREL and one hour for patients treated with placebo. Twenty-eight percent of patients treated with EXPAREL required no rescue medication at 72 hours compared to 10% treated with placebo. For those patients who did require rescue medication, the mean amount of morphine sulfate intramuscular injections used over 72 hours was 22 mg for patients treated with EXPAREL and 29 mg for patients treated with placebo." "There were statistically significant, but small differences in the amount of opioid consumption through 48 hours, the clinical benefit of which has not been demonstrated For those patients who required rescue medication, the mean amount of morphine-equivalent opioid rescue used over 48 hours was 12 mg for patients treated with EXPAREL and 54 mg for patients treated with placebo and 23 mg with EXPAREL vs. 70 mg for placebo over 72 hours. Although at 48 hours, 9 subjects (13%) in the EXPAREL group remained opioid-free compared to 1 subject (1%) in the placebo group, a difference which was statistically significant, at 72 hours, there were 4 (6%) subjects in the EXPAREL group who remained opioid-free compared to 1 (1%) subject in the placebo group, a difference that is not statistically significant."

22348	Caldolor, ibuprofen injection	Mild to moderate pain and moderate to severe pain as an adjunct to opioid analgesics	R, DB, PC elective abdominal hysterectomy	PI, amount of as-needed morphine used	"Efficacy was demonstrated as a statistically significant greater reduction in the mean morphine consumption through 24 hours in patients who received CALDOLOR as compared to those receiving placebo (47 mg and 56 mg, respectively)."
22382	Sprix, ketorolac tromethamine spray	short term (up to 5 days) management of moderate to moderately severe pain that requires analgesia at the opioid level	R, DB, PC abdominal or orthopedic surgery	SPID 48 with rescue medication data capture	"The clinical relevance of this is reflected in the finding that patients treated with SPRIX required 36% less morphine over 48 hours than patients treated with placebo." "The clinical relevance of this is reflected in the finding that patients treated with SPRIX required 26% less morphine over 48 hours than patients treated with placebo."
210450	Orilissa, elagolix tablet	Moderate to severe pain associated with endometriosis	R, DB, PC premenopausal women with endometriosis	Responder analysis requiring both a reduction in pain and not more than a 15% increase in rescue analgesic use (opioid/APAP or naproxen)	"In EM-1 and EM-2, 59% and 60% of patients used an opioid rescue analgesic for pain at baseline. The opioid rescue analgesics used at baseline were predominantly hydrocodone/acetaminophen (HC/APAP) and codeine/APAP at strengths of 5/300-325 mg and 30/300-500 mg. In EM-1, of all patients on an opioid at baseline, 98% and 2% were on HC/APAP and codeine/APAP, respectively. In EM-2, of all patients on an opioid at baseline, 50% were on HC/APAP and 16% were on codeine/APAP. Other data related to opioid rescue analgesic use are summarized in Table 13." [see USPI for Table 13] "The clinical relevance of these data has not been demonstrated."
202379	Zytiga, abiraterone acetate tablet	Metastatic castration-resistant prostate cancer and metastatic high-risk castration-sensitive prostate cancer	R, PC, prostate cancer patients not taking opioids	overall survival and radiographic progression-free survival	"The median time to opiate use for prostate cancer pain was not reached for patients receiving ZYTIGA and was 23.7 months for patients receiving placebo (HR=0.686; 95% CI: [0.566, 0.833], p=0.0001). The time to opiate use result was supported by a delay in patient reported pain progression favoring the ZYTIGA arm."

R Randomized, PC Placebo-controlled, DB Double-blind, SPID 24 Summed Pain Intensity Difference over 24 hours, PI Pain intensity, SPID 48 Summed Pain Intensity Difference over 48 hours

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Appendix 1

Labeling of Approved Drugs with Opioid Sparing

NDA 022348
Caldolor

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CALDOLOR® safely and effectively. See full prescribing information for CALDOLOR.

CALDOLOR (ibuprofen) Injection, for intravenous use
Initial U.S. Approval: 1974

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning

- **Non-steroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. (5.1)**
- **CALDOLOR is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.2)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	11/2015
Indications and Usage (1)	11/2015
Dosage and Administration (2.1, 2.2, 2.3)	11/2015
Warnings and Precautions, Cardiovascular Thrombotic Events (5.1)	11/2015
Warnings and Precautions, Heart Failure and Edema (5.5)	11/2015

----------INDICATIONS AND USAGE----------

CALDOLOR is a nonsteroidal anti-inflammatory drug indicated in adults and pediatric patients six months and older for the:

- Management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics (1)
- Reduction of fever (1)

----------DOSAGE AND ADMINISTRATION----------

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals
- Adult Pain: 400 mg to 800 mg intravenously over 30 minutes every 6 hours as necessary. (2.2)
- Adult Fever: 400 mg intravenously over 30 minutes, followed by 400 mg every 4 to 6 hours or 100-200 mg every 4 hours as necessary. (2.2)
- Pediatric (pain and fever) ages 12 to 17 years of age: 400 mg intravenously over 10 minutes every 4 to 6 hours as necessary (2.3)
- Pediatric (pain and fever) ages 6 months to 12 years of age: 10 mg/kg intravenously over 10 minutes up to a maximum single dose of 400 mg every 4 to 6 hours as necessary (2.3)
- CALDOLOR must be diluted before administration. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

CALDOLOR (ibuprofen) Injection: 800 mg/8 mL (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to ibuprofen or any component of the drug product (4)
- History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- Heart Failure and Edema: Avoid use of CALDOLOR in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of CALDOLOR in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: CALDOLOR is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue CALDOLOR at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 7)

----------ADVERSE REACTIONS----------

The most common adverse reactions are nausea, flatulence, vomiting, headache, hemorrhage and dizziness (>5%).
The most common adverse reactions in pediatric patients are infusion site pain, vomiting, nausea, anemia and headache (≥2%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Cumberland Pharmaceuticals Inc. at 1-877-484-2700 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking CALDOLOR with drugs that interfere with hemostasis. Concomitant use of CALDOLOR and analgesic doses of aspirin is not generally recommended (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with CALDOLOR may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- ACE Inhibitors and ARBs: Concomitant use with CALDOLOR in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)
- Digoxin: Concomitant use with CALDOLOR can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.10, 8.1)
Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of CALDOLOR in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Non-steroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.** ***[see Warnings and Precautions (5.1)]*****.**
- **CALDOLOR is contraindicated in the setting of coronary artery bypass graft (CABG) surgery** ***[see Contraindications (4) and Warnings and Precautions (5.1)]*****.**

Gastrointestinal Bleeding, Ulceration and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events** ***[see Warnings and Precautions (5.2)]*****.**

1 INDICATIONS AND USAGE

CALDOLOR is indicated in adults and pediatric patients six months and older for the:

- management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics
- reduction of fever

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

After observing the response to initial therapy with CALDOLOR, the dose and frequency should be adjusted to suit an individual patient's needs. Do not exceed 3200 mg total daily dose in adults. Do not exceed 40 mg/kg or 2,400 mg, whichever is less, total daily dose in pediatric patients less than 17 years of age.

To reduce the risk of renal adverse reactions, patients must be well hydrated prior to administration of CALDOLOR.

CALDOLOR **must be diluted** prior to administration.

Dilute to a final concentration of 4 mg/mL or less. Appropriate diluents include 0.9% Sodium Chloride Injection USP (normal saline), 5% Dextrose Injection USP (D5W), or Lactated Ringers Solution.

- 100 mg dose: Dilute 1 mL of CALDOLOR in at least 100 mL of diluent
- 200 mg dose: Dilute 2 mL of CALDOLOR in at least 100 mL of diluent
- 400 mg dose: Dilute 4 mL of CALDOLOR in at least 100 mL of diluent
- 800 mg dose: Dilute 8 mL of CALDOLOR in at least 200 mL of diluent

For weight-based dosing at 10 mg/kg ensure that the concentration of CALDOLOR is 4 mg/mL or less.

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

Diluted solutions are stable for up to 24 hours at ambient temperature (approximately 20° C to 25° C) and room lighting.

2.2 Adults

For Analgesia (pain):

The dose is 400 mg to 800 mg intravenously every 6 hours as necessary. Infusion time must be at least 30 minutes. Maximum daily dose is 3,200 mg.

For Fever:

The dose is 400 mg intravenously, followed by 400 mg every 4 to 6 hours or 100 mg to 200 mg every 4 hours as necessary. Infusion time must be at least 30 minutes. Maximum daily dose is 3,200 mg.

2.3 Pediatric Patients

For Analgesia (pain) and Fever

Ages 12 to 17 years of age

The dose is 400 mg intravenously every 4 to 6 hours as necessary. Infusion time must be at least 10 minutes. Maximum daily dose is 2,400 mg.

Ages 6 months to 12 years of age

The dose is 10 mg/kg intravenously up to a maximum single dose of 400 mg every 4 to 6 hours as necessary. Infusion time must be at least 10 minutes. Maximum daily dose is 40 mg/kg or 2,400 mg, whichever is less.

Pediatric Dosing as Necessary for Fever and Pain

Age Group	Dose	Dosing Interval	Min infusion time	Max daily dose
6 months to less than 12 years	10 mg/kg up to 400 mg max	Every 4 to 6 hours as necessary	10 minutes	*40 mg/Kg or 2,400 mg
12 to 17 years	400 mg	Every 4 to 6 hours as necessary	10 minutes	2,400 mg

* Maximum daily dose is 40 mg/kg or 2,400 mg, whichever is less

3 DOSAGE FORMS AND STRENGTHS

CALDOLOR (ibuprofen) Injection is a clear, colorless, non-pyrogenic, aqueous solution intended for intravenous use available in an 800 mg/8 mL (100 mg/mL) single-dose vial.

4 CONTRAINDICATIONS

CALDOLOR is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to ibuprofen or any components of the drug product [*see Warnings and Precautions (5.7, 5.9)*]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7, 5.8)*]
- In the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as ibuprofen, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG *[see Contraindications (4)]*.

Post-MI Patients
Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of CALDOLOR in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If CALDOLOR is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation
NSAIDs, including ibuprofen, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months and in about 2%-4% of patients treated for one year. However, even short-term therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration and Perforation
Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue CALDOLOR until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].

5.3 Hepatotoxicity
Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs, including ibuprofen.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms).If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue CALDOLOR immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension
NSAIDs, including CALDOLOR, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [*see Drug Interactions (7)*].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of ibuprofen may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].

Avoid the use of CALDOLOR in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If CALDOLOR is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of CALDOLOR in patients with advanced renal disease. The renal effects of CALDOLOR may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating CALDOLOR. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of CALDOLOR [*see Drug Interactions (7)*]. Avoid the use of CALDOLOR in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If CALDOLOR is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.7 Anaphylactic Reactions

Ibuprofen has been associated with anaphylactic reactions in patients with and without known hypersensitivity to ibuprofen and in patients with aspirin-sensitive asthma [see *Contraindications (4) and Warnings and Precautions (5.8)*].

Seek emergency help if anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, CALDOLOR is contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When CALDOLOR is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions

NSAIDs, including ibuprofen, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of CALDOLOR at the first appearance of skin rash or any other sign of hypersensitivity. CALDOLOR is contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].

5.10 Premature Closure of Fetal Ductus Arteriosus

Ibuprofen may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including CALDOLOR, in pregnant women starting at 30 weeks of gestation (third trimester) [*see Use in Specific Populations (8.1)*].

5.11 Hematologic Toxicity
Anemia has occurred in NSAID-treated patients. This may be due to occult or gross GI blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with CALDOLOR has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including CALDOLOR may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorder, concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].

CALDOLOR must be diluted prior to use. Infusion of the drug product without dilution can cause hemolysis *[see Dosage and Administration (2.1)]*.

5.12 Masking of Inflammation and Fever
The pharmacological activity of CALDOLOR in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.13 Laboratory Monitoring
Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [*see Warnings and Precautions (5.2, 5.3, 5.6)*].

5.14 Ophthalmological Effects
Blurred or diminished vision, scotomata, and changes in color vision have been reported with oral ibuprofen. Discontinue ibuprofen if a patient develops such complaints, and refer the patient for an ophthalmologic examination that includes central visual fields and color vision testing.

5.15 Aseptic Meningitis
Aseptic meningitis with fever and coma has been observed in patients on oral ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on ibuprofen, give consideration to whether or not the signs or symptoms are related to ibuprofen therapy.

6 ADVERSE REACTIONS
The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events [*see Warnings and Precautions (5.1)*]
- GI Bleeding, Ulceration and Perforation [*see Warnings and Precautions (5.2)*]
- Hepatotoxicity [*see Warnings and Precautions (5.3)*]
- Hypertension [*see Warnings and Precautions (5.4)*]
- Heart Failure and Edema [*see Warnings and Precautions (5.5)*]
- Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*]
- Anaphylactic reactions [*see Warnings and Precautions (5.7)*]
- Serious Skin Reactions [*see Warnings and Precautions (5.9)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.11)*]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be compared directly to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Population
During clinical development, 560 patients were exposed to CALDOLOR, 438 in pain and 122 with fever. In the pain studies, CALDOLOR was started intra-operatively and administered at a dose of 400 mg or 800 mg every six hours for up to three days. In the fever studies, CALDOLOR was administered at doses of 100 mg, 200 mg, or 400 mg every four or six hours for up to 3 days. The most frequent type of adverse reaction occurring with oral ibuprofen is gastrointestinal.

Pain Studies
The incidence rates of adverse reactions listed in the following table were derived from multi-center, controlled clinical studies in post-operative patients comparing CALDOLOR to placebo in patients also receiving morphine as needed for post-operative pain.

Table 1: Post-operative Patients with Adverse Reactions Observed in ≥ 3% of Patients in any CALDOLOR Treatment Group in Pain Studies*

Event	CALDOLOR 400 mg (N=134)	CALDOLOR 800 mg (N=304)	Placebo (N=287)
Any Reaction	*118 (88%)*	*260 (86%)*	*258 (90%)*
Nausea	77 (57%)	161 (53%)	179 (62%)
Vomiting	30 (22%)	46 (15%)	50 (17%)
Flatulence	10 (7%)	49 (16%)	44 (15%)
Headache	12 (9%)	35 (12%)	31 (11%)
Hemorrhage	13 (10%)	13 (4%)	16 (6%)
Dizziness	8 (6%)	13 (4%)	5 (2%)
Edema peripheral	1 (<1%)	9 (3%)	4 (1%)
Urinary retention	7 (5%)	10 (3%)	10 (3%)
Anemia	5 (4%)	7 (2%)	6 (2%)
Decreased hemoglobin	4 (3%)	6 (2%)	3 (1%)
Dyspepsia	6 (4%)	4 (1%)	2 (<1%)
Wound hemorrhage	4 (3%)	4 (1%)	4 (1%)
Abdominal discomfort	4 (3%)	2 (<1%)	0
Cough	4 (3%)	2 (<1%)	1 (<1%)
Hypokalemia	5 (4%)	3 (<1%)	8 (3%)

* All patients received concomitant morphine during these studies.

Fever Studies

Fever studies were conducted in febrile hospitalized patients with malaria and febrile hospitalized patients with varying causes of fever. In hospitalized febrile patients with malaria, the adverse reactions observed in at least two CALDOLOR-treated patients included abdominal pain and nasal congestion.

In hospitalized febrile patients (all causes), adverse reactions observed in more than two patients in any given treatment group are presented in the table below.

Table 2: Patients with Adverse Reactions Observed in ≥ 3% of Patients in any CALDOLOR Treatment Group in All-Cause Fever Study

Event	CALDOLOR 100 mg N=30	CALDOLOR 200 mg N=30	CALDOLOR 400 mg N=31	Placebo N=28
Any Reaction	*27 (87%)*	*25 (83%)*	*23 (74%)*	*25 (89%)*
Anemia	5 (17%)	6 (20%)	11 (36%)	4 (14%)
Eosinophilia	7 (23%)	7 (23%)	8 (26%)	7 (25%)
Hypokalemia	4 (13%)	4 (13%)	6 (19%)	5 (18%)
Hypoproteinemia	3 (10%)	0	4 (13%)	2 (7%)
Neutropenia	2 (7%)	2 (7%)	4 (13%)	2 (7%)
Blood urea increased	0	0	3 (10%)	0
Hypernatremia	2 (7%)	0	3 (10%)	0
Hypertension	0	0	3 (10%)	0
Hypoalbuminemia	3 (10%)	1 (3%)	3 (10%)	1 (4%)
Hypotension	0	2 (7%)	3 (10%)	1 (4%)
Diarrhea	3 (10%)	3 (10%)	2 (7%)	2 (7%)
Pneumonia bacterial	3 (10%)	1 (3%)	2 (7%)	0
Blood LDH increased	3 (10%)	2 (7%)	1 (3%)	1 (4%)
Thrombocythemia	3 (10%)	2 (7%)	1 (3%)	0
Bacteremia	4 (13%)	0	0	0

Pediatric Population

A total of 143 pediatric patients ages 6 months and older have received CALDOLOR in controlled clinical trials. The most common adverse reactions (incidence greater than or equal to 2%) in pediatric patients treated with CALDOLOR were infusion site pain, vomiting, nausea, anemia and headache.

7 DRUG INTERACTIONS

See Table 3 for clinically significant drug interactions with ibuprofen.

Table 3: Clinically Significant Drug Interactions with Ibuprofen

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Ibuprofen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of ibuprofen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of CALDOLOR with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.11)*].
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.2)*].
Intervention:	Concomitant use of CALDOLOR and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.11)*]. CALDOLOR is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of CALDOLOR and ACE-inhibitors, ARBs, or beta- blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of CALDOLOR and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of CALDOLOR with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [*see Warnings and Precautions (5.6)*].
Digoxin	
Clinical Impact:	The concomitant use of ibuprofen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of CADOLOR and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of CALDOLOR and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of CALDOLOR and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical	Concomitant use of CALDOLOR and cyclosporine may increase cyclosporine's nephrotoxicity.

Impact:	
Intervention:	During concomitant use of CALDOLOR and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of ibuprofen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.2)*].
Intervention:	The concomitant use of ibuprofen with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of CALDOLOR and pemetrexed, may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of CALDOLOR and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including CALDOLOR, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including CALDOLOR, in pregnant women starting at 30 weeks gestation (third trimester).

There are no adequate and well-controlled studies of CALDOLOR in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. In published animal reproduction studies, there were no clear developmental effects at doses up to 0.4-times the maximum recommended human dose (MRHD) in the rabbit and 0.5-times in the MRHD rat when dosed throughout gestation. In contrast, an increase in membranous ventricular septal defects was reported in rats treated on Gestation Days 9 & 10 with 0.8-times the MRHD. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as ibuprofen, resulted in increased pre- and post-implantation loss. Advise a pregnant woman of the potential risk to a fetus.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of CALDOLOR during labor or delivery. In animal studies, NSAIDs, including ibuprofen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Animal Data

In a published study, female rabbits given 7.5, 20, or 60 mg/kg ibuprofen (0.04, 0.12, or 0.36-times the maximum recommended human daily dose of 3200 mg of ibuprofen based on body surface area) from Gestation Days 1 to 29, no clear treatment-related adverse developmental effects were noted. This dose was associated with significant maternal toxicity (stomach ulcers, gastric lesions). In the same publication, female rats were administered 7.5, 20, 60, 180 mg/kg ibuprofen (0.02, 0.06, 0.18, 0.54-times the maximum daily dose) did not result in clear adverse developmental effects. Maternal toxicity (gastrointestinal lesions) was noted at 20 mg/kg and above.

In a published study, rats were orally dosed with 300 mg/kg ibuprofen (0.912-times the maximum human daily dose of 3200 mg based on body surface area) during Gestation Days 9 and 10 (critical time points for heart development in rats). Ibuprofen treatment resulted in an increase in the incidence of membranous ventricular septal defects. This dose was associated with significant maternal toxicity including gastrointestinal toxicity. One incidence each of a membranous ventricular septal defect and gastroschisis was noted in fetuses from rabbits treated with 500 mg/kg (3-times the maximum human daily dose) from Gestation Day 9-11.

8.2 Lactation

Risk Summary

No lactation studies have been conducted with CALDOLOR; however, limited published literature reports that, following oral administration, ibuprofen is present in human milk at relative infant doses of 0.06% to 0.6% of the maternal weight-adjusted daily dose. There are no reports of adverse effects on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CALDOLOR and any potential adverse effects on the breastfed infant from the CALDOLOR or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including CALDOLOR, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin- mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including CALDOLOR in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

The safety and effectiveness of CALDOLOR for the treatment of pain and fever in pediatric patients ages 6 months and older is supported by evidence of fever reduction from a multi-center, open-label study of hospitalized febrile pediatric patients along with safety data from exposure to CALDOLOR in 143 pediatric patients ages 6 months and older in two pediatric fever studies and one pediatric pain study, supportive data from other ibuprofen products approved in pediatric patients, and evidence from adequate and well controlled studies in adults. The effectiveness of CALDOLOR for the treatment of pain and fever has not been studied in pediatric patients less than 6 months of age. [*see DOSAGE AND ADMINISTRATION (2), Clinical Study Experience (6.1), Pharmacokinetics (12.3), CLINICAL STUDIES (14)*].

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.13)*].

Clinical studies of CALDOLOR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients are at increased risk for serious GI adverse events.

10 OVERDOSAGE

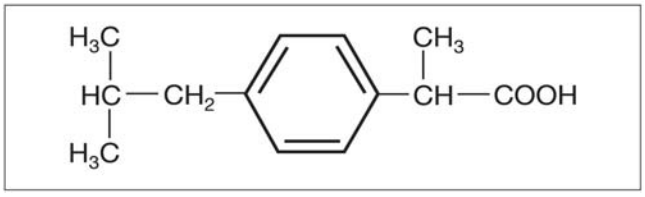
Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)*].

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdosage treatment contact a poison control center at 1-800-222-1222.

11 DESCRIPTION

CALDOLOR (ibuprofen) Injection is a nonsteroidal anti-inflammatory drug, available as an 800 mg/8 mL single-dose vial (100 mg/mL) for intravenous administration. The chemical name is ibuprofen, which is (±)-2-(*p*-isobutylphenyl) propionic acid. Ibuprofen is a white powder with a melting point of 74°C to 77°C. It has a molecular weight of 206.28. It is very slightly soluble in water (<1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone. The structural formula of ibuprofen is represented below:



Each 1 mL of solution contains 100 mg of ibuprofen in Water for Injection, USP. The inactive ingredients in CALDOLOR include: 78 mg/mL arginine at a molar ratio of 0.92:1 arginine:ibuprofen. The solution pH is about 7.4.

CALDOLOR is sterile and is intended for intravenous administration only.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ibuprofen has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of CALDOLOR, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Ibuprofen is a potent inhibitor of prostaglandin synthesis in vitro. Ibuprofen concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because ibuprofen is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.3 Pharmacokinetics

Ibuprofen is a racemic mixture of [-]R- and [+]S-isomers. In vivo and in vitro studies indicate that the [+]S-isomer is responsible for clinical activity. The [-]R-form, while thought to be pharmacologically inactive, is slowly and incompletely (~60%) interconverted into the active [+]S species in adults. The [-]R-isomer serves as a circulating reservoir to maintain levels of active drug. The pharmacokinetic parameters of CALDOLOR determined in a study with volunteers are presented below.

Table 4: Pharmacokinetic Parameters of Intravenous Ibuprofen

	400 mg* CALDOLOR Mean (CV%)	800 mg* CALDOLOR Mean (CV%)
Number of Patients	12	12
AUC (mcg·h/mL)	109.3 (26.4)	192.8 (18.5)
C_{max} (mcg/mL)	39.2 (15.5)	72.6 (13.2)
KEL (1/h)	0.32 (17.9)	0.29 (12.8)
$T_{1/2}$ (h)	2.22 (20.1)	2.44 (12.9)

AUC = Area-under-the-curve
Cmax = Peak plasma concentration
CV = Coefficient of Variation
KEL = First-order elimination rate constant
$T_{1/2}$ = Elimination half-life
* = 60 minute infusion time

The pharmacokinetic parameters of CALDOLOR determined in a study with febrile pediatric patients are presented in Table 5. It was observed that the median T_{max} was at the end of the infusion and that CALDOLOR had a shorter elimination half-life in pediatric patients compared to adults. The volume of distribution and clearance increased with age.

Table 5: Pharmacokinetic Parameters of 10 mg/kg Intravenous Ibuprofen, Pediatric Patients, by Age Group

	6 months to <2 years Mean (CV%)	2 years to <6 years Mean (CV%)	6 years to 16 years Mean (CV%)
Number of Patients	5	12	25
AUC (mcg·h/mL)	71.1 (37.1)	79.2 (37.0)	80.7 (36.9)
C_{max} (mcg/mL)	59.2 (34.8)	64.2 (34.3)	61.9 (26.6)
T_{max} (min)*	10 (10-30)	12 (10-46)	10 (10-40)
$T_{1/2}$ (h)	1.8 (29.9)	1.5 (41.8)	1.55 (26.4)
Cl (mL/h)	1172.5 (38.9)	1967.3 (56.0)	4878.5 (71.0)
Vz (mL)	2805.7 (20.1)	3695.8 (30.0)	10314.2 (67.4)
Cl/WT# (mL/hr/kg)	133.7 (58.6)	130.1 (82.4)	109.2 (41.6)
Vz/WT# (mL/kg)	311.2 (35.4)	227.2 (41.7)	226.8 (30.4)

*Median (minimum-maximum)
#WT: body weight (kg)

Ibuprofen, like most NSAIDs, is highly protein bound (>99% bound at 20 mcg/mL). Protein binding is saturable, and at concentrations >20 mcg/mL binding is nonlinear. Based on oral dosing data, there is an age- or fever-related change in volume of distribution for ibuprofen.

Drug Interaction Studies
Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 3 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Long-term studies in animals to evaluate the carcinogenic potential of ibuprofen have not been conducted.

Mutagenesis
In published studies, ibuprofen was not mutagenic in the in vitro bacterial reverse mutation assay (Ames assay).

Impairment of Fertility
In a published study, dietary administration of ibuprofen to male and female rats 8-weeks prior to and during mating at dose levels of 20 mg/kg (0.06-times the MRHD based on body surface area comparison) did not impact male or female fertility or litter size.

In other studies, adult mice were administered ibuprofen intraperitoneally at a dose of 5.6 mg/kg/day (0.0085-times the MRHD based on body surface area comparison) for 35 or 60 days in males and 35 days in females. There was no effect on sperm motility or viability in males but decreased ovulation was reported in females.

14 CLINICAL STUDIES

14.1 Analgesia (Pain)

The effect of CALDOLOR on acute pain was evaluated in two multi-center, randomized, double-blind, placebo-controlled studies.

In a study of women who had undergone an elective abdominal hysterectomy, 319 patients were randomized and treated with CALDOLOR 800 mg or placebo administered every 6 hours (started intra-operatively) and morphine administered on an as needed basis. Efficacy was demonstrated as a statistically significant greater reduction in the mean morphine consumption through 24 hours in patients who received CALDOLOR as compared to those receiving placebo (47 mg and 56 mg, respectively). The clinical relevance of this finding is supported by a greater reduction in pain intensity over 24 hours for patients treated with CALDOLOR, even though morphine was available on an as needed basis.

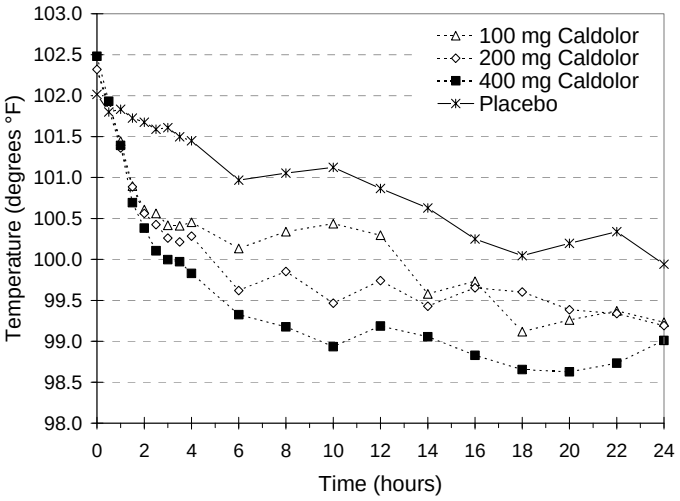
In a study of patients who had undergone an elective abdominal or orthopedic surgery, 406 patients (87 men, 319 women) were randomized to receive CALDOLOR 400 mg, CALDOLOR 800 mg, or placebo administered every 6 hours (started intra-operatively), and morphine on an as needed basis. This study failed to demonstrate a statistically significant difference in outcome between patients receiving CALDOLOR 800 mg or 400 mg and placebo, although there were trends favoring the active treatments.

14.2 Antipyretic (Fever)

The effect of CALDOLOR on fever was evaluated in two randomized, double-blind studies in adults and in one open-label study in pediatric patients.

In a multi-center study, 120 hospitalized patients (88 men, 32 women) with temperatures of 101°F or greater were randomized to CALDOLOR 400 mg, 200 mg, 100 mg or placebo, administered every 4 hours for 24 hours. Each of the three CALDOLOR doses, 100 mg, 200 mg, and 400 mg, resulted in a statistically greater percentage of patients with a reduced temperature (<101°F) after 4 hours, compared to placebo (65%, 73%, 77% and 32%, respectively). The dose response is shown in the figure below.

Figure 1: Temperature Reduction by Treatment Group, Hospitalized Febrile Patients



In a single-center study, 60 hospitalized patients (48 men, 12 women) with uncomplicated *P. falciparum* malaria having temperatures ≥100.4°F were randomized to CALDOLOR 400 mg or placebo, administered every 6 hours for 72 hours of treatment. There was a significant reduction in fever within the first 24 hours of treatment, measured as the area above the temperature 98.6°F *vs*. time curve for patients treated with CALDOLOR.

In a multi-center, open-label study, 100 hospitalized pediatric patients 6 months of age and older with temperatures of 101.0ºF or greater were randomized and treated with 10 mg/kg of CALDOLOR or a low dose of an active comparator every 4 hours as needed for fever.

Efficacy was demonstrated as a statistically significant greater reduction in temperature for the primary endpoint, an area under the curve analyses of temperature versus time for the first 2 hours, as well as over the entire dosing interval. Seventy-four percent of CALDOLOR treated patients became afebrile (temperature <99.5ºF) by the end of first dosing interval.

16 HOW SUPPLIED/STORAGE AND HANDLING

CALDOLOR (ibuprofen) Injection is a clear, colorless, non-pyrogenic, aqueous solution intended for intravenous use available in an **800 mg/8 mL (100 mg/mL)** single-dose vial.

Carton of 25 vials, NDC 66220-287-08

Storage
Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

The stopper in the CALDOLOR vial does not contain natural rubber latex, dry natural rubber, or blends of natural rubber.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Patients, families, or their caregivers should be informed of the following information before initiating therapy with CALDOLOR and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events
Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [*see Warnings and Precautions (5.1)*].

Gastrointestinal Bleeding, Ulceration, and Perforation
Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [*see Warnings and Precautions (5.2)*].

Hepatotoxicity
Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop CALDOLOR and seek immediate medical therapy [*see Warnings and Precautions (5.3)*].

Heart Failure and Edema
Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [*see Warnings and Precautions (5.5)*].

Anaphylactic Reactions
Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Contraindications (4) and Warnings and Precautions (5.7)*].

Serious Skin Reactions
Advise patients to stop CALDOLOR immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9)*].

Female Fertility
Advise females of reproductive potential who desire pregnancy that NSAIDs, including CALDOLOR, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*]

Fetal Toxicity
Inform pregnant women to avoid use of CALDOLOR and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*].

Avoid Concomitant Use of NSAIDs
Inform patients that the concomitant use of CALDOLOR with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [*see Warnings and Precautions (5.2) and Drug Interactions (7)*]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin
Inform patients not to use low-dose aspirin concomitantly with CALDOLOR until they talk to their healthcare provider [*see Drug Interactions (7)*].

Manufactured for:
Cumberland Pharmaceuticals Inc.
Nashville, TN 37203
US Patent Number 6,727,286, 8,871,810, 8,735,452, 9,012,508, 9,114,068 and 9,138,404
CALDOLOR® is a registered trademark of Cumberland Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXPAREL® safely and effectively. See full prescribing information for EXPAREL.

EXPAREL (bupivacaine liposome injectable suspension)
Initial U.S. Approval: 1972

RECENT MAJOR CHANGES

Indications and Usage (1) (04/2018)
Dosage and Administration (2.1, 2.2, 2.3) (04/2018)
Warnings and Precautions (5.2) (04/2018)

INDICATIONS AND USAGE

EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia (1).

Limitations of Use
Safety and efficacy has not been established in other nerve blocks

DOSAGE AND ADMINISTRATION

- EXPAREL is intended for single-dose administration only (2.1).
- Different formulations of bupivacaine are not bioequivalent even if the milligram strength is the same. It is not possible to convert dosing from other formulations of bupivacaine to EXPAREL (2.1. 2.5).
- DO NOT dilute EXPAREL with water for injection or other hypotonic solution (2.1).
- The recommended dose of EXPAREL for local infiltration in adults is up to a maximum dose of 266 mg (20 mL). See Full Prescribing Information for guidance on dose selection (2.2).
- The recommended dose of EXPAREL for interscalene brachial plexus nerve block in adults is 133 mg (10 mL) (2.2).
- See Full Prescribing Information for important injection instructions and compatibility considerations (2.3, 2.4).

DOSAGE FORMS AND STRENGTHS

Injectable suspension:
266 mg/20 mL (13.3 mg/mL) single-dose vial (3)
133 mg/10 mL (13.3 mg/mL) single-dose vial (3)

CONTRAINDICATIONS

EXPAREL is contraindicated in obstetrical paracervical block anesthesia (4).

WARNINGS AND PRECAUTIONS

- Monitor cardiovascular status, neurological status, and vital signs during and after injection of EXPAREL (5.1).
- Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, use EXPAREL cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations (5.1).
- Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL (5.2).

ADVERSE REACTIONS

Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via infiltration were nausea, constipation, and vomiting (6.1).
Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via nerve block were nausea, pyrexia and constipation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pacira Pharmaceuticals, Inc. at 1-855-RX-EXPAREL (1-855-793-9727) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Lidocaine or other non-bupivacaine local anesthetics: Do not admix with EXPAREL. EXPAREL may be administered at least 20 minutes or more following local administration of lidocaine (7).
- Bupivacaine HCl: Do not exceed a milligram dose of bupivacaine HCl solution to EXPAREL of 1:2 when admixing, as this may impact the pharmacokinetics and/or physicochemical properties of the drugs (7).
- Do not dilute EXPAREL with water or other hypotonic agents, as it will result in disruption of the liposomal particles (7).

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm (8.1).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia.

Limitations of Use

Safety and efficacy has not been established in other nerve blocks.

2. DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- EXPAREL is intended for single-dose administration only.
- Different formulations of bupivacaine are not bioequivalent even if the milligram strength is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL. [*see Dosage and Administration (2.5)*].
- DO NOT dilute EXPAREL with water for injection or other hypotonic agents, as it will result in disruption of the liposomal particles.
- Use suspensions of EXPAREL diluted with preservative-free normal (0.9%) saline for injection or lactated Ringer's solution within 4 hours of preparation in a syringe.
- Do not administer EXPAREL if it is suspected that the vial has been frozen or exposed to high temperature (greater than 40°C or 104°F) for an extended period.
- Inspect EXPAREL visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer EXPAREL if the product is discolored.

2.2 Recommended Dosing in Adults

Local Analgesia via Infiltration

The recommended dose of EXPAREL for local infiltration in adults is up to a maximum dose of 266 mg (20 mL), and is based on the following factors:

- Size of the surgical site
- Volume required to cover the area
- Individual patient factors that may impact the safety of an amide local anesthetic

As general guidance in selecting the proper dosing, two examples of infiltration dosing are provided:

- In patients undergoing bunionectomy, a total of 106 mg (8 mL) of EXPAREL was administered, with 7 mL infiltrated into the tissues surrounding the osteotomy, and 1 mL infiltrated into the subcutaneous tissue.
- In patients undergoing hemorrhoidectomy, a total of 266 mg (20 mL) of EXPAREL was diluted with 10 mL of saline, for a total of 30 mL, divided into six 5 mL aliquots, injected by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers to produce a field block.

Regional Analgesia via Interscalene Brachial Plexus Nerve Block

The recommended dose of EXPAREL for interscalene brachial plexus nerve block in adults is 133 mg (10 mL), and is based upon one study of patients undergoing either total shoulder arthroplasty or rotator cuff repair.

2.3 Injection Instructions

EXPAREL should be injected slowly (generally 1 to 2 mL per injection) with frequent aspiration to check for blood and minimize the risk of inadvertent intravascular injection. Do not exceed a maximum dosage of 266 mg (20 mL, 1.3% of undiluted drug) for infiltration and 133 mg (10 mL) for interscalene brachial plexus nerve block.

- Administer EXPAREL undiluted or diluted to increase volume up to a final concentration of 0.89 mg/mL (i.e., 1:14 dilution by volume) with normal (0.9%) saline or lactated Ringer's solution.
- Invert vials of EXPAREL multiple times to re-suspend the particles immediately prior to withdrawal from the vial.
- Administer EXPAREL with a 25 gauge or larger bore needle to maintain the structural integrity of the liposomal bupivacaine particles.

2.4 Compatibility Considerations

Some physicochemical incompatibilities exist between EXPAREL and certain other drugs. Direct contact of EXPAREL with these drugs results in a rapid increase in free (unencapsulated) bupivacaine, altering EXPAREL characteristics and potentially affecting the safety and efficacy of EXPAREL. Therefore, admixing EXPAREL with other drugs prior to administration is not recommended [*See Drug Interactions (7)*].

- Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately

before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2.

The toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity [*See Warnings and Precautions (5.1) and Overdosage (10)*].

- When a topical antiseptic such as povidone iodine (e.g., Betadine®) is applied, the site should be allowed to dry before EXPAREL is administered into the site. EXPAREL should not be allowed to come into contact with antiseptics such as povidone iodine in solution.

Studies conducted with EXPAREL demonstrated that the most common implantable materials (polypropylene, PTFE, silicone, stainless steel, and titanium) are not affected by the presence of EXPAREL any more than they are by saline. None of the materials studied had an adverse effect on EXPAREL.

When administered in recommended doses and concentrations, bupivacaine HCl does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

2.5 Non-Interchangeability with Other Formulations of Bupivacaine

Different formulations of bupivacaine are not bioequivalent even if the milligram dosage is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL and vice versa.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

3. DOSAGE FORMS AND STRENGTHS

EXPAREL (bupivacaine liposome injectable suspension) is a white to off-white, milky aqueous suspension that is available in the following vial sizes:

- 266 mg/20 mL (13.3 mg/mL) single-dose vial
- 133 mg/10 mL (13.3 mg/mL) single-dose vial

4. CONTRAINDICATIONS

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. While EXPAREL has not been tested with this technique, the use of bupivacaine HCl with this technique has resulted in fetal bradycardia and death.

5. WARNINGS AND PRECAUTIONS

5.1 Warnings and Precautions for Bupivacaine Containing Products

The safety and effectiveness of bupivacaine and other amide-containing products depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine, any bupivacaine-containing product should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity [*See Overdosage (10)*].

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after injection of bupivacaine and other amide-containing products. Restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Bupivacaine and other amide-containing products should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs.

Injection of multiple doses of bupivacaine and other amide-containing products may cause significant increases in plasma concentrations with each repeated dose due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood concentrations varies with the status of the patient.

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

Central Nervous System Reactions

The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug. Neurologic effects following infiltration of soft tissue may include persistent anesthesia, paresthesia, weakness, and paralysis, all of which may have slow, incomplete, or no recovery.

Central nervous system reactions are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils. The incidence of convulsions

associated with the use of local anesthetics varies with the procedure used and the total dose administered.

Cardiovascular System Reactions

Toxic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure [*See Warnings and Precautions (5.1) and Overdosage (10)*].

Allergic Reactions

Allergic-type reactions are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Chondrolysis

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been postmarketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric patients and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness, and loss of motion can be variable, but may begin as early as the second month after surgery. Currently, there is no effective treatment for chondrolysis; patients who have experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

5.2 Warnings and Precautions Specific for EXPAREL

As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine, EXPAREL should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity [*See Overdosage (10)*].

Caution should be taken to avoid accidental intravascular injection of EXPAREL. Convulsions and cardiac arrest have occurred following accidental intravascular injection of bupivacaine and other amide-containing products.

Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL *See Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

EXPAREL has not been evaluated for the following uses and, therefore, is not recommended for these types of analgesia or routes of administration.

- epidural
- intrathecal
- regional nerve blocks other than interscalene brachial plexus nerve block
- intravascular or intra-articular use

EXPAREL has not been evaluated for use in the following patient population and, therefore, is not recommended for administration to these groups.

- patients younger than 18 years old
- pregnant patients

The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dosage administered and may last for up to 5 days as seen in clinical trials.

6. ADVERSE REACTIONS

The following serious adverse reactions have been associated with bupivacaine hydrochloride in clinical trials and are described in greater detail in other sections of the labeling:

- Central Nervous System Reactions [*see Warnings and Precautions (5.1*)]
- Cardiovascular System Reactions [*see Warnings and Precautions (5.1)*]
- Allergic Reactions [*see Warnings and Precautions (5.1)*]
- Chondrolysis [*see Warnings and Precautions (5.1)*]
- Accidental intravascular injection [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials

Adverse Reactions Reported in All Local Infiltration Clinical Studies

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety of EXPAREL was evaluated in 10 randomized, double-blind, local administration into the surgical site clinical studies involving 823 patients undergoing various surgical procedures. Patients were administered a dose ranging from 66 to 532 mg of EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, constipation, and vomiting.

The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration were pyrexia, dizziness, edema peripheral, anemia,

hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.

The less common/rare adverse reactions (incidence less than 2%) following EXPAREL administration were chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, dizziness postural, paresthesia, syncope, incision site edema, procedural hypertension, procedural hypotension, procedural nausea, muscular weakness, neck pain, pruritus generalized, rash pruritic, hyperhidrosis, cold sweat, urticaria, bradycardia, palpitations, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, ventricular tachycardia, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory depression, respiratory failure, body temperature increased, blood pressure increased, blood pressure decreased, oxygen saturation decreased, urinary incontinence, vision blurred, tinnitus, drug hypersensitivity, and hypersensitivity.

Neurological and Cardiac Adverse Reactions

In the EXPAREL surgical site infiltration studies, adverse reactions with an incidence greater than or equal to 1% in the Nervous System Disorders system organ class following EXPAREL administration were dizziness (6.2%), headache (3.8%), somnolence (2.1%), hypoesthesia (1.5%), and lethargy (1.3%). The adverse reactions with an incidence greater than or equal to 1% in the Cardiac Disorders system organ class following EXPAREL administration were tachycardia (3.9%) and bradycardia (1.6%).

Adverse Reactions Reported in All Local Infiltration Placebo-Controlled Trials

Adverse reactions with an incidence greater than or equal to 2% reported by patients in clinical studies comparing 8 mL EXPAREL 1.3% (106 mg) to placebo and 20 mL EXPAREL 1.3% (266 mg) to placebo are shown in Table 1.

Table 1: Treatment-Emergent Adverse Reactions (TEAE) with an Incidence Greater than or Equal to 2%: Local Infiltration Placebo-Controlled Studies

	STUDY 1[a]		**STUDY 2[b]**	
System Organ Class Preferred Term	**EXPAREL 8 mL/1.3% (106 mg) (N=97) n (%)**	**Placebo (N=96) n (%)**	**EXPAREL 20 mL/1.3% (266 mg) (N=95) n (%)**	**Placebo (N=94) n (%)**
Any TEAE	53 (54.6)	59 (61.5)	10 (10.5)	17 (18.1)
Gastrointestinal Disorders	41 (42.3)	38 (39.6)	7 (7.4)	13 (13.8)
Nausea	39 (40.2)	36 (37.5)	2 (2.1)	1 (1.1)

	STUDY 1[a]		STUDY 2[b]	
	EXPAREL 8 mL/1.3% (106 mg)	**Placebo**	**EXPAREL 20 mL/1.3% (266 mg)**	**Placebo**
System Organ Class **Preferred Term**	**(N=97)** **n (%)**	**(N=96)** **n (%)**	**(N=95)** **n (%)**	**(N=94)** **n (%)**
Vomiting	27 (27.8)	17 (17.7)	2 (2.1)	4 (4.3)
Constipation	2 (2.1)	1 (1.0)	2 (2.1)	2 (2.1)
Anal Hemorrhage	0 (0.0)	0 (0.0)	3 (3.2)	4 (4.3)
Painful Defecation	0 (0.0)	0 (0.0)	2 (2.1)	5 (5.3)
Rectal Discharge	0 (0.0)	0 (0.0)	1 (1.1)	3 (3.2)
Nervous System Disorders	20 (20.6)	30 (31.3)	0 (0.0)	0 (0.0)
Dizziness	11 (11.3)	25 (26.0)	0 (0.0)	0 (0.0)
Headache	5 (5.2)	8 (8.3)	0 (0.0)	0 (0.0)
Somnolence	5 (5.2)	1 (1.0)	0 (0.0)	0 (0.0)
Syncope	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin And Subcutaneous Tissue Disorders	8 (8.2)	7 (7.3)	0 (0.0)	0 (0.0)
Pruritus Generalized	5 (5.2)	6 (6.3)	0 (0.0)	0 (0.0)
Pruritus	3 (3.1)	1 (1.0)	0 (0.0)	0 (0.0)
Investigations	5 (5.2)	3 (3.1)	4 (4.2)	3 (3.2)
Alanine Aminotransferase Increased	3 (3.1)	3 (3.1)	1 (1.1)	0 (0.0)
Aspartate Aminotransferase Increased	3 (3.1)	2 (2.1)	0 (0.0)	0 (0.0)
Blood Creatinine Increased	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Body Temperature Increased	0 (0.0)	0 (0.0)	3 (3.2)	3 (3.2)

	STUDY 1[a]		STUDY 2[b]	
	EXPAREL 8 mL/1.3% (106 mg)	**Placebo**	**EXPAREL 20 mL/1.3% (266 mg)**	**Placebo**
System Organ Class **Preferred Term**	**(N=97)** **n (%)**	**(N=96)** **n (%)**	**(N=95)** **n (%)**	**(N=94)** **n (%)**
General Disorders And Administration Site Conditions	4 (4.1)	0 (0.0)	1 (1.1)	1 (1.1)
Feeling Hot	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	2 (2.1)	0 (0.0)	1 (1.1)	1 (1.1)
Infections And Infestations	2 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)
Fungal Infection	2 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)
Injury, Poisoning And Procedural Complications	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Post Procedural Swelling	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism And Nutrition Disorders	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)
Decreased Appetite	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)

[a] Study 1: Bunionectomy
[b] Study 2: Hemorrhoidectomy
At each level of summation (overall, system organ class, preferred term), patients are only counted once.
Preferred terms are included where at least 2% of patients reported the event in any treatment group.
TEAE = treatment-emergent adverse event.

Adverse Reactions Reported in All Nerve Block Clinical Studies

The safety of EXPAREL was evaluated in four randomized, double-blind, placebo-controlled nerve block clinical studies involving 469 patients undergoing various surgical procedures. Patients were administered a dose of either 133 or 266 mg of EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, pyrexia, and constipation.

The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration as a nerve block were muscle twitching, dysgeusia, urinary retention, fatigue, headache, confusional state, hypotension, hypertension, hypoesthesia oral, pruritus generalized, hyperhidrosis, tachycardia, sinus tachycardia, anxiety, fall, body

temperature increased, edema peripheral, sensory loss, hepatic enzyme increased, hiccups, hypoxia, post-procedural hematoma.

The less common/rare adverse reactions (incidence less than 2%) following EXPAREL administration as a nerve block were arrhythmia, atrial fibrillation, atrioventricular block first degree, bradycardia, bundle branch block left, bundle branch block right, cardiac arrest, hearing impaired, vision blurred, visual impairment, asthenia, chills, hyperthermia, cellulitis, lung infection, pneumonia, procedural nausea, wound dehiscence, wound secretion, electrocardiogram QT prolonged, white blood cell count increased, arthralgia, back pain, joint swelling, mobility decreased, muscle spasms, muscular weakness, musculoskeletal pain, paraesthesia, presyncope, sedation, somnolence, syncope, delirium, dysuria, urinary incontinence, atelectasis, cough, dyspnea, lung infiltration, blister, drug eruption, erythema, rash, urticaria, deep vein thrombosis, hematoma, orthostatic hypotension.

Adverse reactions with an incidence greater than or equal to 2% reported by patients in clinical studies comparing 10 mL EXPAREL 1.3% (133 mg) and 20 mL EXPAREL 1.3% (266 mg) to placebo are shown in Table 2.

Neurological and Cardiac Adverse Reactions

In the EXPAREL nerve block studies, adverse reactions with an incidence greater than or equal to 1% in the Nervous System Disorders system organ class following EXPAREL administration were motor dysfunction (14.9%), dysgeusia (7.2%), headache (5.1%), hypoesthesia (2.3%), and sensory loss (2.3%). The adverse reactions with an incidence greater than or equal to 1% in the Cardiac Disorders system organ class following EXPAREL administration were tachycardia (3.0%), sinus tachycardia (2.3%), and bradycardia (1.3%).

Table 2: Treatment-Emergent Adverse Reactions with an Incidence Greater than or Equal to 2%: Nerve Block Placebo-Controlled Studies

SYSTEM ORGAN CLASS **Preferred Term**	**133 mg (N=168) n (%)**	**266 mg (N=301) n (%)**	**Placebo (N=357) n (%)**
Number of Subjects with at Least One TEAE	152 (90.5)	260 (86.4)	299 (83.8)
Blood and Lymphatic System Disorders	2 (1.2)	22 (7.3)	15 (4.2)
Anemia	2 (1.2)	18 (6.0)	13 (3.6)
Cardiac Disorders	13 (7.7)	34 (11.3)	38 (10.6)
Atrial Fibrillation	1 (0.6)	4 (1.3)	8 (2.2)
Sinus Tachycardia	3 (1.8)	8 (2.7)	4 (1.1)

Table 2: Treatment-Emergent Adverse Reactions with an Incidence Greater than or Equal to 2%: Nerve Block Placebo-Controlled Studies

SYSTEM ORGAN CLASS Preferred Term	133 mg (N=168) n (%)	266 mg (N=301) n (%)	Placebo (N=357) n (%)
Tachycardia	3 (1.8)	11 (3.7)	10 (2.8)
Gastrointestinal Disorders	84 (50.0)	154 (51.2)	184 (51.5)
Constipation	29 (17.3)	66 (21.9)	68 (19.0)
Dyspepsia	3 (1.8)	7 (2.3)	7 (2.0)
Hypoesthesia Oral	6 (3.6)	8 (2.7)	7 (2.0)
Nausea	62 (36.9)	111 (36.9)	133 (37.3)
Vomiting	17 (10.1)	55 (18.3)	73 (20.4)
General Disorders And Administration Site Conditions	52 (31.0)	102 (33.9)	91 (25.5)
Fatigue	7 (4.2)	15 (5.0)	15 (4.2)
Feeling Cold	0	10 (3.3)	8 (2.2)
Edema Peripheral	4 (2.4)	6 (2.0)	8 (2.2)
Peripheral Swelling	3 (1.8)	8 (2.7)	4 (1.1)
Pyrexia	36 (21.4)	70 (23.3)	64 (17.9)
Injury, Poisoning And Procedural Complications	18 (10.7)	44 (14.6)	32 (9.0)
Anemia Postoperative	0	8 (2.7)	10 (2.8)
Contusion	4 (2.4)	1 (0.3)	0
Fall	4 (2.4)	8 (2.7)	1 (0.3)
Post Procedural Hematoma	4 (2.4)	1 (0.3)	0
Procedural Hypotension	2 (1.2)	13 (4.3)	7 (2.0)

Table 2: Treatment-Emergent Adverse Reactions with an Incidence Greater than or Equal to 2%: Nerve Block Placebo-Controlled Studies

SYSTEM ORGAN CLASS Preferred Term	133 mg (N=168) n (%)	266 mg (N=301) n (%)	Placebo (N=357) n (%)
Investigations	18 (10.7)	31 (10.3)	31 (8.7)
Body Temperature Increased	1 (0.6)	10 (3.3)	4 (1.1)
Hepatic Enzyme Increased	7 (4.2)	1 (0.3)	3 (0.8)
Metabolism and Nutrition Disorders	13 (7.7)	18 (6.0)	25 (7.0)
Hypokalemia	7 (4.2)	9 (3.0)	14 (3.9)
Musculoskeletal And Connective Tissue Disorders	22 (13.1)	47 (15.6)	41 (11.5)
Mobility Decreased	0	6 (2.0)	5 (1.4)
Muscle Twitching	14 (8.3)	21 (7.0)	25 (7.0)
Nervous System Disorders	72 (42.9)	101 (33.6)	112 (31.4)
Dizziness	8 (4.8)	28 (9.3)	40 (11.2)
Dysgeusia	12 (7.1)	22 (7.3)	21 (5.9)
Headache	14 (8.3)	10 (3.3)	10 (2.8)
Hypoesthesia	6 (3.6)	5 (1.7)	2 (0.6)
Motor Dysfunction	35 (20.8)	35 (11.6)	37 (10.4)
Sensory Loss	4 (2.4)	7 (2.3)	1 (0.3)
Psychiatric Disorders	10 (6.0)	33 (11.0)	44 (12.3)
Anxiety	3 (1.8)	9 (3.0)	6 (1.7)
Confusional State	3 (1.8)	15 (5.0)	14 (3.9)
Insomnia	5 (3.0)	10 (3.3)	19 (5.3)

Table 2: Treatment-Emergent Adverse Reactions with an Incidence Greater than or Equal to 2%: Nerve Block Placebo-Controlled Studies

SYSTEM ORGAN CLASS Preferred Term	133 mg (N=168) n (%)	266 mg (N=301) n (%)	Placebo (N=357) n (%)
Renal And Urinary Disorders	9 (5.4)	31 (10.3)	31 (8.7)
Urinary Retention	5 (3.0)	23 (7.6)	22 (6.2)
Respiratory, Thoracic And Mediastinal Disorders	18 (10.7)	30 (10.0)	31 (8.7)
Dyspnea	2 (1.2)	4 (1.3)	8 (2.2)
Hiccups	4 (2.4)	4 (1.3)	1 (0.3)
Hypoxia	4 (2.4)	3 (1.0)	3 (0.8)
Skin And Subcutaneous Tissue Disorders	24 (14.3)	63 (20.9)	84 (23.5)
Hyperhidrosis	1 (0.6)	14 (4.7)	15 (4.2)
Pruritus	10 (6.0)	45 (15.0)	55 (15.4)
Pruritus Generalized	6 (3.6)	7 (2.3)	14 (3.9)
Vascular Disorders	16 (9.5)	30 (10.0)	44 (12.3)
Hypertension	3 (1.8)	15 (5.0)	21 (5.9)
Hypotension	11 (6.5)	8 (2.7)	19 (5.3)

At each level of summation (overall, system organ class, preferred term), patients are only counted once.
Preferred terms are included where at least 2% of patients reported the event in any treatment group.
TEAE = treatment-emergent adverse event.

6.2 Postmarketing Experience

Because adverse reactions reported during postmarketing are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions are consistent with those observed in clinical studies and most commonly involve the following system organ classes (SOCs): Injury, Poisoning, and Procedural Complications (e.g., drug-drug interaction, procedural pain), Nervous System Disorders (e.g., palsy, seizure), General Disorders And Administration Site Conditions (e.g., lack of efficacy,

pain), Skin and Subcutaneous Tissue Disorders (e.g., erythema, rash), and Cardiac Disorders (e.g., bradycardia, cardiac arrest).

7 Drug Interactions

The toxic effects of local anesthetics are additive and their co-administration should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity [*See Dosage and Administration (2.2), Warnings and Precautions (5.1) and Overdosage (10)*]. Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL.

Bupivacaine

Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2.

Non-Bupivacaine Local Anesthetics

EXPAREL should not be admixed with local anesthetics other than bupivacaine. Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. There are no data to support administration of other local anesthetics prior to administration of EXPAREL.

Other than bupivacaine as noted above, EXPAREL should not be admixed with other drugs prior to administration.

Water and Hypotonic Agents

Do not dilute EXPAREL with water or other hypotonic agents, as it will result in disruption of the liposomal particles.

8. Use in Specific Populations

8.1 Pregnancy

Risk Summary

There are no studies conducted with EXPAREL in pregnant women. In animal reproduction studies, embryo-fetal deaths were observed with subcutaneous administration of bupivacaine to rabbits during organogenesis at a dose equivalent to 1.6 times the maximum recommended human dose (MRHD) of 266 mg. Subcutaneous administration of bupivacaine to rats from implantation through weaning produced decreased pup survival at a dose equivalent to 1.5 times the MRHD [*see Data*]. Based on animal data, advise pregnant women of the potential risks to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Clinical Considerations

Labor or Delivery

Bupivacaine is contraindicated for obstetrical paracervical block anesthesia. While EXPAREL has not been studied with this technique, the use of bupivacaine for obstetrical paracervical block anesthesia has resulted in fetal bradycardia and death.

Bupivacaine can rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity [See Clinical Pharmacology (12.3)]. The incidence and degree of toxicity depend upon the procedure performed, the type, and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

Data

Animal Data

Bupivacaine hydrochloride was administered subcutaneously to rats and rabbits during the period of organogenesis (implantation to closure of the hard plate). Rat doses were 4.4, 13.3, and 40 mg/kg/day (equivalent to 0.2, 0.5 and 1.5 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight) and rabbit doses were 1.3, 5.8, and 22.2 mg/kg/day (equivalent to 0.1, 0.4 and 1.6 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight). No embryo-fetal effects were observed in rats at the doses tested with the high dose causing increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity.

Decreased pup survival was noted at 1.5 times the MRHD in a rat pre- and post-natal development study when pregnant animals were administered subcutaneous doses of 4.4, 13.3, and 40 mg/kg/day bupivacaine hydrochloride (equivalent to 0.2, 0.5 and 1.5 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight) from implantation through weaning (during pregnancy and lactation).

8.2 Lactation

Risk Summary

Limited published literature reports that bupivacaine and its metabolite, pipecoloxylidide, are present in human milk at low levels. There is no available information on effects of the drug in the breastfed infant or effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXPAREL and any potential adverse effects on the breastfed infant from EXPAREL or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in the EXPAREL local infiltration clinical studies (N=823), 171 patients were greater than or equal to 65 years of age and 47 patients were greater than or equal to 75 years of age. Of the total number of patients in the EXPAREL nerve block clinical studies (N=531), 241 patients were greater than or equal to 65 years of age and 60 patients were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients. Clinical experience with EXPAREL has not identified differences in efficacy or safety between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients. Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to bupivacaine may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, this should be considered when performing dose selection of EXPAREL.

8.6 Hepatic Impairment

Amide-type local anesthetics, such as bupivacaine, are metabolized by the liver. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations, and potentially local anesthetic systemic toxicity. Therefore, consider increased monitoring for local anesthetic systemic toxicity in subjects with moderate to severe hepatic disease.

8.7 Renal Impairment

Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. This should be considered when performing dose selection of EXPAREL.

10. OVERDOSAGE

Clinical Presentation

Acute emergencies from local anesthetics are generally related to high plasma concentrations encountered during therapeutic use of local anesthetics or to unintended intravascular injection of local anesthetic solution [*See Warnings and Precautions (5) and Adverse Reactions (6)*].

Signs and symptoms of overdose include CNS symptoms (perioral paresthesia, dizziness, dysarthria, confusion, mental obtundation, sensory and visual disturbances and eventually convulsions) and cardiovascular effects (that range from hypertension and tachycardia to myocardial depression, hypotension, bradycardia and asystole).

Plasma levels of bupivacaine associated with toxicity can vary. Although concentrations of 2,500 to 4,000 ng/mL have been reported to elicit early subjective CNS symptoms of bupivacaine toxicity, symptoms of toxicity have been reported at levels as low as 800 ng/mL.

Management of Local Anesthetic Overdose

At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as underventilation or apnea, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to the use of anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine to enhance myocardial contractile force).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

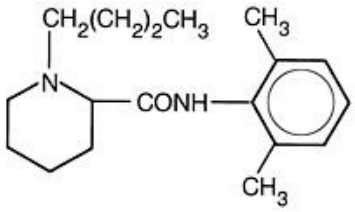
Endotracheal intubation, employing drugs and techniques familiar to the clinician, maybe indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

11. DESCRIPTION

EXPAREL is a sterile, non-pyrogenic white to off-white preservative-free aqueous suspension of multivesicular liposomes (DepoFoam® drug delivery system) containing bupivacaine. Bupivacaine is present at a concentration of 13.3 mg/mL. After injection of EXPAREL, bupivacaine is released from the multivesicular liposomes over a period of time.

Active Ingredient

Bupivacaine is related chemically and pharmacologically to the amide-type local anesthetics. It is a homologue of mepivacaine and is related chemically to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino, or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage. Chemically, Bupivacaine is 1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide with a molecular weight of 288.4. Bupivacaine has the following structural formula:



Lipid Formulation

The median diameter of the liposome particles ranges from 24 to 31 μm. The liposomes are suspended in a 0.9% sodium chloride solution. Each vial contains bupivacaine at a nominal concentration of 13.3 mg/mL. Inactive ingredients and their nominal concentrations are: cholesterol, 4.7 mg/mL; 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), 0.9 mg/mL; tricaprylin, 2.0 mg/mL; and 1, 2-dierucoylphosphatidylcholine (DEPC), 8.2 mg/mL. The pH of EXPAREL is in the range of 5.8 to 7.4.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Local anesthetics block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.2 Pharmacodynamics

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems. At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after accidental intravascular injection of bupivacaine.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors, and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.

12.3 Pharmacokinetics

Administration of EXPAREL results in systemic plasma levels of bupivacaine which can persist for 96 hours after local infiltration and 120 hours after interscalene brachial plexus nerve block. [*See Warnings and Precautions (5.2)*]. In general, peripheral nerve blocks have shown systemic plasma levels of bupivacaine for extended duration when compared to local infiltration. Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy.

Absorption

The rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site.

Pharmacokinetic parameters of EXPAREL after local infiltration and following an interscalene brachial plexus nerve block were evaluated following surgical procedures. Descriptive statistics of pharmacokinetic parameters of representative EXPAREL doses in each study are provided in Table 3.

Table 3: Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of EXPAREL via Local Infiltration and Interscalene Brachial Plexus Nerve Block

Parameters	Surgical Site Administration via Local Infiltration		Interscalene Brachial Plexus Nerve Block
	Bunionectomy 106 mg (8 mL)	Hemorrhoidectomy 266 mg (20 mL)	Total Shoulder Arthroplasty 133 mg (10 mL)
	(N=26)	(N=25)	(N=12)
C_{max} (ng/mL)	166 (92.7)	867 (353)	207 (137)
T_{max} (h)	2 (0.5-24)	0.5 (0.25-36)	48 (3 – 74)
$AUC_{(0-t)}$ (h x ng/mL)	5864 (2038)	16,867 (7868)	11484 (8615)
$AUC_{(inf)}$ (h x ng/mL)	7105 (2283)	18,289 (7569)	11590 (8603)
$t_{½}$ (h)	34 (17)	24 (39)	11 (5)

Note: Arithmetic mean (standard deviation) except T_{max} where it is median (range).

Distribution

After bupivacaine has been released from EXPAREL and is absorbed systemically, bupivacaine distribution is expected to be the same as for any bupivacaine HCl solution formulation.

Local anesthetics including bupivacaine are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Local anesthetics including bupivacaine appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, non-ionized drugs such as bupivacaine readily enter the fetal blood from the maternal circulation.

Elimination

Metabolism

Amide-type local anesthetics, such as bupivacaine, are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecoloxylidide(PPX) is the major metabolite of bupivacaine; approximately 5% of bupivacaine is converted to PPX. Elimination of drug depends largely upon the availability of plasma protein binding sites in the circulation to carry it to the liver where it is metabolized.

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic disease. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics.

Excretion

After bupivacaine has been released from EXPAREL and is absorbed systemically, bupivacaine excretion is expected to be the same as for other bupivacaine formulations.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Only 6% of bupivacaine is excreted unchanged in the urine.

Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Acidifying the urine hastens the renal elimination of local anesthetics. Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of renal disease, factors affecting urinary pH, and renal blood flow.

Specific Populations

Hepatic Impairment

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, the effects of decreased hepatic function on bupivacaine pharmacokinetics following administration of EXPAREL were studied in patients with moderate hepatic impairment. Consistent with the hepatic clearance of bupivacaine, mean plasma concentrations were higher in patients with moderate hepatic impairment than in the healthy control volunteers with approximately 1.5- and

1.6-fold increases in the mean values for C_{max} and the area under the curve (AUC), respectively. [*See Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of bupivacaine have not been conducted.

Mutagenesis

The mutagenic potential of bupivacaine has not been determined.

Impairment of Fertility

The effect of bupivacaine on fertility has not been determined.

14. CLINICAL STUDIES

14.1 Studies Confirming Efficacy

The efficacy of EXPAREL compared to placebo was demonstrated in three multicenter, randomized, double-blinded clinical studies. For local analgesia via infiltration, one study evaluated the treatment in patients undergoing bunionectomy; the other study evaluated the treatment in patients undergoing hemorrhoidectomy. For regional analgesia, one study evaluated the use of EXPAREL as a brachial plexus nerve block via interscalene or supraclavicular approach in patients undergoing total shoulder arthroplasty (TSA) or rotator cuff repair (RCR), however, only two subjects had nerve blocks via the supraclavicular approach. Three additional studies did not provide sufficient efficacy and/or safety data to support a nerve block indication: two studies evaluated the use of EXPAREL via femoral block in patients undergoing total knee arthroplasty (TKA), and one study evaluated the use of EXPAREL via intercostal nerve block for patients undergoing posterolateral thoracotomy.

Study 1: Infiltration for Bunionectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial (NCT00890682) evaluated the safety and efficacy of 106 mg (8 mL) EXPAREL in 193 patients undergoing bunionectomy. The mean age was 43 years (range 18 to 72).

Study medication was administered directly into the site at the conclusion of the surgery, prior to closure. There was an infiltration of 7 mL of EXPAREL into the tissues surrounding the osteotomy and 1 mL into the subcutaneous tissue.

Pain intensity was rated by the patients on a 0 to 10 numeric rating scale (NRS) out to 72 hours. Postoperatively, patients were allowed rescue medication (5 mg oxycodone/325 mg acetaminophen orally every 4 to 6 hours as needed) or, if that was insufficient within the first 24 hours, ketorolac (15 to 30 mg IV). The primary outcome measure was the area under the curve

(AUC) of the NRS pain intensity scores (cumulative pain scores) collected over the first 24-hour period. There was a significant treatment effect for EXPAREL compared to placebo. EXPAREL demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours. There was no significant difference in the amount of morphine equivalents used through 72 hours post-surgery, 43 mg versus 42 mg for placebo and EXPAREL, respectively. In addition, there was not a significant difference in the percentage of patients that used ketorolac, 43% versus 31% for placebo and EXPAREL, respectively.

Study 2: Infiltration for Hemorrhoidectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial (NCT00890721) evaluated the safety and efficacy of 266 mg (20 mL) EXPAREL in 189 patients undergoing hemorrhoidectomy. The mean age was 48 years (range 18 to 86).

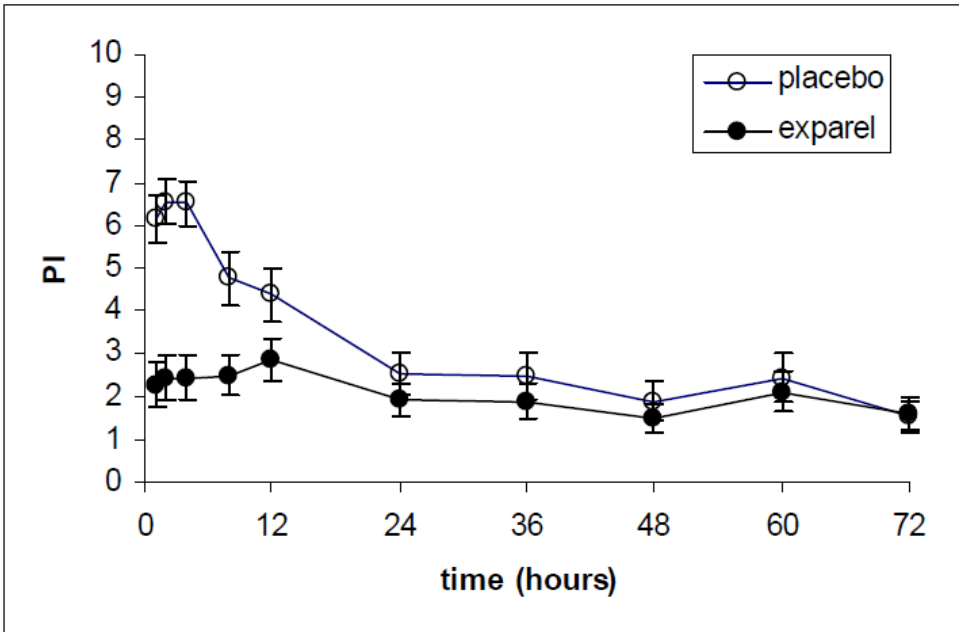
Study medication was administered directly into the site (greater than or equal to 3 cm) at the conclusion of the surgery. Dilution of 20 mL of EXPAREL with 10 mL of saline, for a total of 30 mL, was divided into six 5-mL aliquots. A field block was performed by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers.

Pain intensity was rated by the patients on a 0 to 10 NRS at multiple time points up to 72 hours. Postoperatively, patients were allowed rescue medication (morphine sulfate 10 mg intramuscular every 4 hours as needed).

The primary outcome measure was the AUC of the NRS pain intensity scores (cumulative pain scores) collected over the first 72-hour period.

There was a significant treatment effect for EXPAREL compared to placebo. See Figure 1 for the mean pain intensity over time for the EXPAREL and placebo treatment groups for the 72-hour efficacy period.

Figure 1. Mean Pain Intensity versus Time plot for hemorrhoidectomy study (C-316)



There were statistically significant, but small differences in the amount of opioid rescue analgesia used across the treatment groups, the clinical benefit of which has not been established. The median time to rescue analgesic use was 15 hours for patients treated with EXPAREL and one hour for patients treated with placebo. Twenty-eight percent of patients treated with EXPAREL required no rescue medication at 72 hours compared to 10% treated with placebo. For those patients who did require rescue medication, the mean amount of morphine sulfate intramuscular injections used over 72 hours was 22 mg for patients treated with EXPAREL and 29 mg for patients treated with placebo.

Study 3: Interscalene Brachial Plexus Nerve Block for Total Shoulder Arthroplasty or Rotator Cuff Repair

A multicenter, randomized, double-blind, placebo-controlled study (NCT02713230) was conducted in 156 patients undergoing primary unilateral total shoulder arthroplasty or rotator cuff repair with general anesthesia. The mean age was 61 years (range 33 to 80). Prior to the surgical procedure, patients received 10 mL of EXPAREL (133 mg) expanded with normal saline to 20 mL as a brachial plexus nerve block via interscalene or supraclavicular approach with ultrasound guidance. Only two patients received nerve block with EXPAREL by supraclavicular approach. Postsurgically, patients were administered acetaminophen/paracetamol up to 1000 mg PO or IV every 8 hours (q8h) unless contraindicated. Patients were allowed opioid rescue medication administered initially as oral immediate-release oxycodone (initiating at 5-10 mg every 4 hours or as needed). If a patient could not tolerate oral medication, IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) could be administered every 4 hours or as needed.

In this study, there was a statistically significant treatment effect for EXPAREL compared to placebo in cumulative pain scores through 48 hours as measured by the AUC of the visual analog scale (VAS) pain intensity scores. There were statistically significant, but small differences in the amount of opioid consumption through 48 hours, the clinical benefit of which has not been demonstrated. For those patients who required rescue medication, the mean amount of morphine-equivalent opioid rescue used over 48 hours was 12 mg for patients treated with EXPAREL and 54 mg for patients treated with placebo and 23 mg with EXPAREL vs. 70 mg for placebo over 72 hours.

Although at 48 hours, 9 subjects (13%) in the EXPAREL group remained opioid-free compared to 1 subject (1%) in the placebo group, a difference which was statistically significant, at 72 hours, there were 4 (6%) subjects in the EXPAREL group who remained opioid-free compared to 1 (1%) subject in the placebo group, a difference that is not statistically significant.

14.2 Studies That Do Not Support an Indication In Nerve Block

Studies 4 and 5: Femoral Nerve Block in Total Knee Arthroplasty

EXPAREL was administered via a femoral nerve block in two placebo-controlled studies. The results of these studies did not support a femoral nerve block indication due to inadequate safety data (Study 4 and Study 5) or due to inadequate efficacy findings (Study 5). In addition, patient

falls were reported only in the EXPAREL treatment groups and none was reported in placebo groups.

Study 4

Study 4, a multicenter, randomized, double-blind, parallel-group, placebo-controlled study (NCT01683071), was conducted in 196 patients undergoing primary unilateral total knee arthroplasty (TKA) under general or spinal anesthesia. The mean age was 65 years (range 42 to 88). Prior to the surgical procedure, 20 mL of EXPAREL (266 mg) was administered as a femoral nerve block with ultrasound guidance. Postsurgically, patients were allowed opioid rescue medication administered initially by intravenous injection of hydromorphone and subsequently by a patient-controlled analgesia (PCA) pump containing morphine or hydromorphone only. Once patients were tolerating oral medication, oral immediate-release oxycodone was administered on an as-needed basis (but not more than 10 mg every 4 hours) or, if that was insufficient, a third rescue of bupivacaine HCl (0.125%, 1.25 mg/mL) was administered at a rate of 8 mL per hour via the previously placed femoral nerve catheter.

In this study, there was a statistically significant treatment effect for EXPAREL compared to placebo in cumulative pain scores through 72 hours as measured by the AUC of the NRS pain (at rest) intensity scores.

There was a statistically significant, although small decrease in opioid consumption for the EXPAREL treatment group compared to the placebo group, the clinical benefit of which has not been established. All patients in both the EXPAREL and placebo treatment groups required opioid rescue medication during the first 72 hours. The mean amount of opioid rescue used over 72 hours was 76 mg for patients treated with EXPAREL and 103 mg for patients treated with placebo.

The study was inadequate to fully characterize the safety of EXPAREL when used for femoral nerve block due to patient falls, which occurred only in the EXPAREL-treated patients and not the placebo-treated patients.

Study 5

Study 5, a multicenter, randomized, double-blind, parallel-group, placebo-controlled study (NCT02713178), was conducted in 230 patients undergoing primary unilateral total knee arthroplasty (TKA) under general or spinal anesthesia. The mean age was 65 years (range 39 to 89). Prior to the surgical procedure, either 20 mL of EXPAREL (266 mg) or 10 mL of EXPAREL (133 mg) plus 10 mL of normal saline was administered as a femoral nerve block with ultrasound guidance. In addition to study drug, 8 mL of bupivacaine HCl (0.5%) diluted with 8 mL of normal saline was administered by the surgeon as a periarticular infiltration to the posterior capsule (8 mL each behind the medial and lateral condyles) before placement of the prosthesis. Postsurgically, patients were allowed opioid rescue medication consisting of oral immediate-release oxycodone (initiated at 5 to 10 mg every 4 hours or as needed). If a subject could not tolerate oral medication, IV morphine (2.5 to 5 mg) or hydromorphone (0.5 to 1 mg) was permitted every 4 hours or as needed. Patient-controlled analgesia was not permitted. No other analgesic agents, including NSAIDs, were permitted through 108 hours. However, to reflect the current standard of care of postsurgical multimodal therapy, all subjects received cyclobenzaprine (a single dose of 10 mg orally or as needed) and acetaminophen/paracetamol

(up to 1000 mg orally or IV every 8 hours for a maximum total daily dose of 3000 mg) postsurgically.

In this study there were no statistically significant treatment effects for the EXPAREL group compared to the placebo group in cumulative pain intensity scores or total opioid consumption. All patients in the EXPAREL and placebo treatment groups required opioid rescue medication over 72 hours. The mean amount of opioid rescue used over 72 hours was 69 mg for patients treated with EXPAREL 133 mg; 74 mg for patients treated with EXPAREL 266 mg, and 81 mg for patients treated with placebo. The median Tmax of bupivacaine observed in this study was 72 h with a range of 2.5 h to 108 h. Similarly to Study 4, patient falls only occurred in the EXPAREL-treated patients and not the placebo-treated patients.

Study 6: Intercostal Nerve Block for Posterolateral Thoracotomy

A multicenter, randomized, double-blind, placebo-controlled study was conducted in 191 patients undergoing posterolateral thoracotomy under general anesthesia (NCT01802411). The mean age was 58 years (range 18 to 82).

After the surgical procedure was completed but prior to the surgical site closure, 20 mL of EXPAREL was administered by the surgeon as an intercostal nerve block divided into three equal doses in three syringes of approximately 88 mg in 6.6 mL volume per nerve, and administered to each of three nerve segments (index nerve, nerve above, and nerve below). Postsurgically, patients were allowed opioid rescue medication administered initially by intravenous fentanyl 100 mcg, which was to be administered once via bolus only. For the US sites, the second rescue medication was to be PCA-administered morphine or hydromorphone. For the European sites, the second rescue medication was to be intramuscular administered morphine up to10 mg every 4 hours. At all sites, once a subject was tolerating oral medication, oral immediate-release oxycodone was administered (but not more than 10 mg every 4 hours). Subjects who did not achieve adequate pain relief with this regimen were to be withdrawn from the study and followed for safety only.

In this study there were no statistically significant treatment effects for EXPAREL 266 mg compared to placebo in cumulative pain intensity scores or total opioid consumption. Four percent of patients treated with EXPAREL required no rescue medication at 72 hours compared to 1% treated with placebo. For those patients who did require rescue medication, the mean amount of opioid rescue used over 72 hours was 71 mg for patients treated with EXPAREL and 71 mg for patients treated with placebo. The median T_{max} of bupivacaine observed in this study was 1 h with a range of 0.5 h to 50 h.

16. HOW SUPPLIED/STORAGE AND HANDLING

EXPAREL (bupivacaine liposome injectable suspension) is a white to off-white milky aqueous suspension that is available in the following single-dose vials.

266 mg/20 mL (13.3 mg/mL) single-dose vial, (NDC 65250-266-20) packaged in cartons of 10 (NDC 65250-266-09) and cartons of 4 (NDC 65250-266-04)

133 mg/10 mL (13.3 mg/mL) single-dose vial, (NDC 65250-133-10) packaged in cartons of 10 (NDC-65250-133-09) and cartons of 4 (NDC 65250-133-04)

Storage

Store EXPAREL vials refrigerated between 2°C to 8°C (36°F to 46°F). EXPAREL may be held at a controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 30 days in sealed, intact (unopened) vials. Do not re-refrigerate vials.

Do not freeze or expose EXPAREL to high temperatures (greater than 40°C or 104°F) for an extended period. Do not administer EXPAREL if it is suspected of having been frozen or exposed to high temperatures. Do not use the vial if the stopper is bulging.

Handling

- Invert vials of EXPAREL to re-suspend the particles immediately prior to withdrawal from the vial. Multiple inversions may be necessary to re-suspend the particles if the contents of the vial have settled.
- Visually inspect vials for particulate matter and discoloration before use.
- Do not filter.
- Do not heat before use.
- Do not autoclave.
- Following withdrawal from the vial, store EXPAREL at controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 4 hours prior to administration.
- Discard any unused portion in an appropriate manner.

17 PATIENT COUNSELING INFORMATION

Inform patients in advance that EXPAREL can cause temporary loss of sensation or motor activity that may last for up to 5 days.

Pacira Pharmaceuticals, Inc.

San Diego, CA 92121 USA

Patent Numbers:

6,132,766

5,766,627

5,891,467

8,182,835

Trademark of Pacira Pharmaceuticals, Inc.

For additional information call 1-855-RX-EXPAREL (1-855-793-9727) or visit www.EXPAREL.com

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OFIRMEV® safely and effectively. See full prescribing information for OFIRMEV.

OFIRMEV (acetaminophen) Injection
Initial U.S. Approval: 1951

WARNING:
RISK OF MEDICATION ERRORS AND HEPATOTOXICITY

See full prescribing information for complete boxed warning

Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death.

OFIRMEV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the recommended maximum daily limits, and often involve more than one acetaminophen-containing product (5.1).

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.4) 11/2016

Dosage and Administration, Recommended Dosage: Neonates and Infants (2.4) 01/2017

----------INDICATIONS AND USAGE----------
OFIRMEV (acetaminophen) injection is indicated for the

- Management of mild to moderate pain in adult and pediatric patients 2 years and older (1)
- Management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older (1)
- Reduction of fever in adult and pediatric patients

----------DOSAGE AND ADMINISTRATION----------

- OFIRMEV may be given as a single or repeated dose. (2.1)
- OFIRMEV should be administered only as a 15-minute intravenous infusion. (2.4)

Adults and Adolescents Weighing 50 kg and Over:

- 1000 mg every 6 hours or 650 mg every 4 hours to a maximum of 4000 mg per day. Minimum dosing interval of 4 hours. (2.2)

Adults and Adolescents Weighing Under 50 kg:

- 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.2)

Children:

- Children 2 to 12 years of age: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg per day. Minimum dosing interval of 4 hours. (2.3)

Neonates and Infants:

- Neonates including premature neonates born at ≥ 32 weeks gestational age to 28 days chronological age, 12.5 mg/kg every 6 hours to a maximum of 50 mg/kg per day. Minimum dosing interval of 6 hours. (2.4)
- Infants (29 days to 2 years of age):
  15 mg/kg every 6 hours to a maximum of 60 mg/kg per day. Minimum dosing interval of 6 hours. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection for intravenous infusion.
- Each 100 mL glass vial or bag contains 1000 mg acetaminophen (10 mg/mL). (3)

----------CONTRAINDICATIONS----------
Acetaminophen is contraindicated:

- In patients with known hypersensitivity to acetaminophen or to any of the excipients in the IV formulation. (4)
- In patients with severe hepatic impairment or severe active liver disease. (4)

----------WARNINGS AND PRECAUTIONS----------

- Administration of acetaminophen in doses higher than recommended (by all routes of administration and from all acetaminophen-containing products including combination products) may result in hepatic injury, including the risk of liver failure and death. (5.1)
- Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, in cases of alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment (creatinine clearance ≤ 30 mL/min). (5.1)
- Discontinue OFIRMEV immediately at the first appearance of skin rash and if symptoms associated with allergy or hypersensitivity occur. Do not use in patients with acetaminophen allergy. (5.2, 5.4)
- Take care when prescribing, preparing, and administering OFIRMEV injection to avoid dosing errors which could result in accidental overdose and death. (5.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions in patients treated with OFIRMEV were nausea, vomiting, headache, and insomnia in adult patients; nausea, vomiting, constipation, and pruritus in pediatric patients. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mallinckrodt Hospital Products Inc. at 1-800-778-7898 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. (7.1)
- Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Pediatric Use: The effectiveness of OFIRMEV for the treatment of acute pain in pediatric patients younger than 2 years of age has not been established. The safety and effectiveness of OFIRMEV in pediatric patients is supported by evidence from adequate and well controlled studies in adults with additional safety and pharmacokinetic data for this age group. (8.4)
- Geriatric Use: No overall differences in safety or effectiveness were observed between geriatric and younger subjects. (8.5)
- Hepatic Impairment: OFIRMEV is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease. (4, 5.1, 8.6)
- Renal Impairment: In cases of severe renal impairment, longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted. (5.1, 8.7)

Revised: 01/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: Risk of Medication Errors and Hepatotoxicity

Take care when prescribing, preparing, and administering OFIRMEV Injection to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that:

- **the dose in milligrams (mg) and milliliters (mL) is not confused;**
- **the dosing is based on weight for patients under 50 kg;**
- **infusion pumps are properly programmed; and**
- **the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.**

OFIRMEV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limits, and often involve more than one acetaminophen-containing product *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

OFIRMEV® (acetaminophen) injection is indicated for

- the management of mild to moderate pain in adult and pediatric patients 2 years and older
- the management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older
- the reduction of fever in adult and pediatric patients

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

OFIRMEV may be given as a single or repeated dose for the treatment of acute pain or fever. No dose adjustment is required when converting between oral acetaminophen and OFIRMEV dosing in adults and adolescents who weigh 50 kg and above. Calculated maximum daily dose of acetaminophen is based on all routes of administration (i.e., intravenous, oral, and rectal) and all products containing acetaminophen. Exceeding the maximum mg/kg daily dose of acetaminophen as described in Tables 1-3 may result in hepatic injury, including the risk of liver failure and death. To avoid the risk of overdose, ensure that the total amount of acetaminophen from all routes and from all sources does not exceed the maximum recommended dose.

2.2 Recommended Dosage: Adults and Adolescents

Adults and adolescents weighing 50 kg and over: the recommended dosage of OFIRMEV is 1000 mg every 6 hours or 650 mg every 4 hours, with a maximum single dose of OFIRMEV of 1000 mg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 4000 mg per day (includes all routes of administration and all acetaminophen-containing products including combination products).

Adults and adolescents weighing under 50 kg: the recommended dosage of OFIRMEV is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of OFIRMEV of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per

day (includes all routes of administration and all acetaminophen-containing products including combination products).

Table 1. Dosing for Adults and Adolescents

Age group	Dose given every 4 hours	Dose given every 6 hours	Maximum single dose	Maximum total daily dose of acetaminophen (by all routes)
Adults and adolescents (13 years and older) weighing ≥ 50 kg	650 mg	1000 mg	1000 mg	4000 mg in 24 hours
Adults and adolescents (13 years and older) weighing < 50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)

2.3 Recommended Dosage: Children

Children 2 to 12 years of age: the recommended dosage of OFIRMEV is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of OFIRMEV of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day.

Table 2. Dosing for Children

Age group	Dose given every 4 hours	Dose given every 6 hours	Maximum single dose	Maximum total daily dose of acetaminophen (by all routes)
Children 2 to 12 years of age	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)

2.4 Recommended Dosage For Treatment of Fever in Neonates and Infants

Neonates, including premature neonates born at ≥ 32 weeks gestational age, up to 28 days chronological age: the recommended dosage of OFIRMEV is 12.5 mg/kg every 6 hours, to a maximum daily dose of acetaminophen of 50 mg/kg per day, with a minimum dosing interval of 6 hours.

Infants 29 days to 2 years of age: the recommended dosage of OFIRMEV is 15 mg/kg every 6 hours, to a maximum daily dose of acetaminophen of 60 mg/kg per day, with a minimum dosing interval of 6 hours.

Table 3. Dosing for Treatment of Fever in Neonates and Infants

Age group	Dose given every 6 hours	Maximum total daily dose of acetaminophen (by all routes)
Neonates (birth to 28 days)	12.5 mg/kg	50 mg/kg
Infants (29 days to 2 years)	15 mg/kg	60 mg/kg

2.5 Instructions for Intravenous Administration

For adult and adolescent patients weighing ≥ 50 kg requiring 1000 mg doses of OFIRMEV, administer the dose by inserting a vented intravenous set through the septum of the 100 mL vial or a non-vented intravenous set through the administration spike port of the 100 mL bag. OFIRMEV may be administered without further dilution. DO NOT USE if particulate matter or discoloration is observed. Administer the contents of the vial intravenously over 15-minutes. Use aseptic technique when preparing OFIRMEV for intravenous infusion. Do not add other medications to the OFIRMEV vial or infusion device.

For doses less than 1000 mg, the appropriate dose must be withdrawn from the container and placed into a separate container prior to administration. Using aseptic technique, withdraw the appropriate dose (650 mg or weight-based) from an intact sealed OFIRMEV container and place the measured dose in a separate empty, sterile container (e.g., glass bottle, plastic intravenous container, or syringe) for intravenous infusion to avoid the inadvertent delivery and administration of the total volume of the commercially available container. The entire 100 mL container of OFIRMEV is not intended for use in patients weighing less than 50 kg. OFIRMEV is supplied in a single-dose container and the unused portion must be discarded.

Place small volume pediatric doses up to 60 mL in volume in a syringe and administer over 15 minutes using a syringe pump.

Monitor the end of the infusion in order to prevent the possibility of an air embolism, especially in cases where the OFIRMEV infusion is the primary infusion.

Once the container seal has been penetrated, or the contents transferred to another container, administer the dose of OFIRMEV within 6 hours.

For bags, refrain from applying excessive pressure causing distortion to the bag, such as wringing or twisting, since such handling could result in breakage of the bag.

Do not add other medications to the OFIRMEV solution. Diazepam and chlorpromazine hydrochloride are physically incompatible with OFIRMEV, therefore do not administer simultaneously.

3 DOSAGE FORMS AND STRENGTHS

OFIRMEV is a sterile, clear, colorless, non pyrogenic, preservative free, isotonic formulation of acetaminophen intended for intravenous infusion. Each 100 mL glass vial or 100 mL bag contains 1000 mg acetaminophen (10 mg/mL).

4 CONTRAINDICATIONS

Acetaminophen is contraindicated:

- in patients with known hypersensitivity to acetaminophen or to any of the excipients in the intravenous formulation.
- in patients with severe hepatic impairment or severe active liver disease *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of liver failure and death *[see Overdosage (10)]*. Do not exceed the maximum recommended daily dose of acetaminophen *[see Dosage and Administration (2)]*. The maximum recommended daily dose of acetaminophen includes all routes of acetaminophen administration and all acetaminophen-containing products administered, including combination products.

Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance ≤ 30 mL/min) *[see Use in Specific Populations (8.6, 8.7)]*.

5.2 Serious Skin Reactions

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

5.3 Risk of Medication Errors

Take care when prescribing, preparing, and administering OFIRMEV (acetaminophen) Injection in order to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that:

- the dose in milligrams (mg) and milliliters (mL) is not confused;
- the dosing is based on weight for patients under 50 kg;
- infusion pumps are properly programmed; and
- the total daily dose of acetaminophen from all sources does not exceed maximum daily limits *[see Dosage and Administration (2)]*.

5.4 Allergy and Hypersensitivity

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus. There were infrequent reports of life-threatening anaphylaxis requiring emergent medical attention. Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur. Do not use OFIRMEV in patients with acetaminophen allergy.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hepatic Injury *[see Warnings and Precautions (5.1)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.2)]*

- Allergy and Hypersensitivity *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

Adult Population

A total of 1020 adult patients have received OFIRMEV in clinical trials, including 37.3% (n=380) who received 5 or more doses, and 17.0% (n=173) who received more than 10 doses. Most patients were treated with OFIRMEV 1000 mg every 6 hours. A total of 13.1% (n=134) received OFIRMEV 650 mg every 4 hours.

All adverse reactions that occurred in adult patients treated with either OFIRMEV or placebo in repeated dose, placebo-controlled clinical trials at an incidence ≥ 3% and at a greater frequency than placebo are listed in Table 4. The most common adverse events in adult patients treated with OFIRMEV (incidence ≥ 5% and greater than placebo) were nausea, vomiting, headache, and insomnia.

Table 4. Treatment-Emergent Adverse Reactions Occurring in ≥ 3% of OFIRMEV-treated Adult Patients and at a greater frequency than Placebo in Placebo-Controlled, Repeated Dose Studies

System Organ Class – Preferred Term	OFIRMEV (N=402) n (%)	Placebo (N=379) n (%)
Gastrointestinal Disorders		
Nausea	138 (34)	119 (31)
Vomiting	62 (15)	42 (11)
General Disorders and Administration Site Conditions		
Pyrexia*	22 (5)	52 (14)
Nervous System Disorders		
Headache	39 (10)	33 (9)
Psychiatric Disorders		
Insomnia	30 (7)	21 (5)

* Pyrexia adverse reaction frequency data is included in order to alert healthcare practitioners that the antipyretic effects of OFIRMEV may mask fever.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Adults

The following additional treatment-emergent adverse reactions were reported by adult subjects treated with OFIRMEV in all clinical trials (n=1020) that occurred with an incidence of at least 1% and at a frequency greater than placebo (n=525).

Blood and lymphatic system disorders: anemia

General disorders and administration site conditions: fatigue, infusion site pain, edema peripheral

Investigations: aspartate aminotransferase increased, breath sounds abnormal

Metabolism and nutrition disorders: hypokalemia

Musculoskeletal and connective tissue disorders: muscle spasms, trismus

Psychiatric disorders: anxiety

Respiratory, thoracic and mediastinal disorders: dyspnea

Vascular disorders: hypertension, hypotension

Pediatric Population

A total of 483 pediatric patients (72 neonates, 167 infants, 171 children, and 73 adolescents) have received OFIRMEV in active-controlled (n=250) and open-label clinical trials (n=225), including 43.9% (n=212) who received 5 or more doses and 31.2% (n=153) who received more than 10 doses. Pediatric patients received OFIRMEV doses up to 15 mg/kg on an every 4 hours, every 6 hours, or every 8 hours schedule. The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively.

The most common adverse events (incidence ≥ 5%) in pediatric patients treated with OFIRMEV were nausea, vomiting, constipation, and pruritus.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Pediatrics

The following additional treatment-emergent adverse reactions were reported by pediatric subjects treated with OFIRMEV (n=483) that occurred with an incidence of at least 1%.

Blood and lymphatic system disorders: anemia

Gastrointestinal disorders: diarrhea

General disorders and administration site conditions: pyrexia, injection site pain

Metabolism and nutrition disorders: hypokalemia, hypomagnesemia, hypoalbuminemia, hypophosphatemia

Musculoskeletal and connective tissue disorders: muscle spasm

Nervous system disorders: headache

Psychiatric disorders: agitation

Renal and urinary disorders: oliguria

Respiratory, thoracic and mediastinal disorders: atelectasis, pleural effusion, pulmonary edema, stridor, wheezing

Vascular disorders: hypotension, hypertension

7 DRUG INTERACTIONS

7.1 Effects of other Substances on Acetaminophen

Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.

7.2 Anticoagulants

Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of OFIRMEV in patients on oral anticoagulants, more frequent assessment of INR may be appropriate in such circumstances.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published epidemiological studies with oral acetaminophen use during pregnancy have not reported a clear association with acetaminophen use and birth defects, miscarriage, or adverse maternal or fetal outcomes *[see Data]*. Animal reproduction studies have not been conducted with IV acetaminophen. Reproductive and developmental studies in rats and mice from the published literature identified adverse events at clinically relevant doses with acetaminophen. Treatment of pregnant rats with doses of acetaminophen approximately equal to the maximum human daily dose (MHDD) showed evidence of fetotoxicity and increases in bone variations in the fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately equal to the MHDD. In mice and rats treated with acetaminophen at doses within the clinical dosing range, cumulative adverse effects on reproductive capacity were reported. In mice, a reduction in number of litters of the parental mating pair was observed as well as retarded growth, abnormal sperm in their offspring and reduced birth weight in the next generation. In rats, female fertility was decreased following in utero exposure to acetaminophen *[see Data]*.

The estimated background risk of major birth defects and miscarriages for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

The results from a large population-based prospective cohort, including data from 26,424 women with live born singletons who were exposed to oral acetaminophen during the first trimester, indicate no increased risk for congenital malformations, compared to a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group. Other epidemiological data showed similar results. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including recall bias.

Animal Data

Studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no

evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD, based on a body surface area comparison.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison.

8.2 Lactation

Risk Summary

There is no information regarding the presence of OFIRMEV in human milk, the effects on the breastfed infant, or the effects on milk production. However, limited published studies report that acetaminophen passes rapidly into human milk with similar levels in the milk and plasma. Average and maximum neonatal doses of 1% and 2%, respectively, of the weight-adjusted maternal dose are reported after a single oral administration of 1 gram APAP. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OFIRMEV and any potential adverse effects on the breastfed infant from OFIRMEV or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Based on animal data use of acetaminophen may cause reduced fertility in males and females of reproductive potential. It is not known whether these effects on fertility are reversible. Published animal studies reported that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, and reduced fertility. In female animals given the same doses, reduced implantation sites were reported. Additional published animal studies indicate that acetaminophen exposure in utero adversely impacts reproductive capacity of both male and female offspring at clinically relevant exposures [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

Treatment of Acute Pain

The safety and effectiveness of OFIRMEV for the treatment of acute pain in pediatric patients ages 2 years and older is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults and safety and pharmacokinetic data from adult and 483 pediatric patients across all age groups *[see Dosage and Administration (2.3) and Pharmacokinetics (12.3)]*.

The effectiveness of OFIRMEV for the treatment of acute pain in pediatric patients younger than 2 years of age has not been established.

In patients younger than 2 years, efficacy was not demonstrated in a double-blind, placebo-controlled study of 198 pediatric patients younger than 2 years. Pediatric patients less than 2 years of age, including neonates from 28 to 40 weeks gestational age at birth, were randomized to receive opioid plus acetaminophen or opioid plus placebo. No difference in analgesic effect of intravenous

acetaminophen, measured by assessment of reduced need for additional opioid treatment for pain control, was observed.

Treatment of Fever

The safety and effectiveness of OFIRMEV for the treatment of fever in pediatric patients, including premature neonates born at ≥ 32 weeks gestational age is supported by adequate and well-controlled studies of OFIRMEV in adults, clinical studies in 244 pediatric patients 2 years and older, and safety and pharmacokinetic data from 239 patients younger than 2 years including neonates ≥ 32 weeks gestational age

8.5 Geriatric Use

Of the total number of subjects in clinical studies of OFIRMEV, 15% were age 65 and over, while 5% were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12)]*. A reduced total daily dose of acetaminophen may be warranted.

8.7 Patients with Renal Impairment

In cases of severe renal impairment (creatinine clearance ≤ 30 mL/min), longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted.

10 OVERDOSAGE

Signs and Symptoms

In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Plasma acetaminophen levels > 300 mcg/mL at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/mL or < 37.5 mcg/mL at 12 hours after ingestion. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment

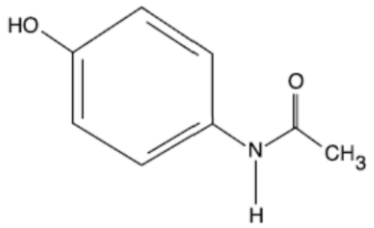
If an acetaminophen overdose is suspected, obtain a serum acetaminophen assay as soon as possible, but no sooner than 4 hours following oral ingestion. Obtain liver function studies initially and repeat at 24-hour intervals. Administer the antidote N-acetylcysteine (NAC) as early as possible. As a guide to treatment of acute ingestion, the acetaminophen level can be plotted against time since oral ingestion on a nomogram (Rumack-Matthew). The lower toxic line on the nomogram is equivalent to 150 mcg/mL at 4 hours and 37.5 mcg/mL at 12 hours. If serum level is above the lower line,

administer the entire course of NAC treatment. Withhold NAC therapy if the acetaminophen level is below the lower line.

For additional information, call a poison control center at 1-800-222-1222.

11 DESCRIPTION

Acetaminophen is a non-salicylate antipyretic and non-opioid analgesic agent. Its chemical name is N-acetyl-p-aminophenol. Acetaminophen has a molecular weight of 151.16. Its structural formula is:



OFIRMEV injection is a sterile, clear, colorless, non pyrogenic, isotonic formulation of acetaminophen intended for intravenous infusion. It has a pH of approximately 5.5 and an osmolality of approximately 290 mOsm/kg. Each 100 mL contains 1000 mg acetaminophen, USP, 3850 mg mannitol, USP, 25 mg cysteine hydrochloride, monohydrate, USP, and 10.4 mg dibasic sodium phosphate, USP. pH is adjusted with hydrochloric acid and/or sodium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism of the analgesic and antipyretic properties of acetaminophen is not established but is thought to primarily involve central actions.

12.2 Pharmacodynamics

Acetaminophen has been shown to have analgesic and antipyretic activities in animal and human studies.

Single doses of OFIRMEV up to 3000 mg and repeated doses of 1000 mg every 6 hours for 48 hours have not been shown to cause a significant effect on platelet aggregation. Acetaminophen does not have any immediate or delayed effects on small-vessel hemostasis. Clinical studies of both healthy subjects and patients with hemophilia showed no significant changes in bleeding time after receiving multiple doses of oral acetaminophen.

12.3 Pharmacokinetics

Distribution

The pharmacokinetics of OFIRMEV have been studied in patients and healthy subjects up to 60 years old. The pharmacokinetic profile of OFIRMEV has been demonstrated to be dose proportional in adults following administration of single doses of 500, 650, and 1000 mg.

The maximum concentration (C_{max}) occurs at the end of the 15 minute intravenous infusion of OFIRMEV. Compared to the same dose of oral acetaminophen, the C_{max} following administration of

OFIRMEV is up to 70% higher, while overall exposure (area under the concentration time curve [AUC]) is very similar.

Pharmacokinetic parameters of OFIRMEV (AUC, C_{max}, terminal elimination half-life [$T_{½}$], systemic clearance [CL], and volume of distribution at steady state [Vss]) following administration of a single intravenous dose of 15 mg/kg in children and adolescents and 1000 mg in adults are summarized in Table 5.

Table 5. OFIRMEV Pharmacokinetic Parameters

Subpopulations	Mean (SD)				
	AUC_{0-6h} (µg × h/mL)	**C_{max} (µg/mL)**	**$T_{½}$ (h)**	**CL (L/h/kg)**	**Vss (L/kg)**
Children	38 (8)	29 (7)	3.0 (1.5)	0.34 (0.10)	1.2 (0.3)
Adolescents	41 (7)	31 (9)	2.9 (0.7)	0.29 (0.08)	1.1 (0.3)
Adults	43 (11)	28 (21)	2.4 (0.6)	0.27 (0.08)	0.8 (0.2)

The concentrations of acetaminophen observed in neonates greater than 32 weeks gestational age at birth treated with 12.5 mg/kg dose are similar to infants, children and adolescents treated with a 15 mg/kg dose, and similar to adults treated with a 1000 mg dose.

At therapeutic levels, binding of acetaminophen to plasma proteins is low (ranging from 10% to 25%). Acetaminophen appears to be widely distributed throughout most body tissues except fat.

Metabolism and Excretion

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: Conjugation with glucuronide, conjugation with sulfate, and oxidation via the cytochrome P450 enzyme pathway, primarily CYP2E1, to form a reactive intermediate metabolite (N-acetyl-p-benzoquinone imine or NAPQI). With therapeutic doses, NAPQI undergoes rapid conjugation with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates.

Acetaminophen metabolites are mainly excreted in the urine. Less than 5% is excreted in the urine as unconjugated (free) acetaminophen and more than 90% of the administered dose is excreted within 24 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (0.7 times) or mice (1.2-1.4 times the MHDD, based on a body surface area comparison).

Mutagenesis

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive in the in vitro mouse lymphoma assay and the in vitro chromosomal aberration assay using human lymphocytes. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

Impairment of Fertility

In studies conducted by the National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment.

In a published mouse study, oral administration of 50 mg/kg acetaminophen to pregnant mice from Gestation Day 7 to delivery (0.06 times the MHDD, based on a body surface area comparison) reduced the number of primordial follicles in female offspring and reduced the percentage of full term pregnancies and number of pups born to these females exposed to acetaminophen in utero.

In a published study, oral administration of 350 mg/kg acetaminophen to pregnant rats (0.85 times the MHDD, based on a body surface area comparison) from Gestation Day 13 to 21 (dams) reduced the number of germ cells in the fetal ovary, decreased ovary weight, and reduced the number of pups per litter in F_1 females as well as reduced ovary weights in F_2 females.

14 CLINICAL STUDIES

14.1 Adult Acute Pain

The efficacy of OFIRMEV in the treatment of acute pain in adults was evaluated in two randomized, double-blind, placebo-controlled clinical trials in patients with postoperative pain.

Pain Study 1 evaluated the analgesic efficacy of repeated doses of OFIRMEV 1000 mg vs. placebo every 6 hours for 24 hours in 101 patients with moderate to severe pain following total hip or knee replacement. OFIRMEV was statistically superior to placebo for reduction in pain intensity over 24 hours. There was an attendant decrease in opioid consumption, the clinical benefit of which was not demonstrated.

Pain Study 2 evaluated the analgesic efficacy of repeated doses of OFIRMEV 1000 mg every 6 hours or 650 mg every 4 hours for 24 hours versus placebo in the treatment of 244 patients with moderate to severe postoperative pain after abdominal laparoscopic surgery. Patients receiving

OFIRMEV experienced a statistically significant greater reduction in pain intensity over 24 hours compared to placebo.

14.2 Adult Fever

The efficacy of OFIRMEV 1000 mg in the treatment of adult fever was evaluated in one randomized, double-blind, placebo-controlled clinical trial. The study was a 6-hour, single-dose, endotoxin-induced fever study in 60 healthy adult males. A statistically significant antipyretic effect of OFIRMEV was demonstrated through 6 hours in comparison to placebo. The mean temperature over time is shown in Figure 1.

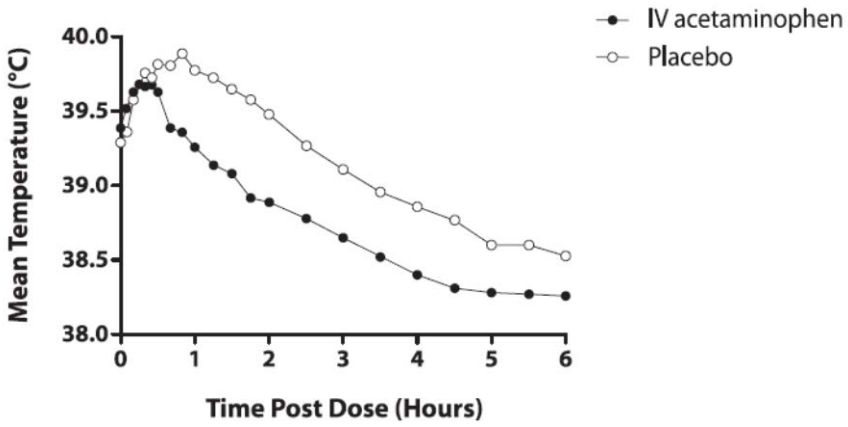


Figure 1: Mean Temperature (°C) Over Time

14.3 Pediatric Acute Pain and Fever

OFIRMEV was studied in pediatric patients in three active-controlled trials and three open-label safety and pharmacokinetic trials *[see Use in Specific Populations (8.4)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 43825-102-01 - OFIRMEV (acetaminophen) Injection is supplied in a 100 mL glass vial containing 1000 mg acetaminophen (10 mg/mL) in cartons of 24 vials.

NDC 43825-102-03 - OFIRMEV (acetaminophen) Injection is supplied in a 100 mL bag containing 1000 mg acetaminophen (10 mg/mL) in cartons of 24 bags.

Do not remove unit from overwrap until ready for use.

To open, tear outer wrap at the notch and remove solution bag. After removing the outer wrap, check the container for minute leaks by squeezing the solution bag firmly. If leaks are found, discard the solution because the sterility may be impaired. A small amount of moisture may be present inside the outer wrap.

OFIRMEV should be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

For single-dose only. The product should be used within 6 hours after opening. Do not refrigerate or freeze.

Manufactured for:

Mallinckrodt Hospital Products Inc.
Hazelwood, MO 63042 USA

Revised: 01/2017

U.S. PATENT NUMBERS:
6,028,222; 6,992,218

1291306A2

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ORILISSA safely and effectively. See full prescribing information for ORILISSA.

ORILISSA™ (elagolix) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
ORILISSA is a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the management of moderate to severe pain associated with endometriosis. (1)

----------DOSAGE AND ADMINISTRATION----------
Normal liver function or mild hepatic impairment: 150 mg once daily for up to 24 months or 200 mg twice daily for up to 6 months. (2.1)

Moderate hepatic impairment: 150 mg once daily for up to 6 months. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Oral tablets: 150 mg and 200 mg (3)

----------CONTRAINDICATIONS----------
- Pregnancy (4)
- Known osteoporosis (4)
- Severe hepatic impairment (4)
- Strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (4)

----------WARNINGS AND PRECAUTIONS----------
- Bone Loss: Dose- and duration-dependent decreases in bone mineral density (BMD) that may not be completely reversible. Assess BMD in women with additional risk factors for bone loss (5.1)
- Reduced Ability to Recognize Pregnancy: ORILISSA may alter menstrual bleeding, which may reduce the ability to recognize pregnancy. Perform testing if pregnancy is suspected. Discontinue if pregnancy is confirmed (5.2)
- Suicidal Ideation and Mood Disorders: Advise patients to seek medical attention for suicidal ideation, suicidal behavior, new onset or worsening depression, anxiety, or other mood changes (5.3)
- Hepatic Transaminase Elevations: Dose-dependent elevations in serum alanine aminotransferase (ALT). Counsel patients on signs and symptoms of liver injury (5.4)
- Potential for Reduced Efficacy with Estrogen-Containing Contraceptives: Use non-hormonal contraception during treatment and for one week after discontinuing ORILISSA (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>5%) in clinical trials included hot flushes and night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions and mood changes (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
See full prescribing information for a list of clinically important drug interactions (7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ORILISSA is indicated for the management of moderate to severe pain associated with endometriosis.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

- Exclude pregnancy before starting ORILISSA or start ORILISSA within 7 days from the onset of menses.
- Take ORILISSA at approximately the same time each day, with or without food.
- Use the lowest effective dose, taking into account the severity of symptoms and treatment objectives *[see Warnings and Precautions (5.1, 5.3, 5.4) and Clinical Studies (14)]*.
- Limit the duration of use because of bone loss (Table 1) *[see Warnings and Precautions (5.1)]*.

Table 1. Recommended Dosage and Duration of Use

Dosing Regimen	**Maximum Treatment Duration**	**Coexisting Condition**
Initiate treatment with ORILISSA 150 mg once daily	24 months	None
Consider initiating treatment with ORILISSA 200 mg twice daily	6 months	Dyspareunia
Initiate treatment with ORILISSA 150 mg once daily. Use of 200 mg twice daily is not recommended.	6 months	Moderate hepatic impairment (Child-Pugh Class B)

2.2 Hepatic Impairment

No dosage adjustment of ORILISSA is required in women with mild hepatic impairment (Child-Pugh A).

Compared to women with normal liver function, those with moderate hepatic impairment had approximately 3-fold higher elagolix exposures and those with severe hepatic impairment had approximately 7-fold higher elagolix exposures. Because of these increased exposures and risk for bone loss:

- ORILISSA 150 mg once daily is recommended for women with moderate hepatic impairment (Child-Pugh B) with the duration of treatment limited to 6 months. Use of ORILISSA 200 mg twice daily is not recommended for women with moderate hepatic impairment *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

- ORILISSA is contraindicated in women with severe hepatic impairment (Child-Pugh C) *[see Contraindications (4), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.3 Missed Dose

Instruct the patient to take a missed dose of ORILISSA on the same day as soon as she remembers and then resume the regular dosing schedule.

- 150 mg once daily: take no more than 1 tablet each day.
- 200 mg twice daily: take no more than 2 tablets each day.

3 DOSAGE FORMS AND STRENGTHS

The 150 mg tablets are light pink, oblong, film-coated tablets with “EL 150” debossed on one side. Each tablet contains 155.2 mg of elagolix sodium equivalent to 150 mg of elagolix.

The 200 mg tablets are light orange, oblong, film-coated tablets with “EL 200” debossed on one side. Each tablet contains 207.0 mg of elagolix sodium equivalent to 200 mg of elagolix.

4 CONTRAINDICATIONS

ORILISSA is contraindicated in women:

- Who are pregnant *[see Use in Specific Populations (8.1)]*. Exposure to ORILISSA early in pregnancy may increase the risk of early pregnancy loss.
- With known osteoporosis because of the risk of further bone loss *[see Warnings and Precautions (5.1)]*
- With severe hepatic impairment because of the risk of bone loss *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*
- With concomitant use of strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine and gemfibrozil) *[see Drug Interactions (7.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Bone Loss

ORILISSA causes a dose-dependent decrease in bone mineral density (BMD). BMD loss is greater with increasing duration of use and may not be completely reversible after stopping treatment *[see Adverse Reactions (6.1)]*. The impact of these BMD decreases on long-term bone health and future fracture risk are unknown. Consider assessment of BMD in patients with a history of a low-trauma fracture or other risk factors for osteoporosis or bone loss, and do not use

in women with known osteoporosis. Limit the duration of use to reduce the extent of bone loss *[see Dosage and Administration (2.2)]*.

Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients.

5.2 Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

Women who take ORILISSA may experience a reduction in the amount, intensity or duration of menstrual bleeding, which may reduce the ability to recognize the occurrence of a pregnancy in a timely manner *[see Adverse Reactions (6.1)]*. Perform pregnancy testing if pregnancy is suspected, and discontinue ORILISSA if pregnancy is confirmed.

5.3 Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ORILISSA in the endometriosis clinical trials. ORILISSA subjects had a higher incidence of depression and mood changes compared to placebo, and ORILISSA subjects with a history of suicidality or depression had a higher incidence of depression compared to subjects without such a history *[see Adverse Reactions (6.1)]*. Promptly evaluate patients with depressive symptoms to determine whether the risks of continued therapy outweigh the benefits *[see Adverse Reactions (6.1)]*. Patients with new or worsening depression, anxiety or other mood changes should be referred to a mental health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing ORILISSA if such events occur.

5.4 Hepatic Transaminase Elevations

In clinical trials, dose-dependent elevations of serum alanine aminotransferase (ALT) at least 3-times the upper limit of the reference range occurred with ORILISSA. Use the lowest effective dose of ORILISSA and instruct patients to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice. Promptly evaluate patients with elevations in liver tests to determine whether the benefits of continued therapy outweigh the risks *[see Adverse Reactions (6.1)]*.

5.5 Reduced Efficacy with Estrogen-Containing Contraceptives

Based on the mechanism of action of ORILISSA, estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA. The effect of progestin-only contraceptives on

the efficacy of ORILISSA is unknown. Advise women to use non-hormonal contraceptives during treatment with ORILISSA and for one week after discontinuing ORILISSA *[see Use in Specific Populations (8.1, 8.3), Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

- Bone loss *[see Warnings and Precautions (5.1)]*
- Change in menstrual bleeding pattern and reduced ability to recognize pregnancy *[see Warnings and Precautions (5.2)]*
- Suicidal ideation, suicidal behavior, and exacerbation of mood disorders *[see Warnings and Precautions (5.3)]*
- Hepatic transaminase elevations *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of ORILISSA was evaluated in two six-month, randomized, double-blind, placebo-controlled clinical trials [EM-1 (NCT01620528) and EM-2 (NCT01931670)] in which a total of 952 adult women with moderate to severe pain associated with endometriosis were treated with ORILISSA (475 with 150 mg once daily and 477 with 200 mg twice daily) and 734 were treated with placebo. The population age range was 18-49 years old. Women who completed six months of treatment and met eligibility criteria continued treatment in two uncontrolled, blinded six-month extension trials [EM-3 (NCT01760954) and EM-4 (NCT02143713)], for a total treatment duration of up to 12 months.

Serious Adverse Events

Overall, the most common serious adverse events reported for subjects treated with ORILISSA in the two placebo-controlled clinical trials (Studies EM-1 and EM-2) included appendicitis (0.3%), abdominal pain (0.2%), and back pain (0.2%). In these trials, 0.2% of subjects treated with ORILISSA 150 mg once daily and 0.2% of subjects treated with ORILISSA 200 mg twice

daily discontinued therapy due to serious adverse reactions compared to 0.5% of those given placebo.

Adverse Reactions Leading to Study Discontinuation

In the two placebo-controlled clinical trials (Studies EM-1 and EM-2), 5.5% of subjects treated with ORILISSA 150 mg once daily and 9.6% of subjects treated with ORILISSA 200 mg twice daily discontinued therapy due to adverse reactions compared to 6.0% of those given placebo. Discontinuations were most commonly due to hot flushes or night sweats (1.1% with 150 mg once daily and 2.5% with 200 mg twice daily) and nausea (0.8% with 150 mg once daily and 1.5% with 200 mg twice daily) and were dose-related. The majority of discontinuations due to hot flushes or night sweats (10 of 17, 59%) and nausea (7 of 11, 64%) occurred within the first 2 months of therapy.

In the two extension trials (Studies EM-3 and EM-4), discontinuations were most commonly due to decreased BMD and were dose-related. In these trials, 0.3% of subjects treated with ORILISSA 150 mg once daily and 3.6% of subjects treated with ORILISSA 200 mg twice daily discontinued therapy due to decreased BMD.

Common Adverse Reactions:

Adverse reactions reported in ≥ 5% of women in the two placebo-controlled trials in either ORILISSA dose group and at a greater frequency than placebo are noted in the following table.

Table 2. Percentage of Subjects in Studies EM-1 and EM-2 with Treatment-Emergent Adverse Reactions Occurring in at Least 5% of Subjects (either ORILISSA Dose Group) and at a Greater Incidence than with Placebo

	ORILISSA 150 mg Once Daily N=475	**ORILISSA 200 mg Twice Daily N=477**	**Placebo N=734**
	%	**%**	**%**
Hot Flush or Night Sweats	24	46	9
Headache	17	20	12
Nausea	11	16	13
Insomnia	6	9	3
Mood altered, mood swings	6	5	3
Amenorrhea	4	7	<1
Depressed mood, depression, depressive symptoms and/or tearfulness	3	6	2

Anxiety	3	5	3
Arthralgia	3	5	3

Less Common Adverse Reactions:

In Study EM-1 and Study EM-2, adverse reactions reported in ≥ 3% and < 5% in either ORILISSA dose group and greater than placebo included: decreased libido, diarrhea, abdominal pain, weight gain, dizziness, constipation and irritability.

The most commonly reported adverse reactions in the extension trials (EM-3 and EM-4) were similar to those in the placebo-controlled trials.

Bone Loss

The effect of ORILISSA on BMD was assessed by dual-energy X-ray absorptiometry (DXA).

In Studies EM-1 and EM-2, there was a dose-dependent decrease in BMD in ORILISSA-treated subjects compared to an increase in placebo-treated subjects.

In Study EM-1, compared to placebo, the mean change from baseline in lumbar spine BMD at 6 months was -0.9% (95% CI: -1.3, -0.4) with ORLISSA 150 mg once daily and -3.1% (95% CI: -3.6, -2.6) with ORILISSA 200 mg twice daily (Table 3). The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the placebo-controlled treatment period was 2% with ORILISSA 150 mg once daily, 7% with ORILISSA 200 mg twice daily and < 1% with placebo. In the blinded extension Study EM-3, continued bone loss was observed with 12 months of continuous treatment with ORILISSA. The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 8% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily.

In Study EM-2, compared to placebo, the mean change from baseline in lumbar spine BMD at 6 months was -1.3% (95% CI: -1.8, -0.8) with ORLISSA 150 mg once daily and -3.0% (95% CI: -3.5, -2.6) with ORILISSA 200 mg twice daily (Table 3). The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the placebo-controlled treatment period was < 1% with ORILISSA 150 mg once daily, 6% with ORILISSA 200 mg twice daily and 0% with placebo. In the blinded extension Study EM-4, continued bone loss was observed with 12 months of continuous treatment with

ORILISSA. The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 2% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily.

Table 3. Percent Change from Baseline in Lumbar Spine BMD at Month 6

	ORILISSA 150 mg Once Daily	**ORILISSA 200 mg Twice Daily**	**Placebo**
EM-1			
N	183	180	277
Percent Change from Baseline, %	-0.3	-2.6	0.5
Treatment Difference, % (95% CI)	-0.9 (-1.3, -0.4)	-3.1 (-3.6, -2.6)	
EM-2			
N	174	183	271
Percent Change from Baseline, %	-0.7	-2.5	0.6
Treatment Difference, % (95% CI)	-1.3 (-1.8, -0.8)	-3.0 (-3.5, -2.6)	

To assess for recovery, the change in lumbar spine BMD over time was analyzed for subjects who received continuous treatment with ORILISSA 150 mg once daily or ORILISSA 200 mg twice daily for up to 12 months and who were then followed after cessation of therapy for an additional 6 months. Partial recovery of BMD was seen in these subjects (Figure 1).

In Study EM-3, if a subject had BMD loss of more than 1.5% at the lumbar spine or more than 2.5% at the total hip at the end of treatment, follow-up DXA was required after 6 months off-treatment. In Study EM-4, all subjects were required to have a follow-up DXA 6 months off treatment regardless of change in BMD and if a subject had BMD loss of more than 1.5% at the lumbar spine or more than 2.5% at the total hip after 6 months off treatment, follow-up DXA was required after 12 months off-treatment. Figure 2 shows the change in lumbar spine BMD for the subjects in Study EM-2/EM-4 who completed 12 months of treatment with ORILISSA and who had a follow-up DXA 12-months off treatment.

Figure 1. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 6 Months off Therapy in Studies EM-2/EM-4

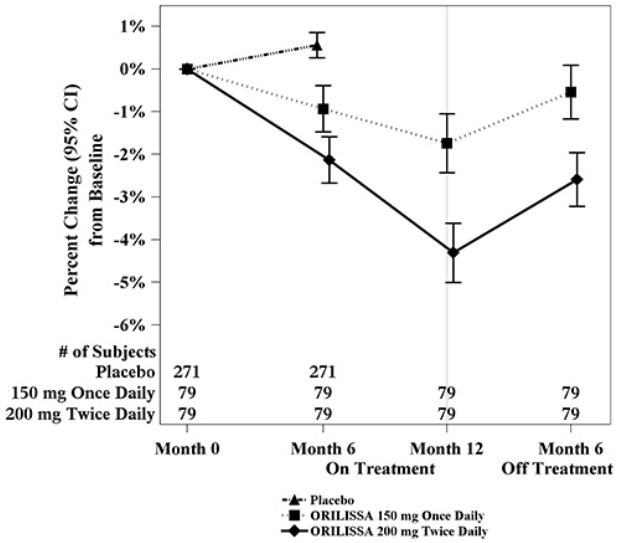
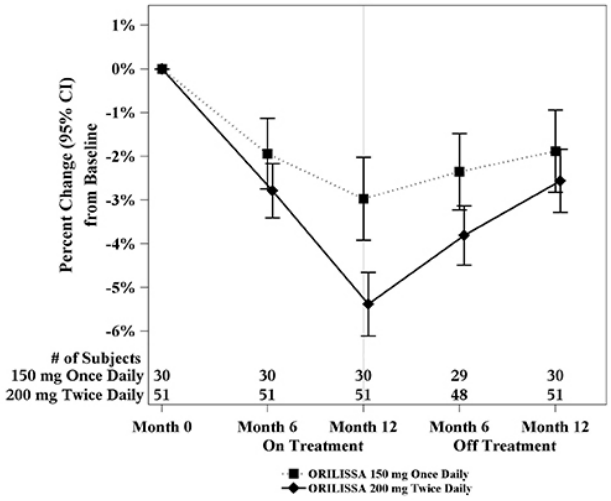


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



Suicidal Ideation, Suicidal Behavior and Exacerbation of Mood Disorders

In the placebo-controlled trials (Studies EM-1 and EM-2), ORILISSA was associated with adverse mood changes (see Table 2 and Table 4), particularly in those with a history of depression.

Table 4. Suicidal Ideation and Suicidal Behavior in Studies EM-1 and EM-2

Adverse Reactions	**ORILISSA**		
	150 mg Once Daily (N=475) n (%)	**200 mg Twice Daily (N=477) n (%)**	**Placebo (N=734) n (%)**
Completed suicide	1 (0.2)	0	0
Suicidal ideation	1 (0.2)	1 (0.2)	0

A 44-year-old woman received 31 days of ORILISSA 150 mg once daily then completed suicide 2 days after ORILISSA discontinuation. She had no relevant past medical history; life stressors were noted.

Among the 2090 subjects exposed to ORILISSA in the endometriosis Phase 2 and Phase 3 studies, there were four reports of suicidal ideation. In addition to the two subjects in Table 4, there were two additional reports of suicidal ideation: one subject in EM-3 (150 mg once daily) and one in a Phase 2 study (75 mg once daily, an unapproved dose). Three of these subjects had a history of depression. Two subjects discontinued ORILISSA and two completed the clinical trial treatment periods.

Hepatic Transaminase Elevations

In the placebo-controlled clinical trials (Studies EM-1 and EM-2), dose-dependent asymptomatic elevations of serum ALT to at least 3-times the upper limit of the reference range occurred during treatment with ORILISSA (150 mg once daily – 1/450, 0.2%; 200 mg twice daily – 5/443, 1.1%; placebo – 1/696, 0.1%). Similar increases were seen in the extension trials (Studies EM-3 and EM-4).

Changes in Lipid Parameters

Dose-dependent increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and serum triglycerides were noted during ORILISSA

treatment in EM-1 and EM-2. In EM-1 and EM-2, 12% and 1% of subjects with mildly elevated LDL-C (130-159 mg/dL) at baseline had an increase in LDL-C concentrations to 190 mg/dL or higher during treatment with ORILISSA and placebo, respectively. In EM-1 and EM-2, 4% and 1% of subjects with mildly elevated serum triglycerides (150-300 mg/dL) at baseline had an increase in serum triglycerides to at least 500 mg/dL during treatment with ORILISSA and placebo, respectively. The highest measured serum triglyceride concentration during treatment with ORILISSA was 982 mg/dL.

Table 5. Mean Change and Maximum Increase from Baseline in Serum Lipids in Studies EM-1 and EM-2

	ORILISSA 150 mg Once Daily N=475	**ORILISSA 200 mg Twice Daily N=477**	**Placebo N=734**
LDL-C (mg/dL)			
Mean change at Month 6	5	13	-3
Maximum increase during Treatment Period	137	107	122
HDL-C (mg/dL)			
Mean change at Month 6	2	4	1
Maximum increase during Treatment Period	43	52	45
Triglycerides (mg/dL)			
Mean change at Month 6	<1	11	-3
Maximum increase during Treatment Period	624	484	440

Lipid increases occurred within 1 to 2 months after the start of ORILISSA and remained stable thereafter over 12 months.

Hypersensitivity Reactions

In Studies EM-1 and EM-2, non-serious hypersensitivity reactions including rash occurred in 5.8% of ORILISSA treated-subjects and 6.1% of placebo-treated subjects. These events led to study drug discontinuation in 0.4% of ORILISSA-treated subjects and 0.5% of placebo-treated subjects.

Endometrial Effects

Endometrial biopsies were performed in subjects in Study EM-1 and its extension at Month 6 and Month 12. These biopsies showed a dose-dependent decrease in proliferative and secretory biopsy patterns and an increase in quiescent/minimally stimulated biopsy patterns. There were no abnormal biopsy findings on treatment, such as endometrial hyperplasia or cancer.

Based on transvaginal ultrasound, during the course of a 3-menstrual cycle study in healthy women, ORILISSA 150 mg once daily and 200 mg twice daily resulted in a dose-dependent decrease from baseline in mean endometrial thickness.

Effects on menstrual bleeding patterns

The effects of ORILISSA on menstrual bleeding were evaluated for up to 12 months using an electronic daily diary where subjects classified their flow of menstrual bleeding (if present in the last 24 hours) as spotting, light, medium, or heavy. ORILISSA led to a dose-dependent reduction in mean number of bleeding and spotting days and bleeding intensity in those subjects who reported menstrual bleeding.

Table 6. Mean Bleeding/Spotting Days and Mean Intensity Scores at Month 3

	ORILISSA 150mg Once Daily		**ORILISSA 200mg Twice Daily**		**Placebo**	
	Baseline	**Month 3**	**Baseline**	**Month 3**	**Baseline**	**Month 3**
Mean bleeding/ spotting days in prior 28 days	5.3	2.8	5.7	0.8	5.4	4.6
Mean Intensity score[a]	2.6	2.2	2.5	2.0	2.6	2.4
[a]Intensity for subjects who reported at least 1 day of bleeding or spotting during 28 day interval. Scale ranges from 1 to 4, 1 = spotting, 2 = light, 3 = medium, 4 = heavy						

ORILISSA also demonstrated a dose-dependent increase in the percentage of women with amenorrhea (defined as no bleeding or spotting in a 56-day interval) over the treatment period. The incidence of amenorrhea during the first six months of treatment ranged from 6-17% for ORILISSA 150 mg once daily, 13-52% for ORILISSA 200 mg twice daily and less than 1% for

placebo. During the second 6 months of treatment, the incidence of amenorrhea ranged from 11-15% for ORILISSA 150 mg once daily and 46-57% for ORILISSA 200 mg twice daily.

After 6 months of therapy with ORILISSA 150 mg once daily, resumption of menses after stopping treatment was reported by 59%, 87% and 95% of women within 1, 2, and 6 months, respectively. After 6 months of therapy with ORILISSA 200 mg twice daily, resumption of menses after stopping treatment was reported by 60%, 88%, and 97% of women within 1, 2, and 6 months, respectively.

After 12 months of therapy with ORILISSA 150 mg once daily resumption of menses after stopping treatment was reported by 77%, 95% and 98% of women within 1, 2, and 6 months respectively. After 12 months of therapy with ORILISSA 200 mg twice daily resumption of menses after stopping treatment was reported by 55%, 91% and 96% of women within 1, 2, and 6 months respectively.

7 DRUG INTERACTIONS

7.1 Potential for ORILISSA to Affect Other Drugs

Elagolix is a weak to moderate inducer of cytochrome P450 (CYP) 3A. Co-administration with ORILISSA may decrease plasma concentrations of drugs that are substrates of CYP3A.

Elagolix is an inhibitor of efflux transporter P-glycoprotein (P-gp). Co-administration with ORILISSA may increase plasma concentrations of drugs that are substrates of P-gp (e.g., digoxin).

7.2 Potential for Other Drugs to Affect ORILISSA

Elagolix is a substrate of CYP3A, P-gp, and OATP1B1.

Concomitant use of ORILISSA 200 mg twice daily and strong CYP3A inhibitors for more than 1 month is not recommended. Limit concomitant use of ORILISSA 150 mg once daily and strong CYP3A inhibitors to 6 months.

Co-administration of ORILISSA with drugs that induce CYP3A may decrease elagolix plasma concentrations.

The effect of concomitant use of P-gp inhibitors or inducers on the pharmacokinetics of ORILISSA is unknown. Co-administration of ORILISSA with drugs that inhibit OATP1B1 may

increase elagolix plasma concentrations. Concomitant use of ORILISSA and strong OATP1B1 inhibitors (e.g., cyclosporine and gemfibrozil) is contraindicated.

7.3 Drug Interactions- Examples and Clinical Management

Table 7 summarizes the effect of co-administration of ORILISSA on concentrations of concomitant drugs and the effect of concomitant drugs on ORILISSA.

Table 7. Established Drug Interactions Based on Drug Interaction Trials

Concomitant Drug Class: **Drug Name**	**Effect on Plasma Exposure of Elagolix or Concomitant Drug**	**Clinical Recommendations**
Antiarrhythmics digoxin	↑ digoxin	Clinical monitoring is recommended for digoxin when co-administered with ORILISSA.
Antimycobacterial rifampin	↑ elagolix	Concomitant use of ORILISSA 200 mg twice daily and rifampin is not recommended. Limit concomitant use of ORILISSA 150 mg once daily and rifampin to 6 months.
Benzodiazepines oral midazolam	↓ midazolam	Consider increasing the dose of midazolam and individualize therapy based on the patient's response.
Statins rosuvastatin	↓ rosuvastatin	Consider increasing the dose of rosuvastatin.
See Clinical Pharmacology, Tables 8 and 9. The direction of the arrow indicates the direction of the change in the area under the curve (AUC) (↑ = increase, ↓ = decrease).		

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Exposure to ORILISSA early in pregnancy may increase the risk of early pregnancy loss. Use of ORILISSA is contraindicated in pregnant women. Discontinue ORILISSA if pregnancy occurs during treatment.

The limited human data with the use of ORILISSA in pregnant women are insufficient to determine whether there is a risk for major birth defects or miscarriage. Although two cases of

congenital malformations were reported in clinical trials with ORILISSA, no pattern was identified and miscarriages were reported at a similar incidence across treatment groups *(see Data).*

When pregnant rats and rabbits were orally dosed with elagolix during the period of organogenesis, postimplantation loss was observed in pregnant rats at doses 20 times the maximum recommended human dose (MRHD). Spontaneous abortion and total litter loss was observed in rabbits at doses 7 and 12 times the MRHD. There were no structural abnormalities in the fetuses at exposures up to 40 and 12 times the MRHD for the rat and rabbit, respectively *(see Data).*

The background risk for major birth defects and miscarriage in the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

There were 49 pregnancies reported in clinical trials of more than 3,500 women (of whom more than 2,000 had endometriosis) treated with ORILISSA for up to 12 months. These pregnancies occurred while the women were receiving ORILISSA or within 30 days after stopping ORILISSA. Among these 49 pregnancies, two major congenital malformations were reported. In one case of infant cleft palate, the mother was treated with ORILISSA 150 mg daily and the estimated fetal exposure to ORILISSA occurred during the first 30 days of pregnancy. In one case of infant tracheoesophageal fistula, the mother was treated with ORILISSA 150 mg daily and the estimated fetal exposure to ORILISSA occurred during the first 15 days of pregnancy.

Among these 49 pregnancies, there were five cases of spontaneous abortion (miscarriage) compared to five cases among the 20 pregnancies that occurred in more than 1100 women treated with placebo. Although the duration of fetal exposure was limited in ORILISSA clinical trials, there were no apparent decreases in birth weights associated with ORILISSA in comparison to placebo.

Animal Data

Embryofetal development studies were conducted in the rat and rabbit. Elagolix was administered by oral gavage to pregnant rats (25 animals/dose) at doses of 0, 300, 600 and 1200

mg/kg/day and to rabbits (20 animals/dose) at doses of 0, 100, 150, and 200 mg/kg/day, during the period of organogenesis (gestation day 6-17 in the rat and gestation day 7-20 in the rabbit).

In rats, maternal toxicity was present at all doses and included six deaths and decreases in body weight gain and food consumption. Increased postimplantation losses were present in the mid dose group, which was 20 times the MRHD based on AUC. In rabbits, three spontaneous abortions and a single total litter loss were observed at the highest, maternally toxic dose, which was 12 times the MRHD based on AUC. A single total litter loss occurred at a lower non-maternally toxic dose of 150 mg/kg/day, which was 7 times the MRHD.

No fetal malformations were present at any dose level tested in either species even in the presence of maternal toxicity. At the highest doses tested, the exposure margins were 40 and 12 times the MRHD for the rat and rabbit, respectively. However, because elagolix binds poorly to the rat gonadotropin-releasing hormone (GnRH) receptor (~1000 fold less than to the human GnRH receptor), the rat study is unlikely to identify pharmacologically mediated effects of elagolix on embryofetal development. The rat study is still expected to provide information on potential non-target-related effects of elagolix.

In a pre- and postnatal development study in rats, elagolix was given in the diet to achieve doses of 0, 100 and 300 mg/kg/day (25 per dose group) from gestation day 6 to lactation day 20. There was no evidence of maternal toxicity. At the highest dose, two dams had total litter loss, and one failed to deliver. Pup survival was decreased from birth to postnatal day 4. Pups had lower birth weights and lower body weight gains were observed throughout the pre-weaning period at 300 mg/kg/day. Smaller body size and effect on startle response were associated with lower pup weights at 300 mg/kg/day. Post-weaning growth, development and behavioral endpoints were unaffected.

Maternal plasma concentrations in rats on lactation day 21 at 100 and 300 mg/kg/day (47 and 125 ng/mL) were 0.06-fold and 0.16-fold the maximal elagolix concentration (C_{max}) in humans at the MRHD. Because the exposures achieved in rats were much lower than the human MRHD, this study is not predictive of potentially higher lactational exposure in humans.

8.2 Lactation

Risk Summary

There is no information on the presence of elagolix or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. There are no adequate animal data on

the excretion of ORILISSA in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ORILISSA and any potential adverse effects on the breastfed child from ORILISSA.

Data

There are no adequate animal data on excretion of ORILISSA in milk.

8.3 Females and Males of Reproductive Potential

Based on the mechanism of action, there is a risk of early pregnancy loss if ORILISSA is administered to a pregnant woman *[see Use in Specific Populations (8.1), Clinical Pharmacology (12.1)]*.

Pregnancy Testing

Exclude pregnancy before initiating treatment with ORILISSA. Perform pregnancy testing if pregnancy is suspected during treatment with ORILISSA *[see Warnings and Precautions (5.2)]*.

Contraception

Advise women to use effective non-hormonal contraception during treatment with ORILISSA and for one week after discontinuing ORILISSA *[see Warnings and Precautions (5.2) and Drug Interactions (7.3)]*.

8.4 Pediatric Use

Safety and effectiveness of ORILISSA in patients less than 18 years of age have not been established.

8.6 Renal Impairment

No dose adjustment of ORILISSA is required in women with any degree of renal impairment or end-stage renal disease (including women on dialysis) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment of ORILISSA is required for women with mild hepatic impairment (Child-Pugh A). Only the 150 mg once daily regimen is recommended for women with moderate hepatic impairment (Child-Pugh B) and the duration of treatment should be limited to 6 months.

ORILISSA is contraindicated in women with severe hepatic impairment (Child-Pugh C) *[see Contraindications (4), and Clinical Pharmacology (12.3)]*.

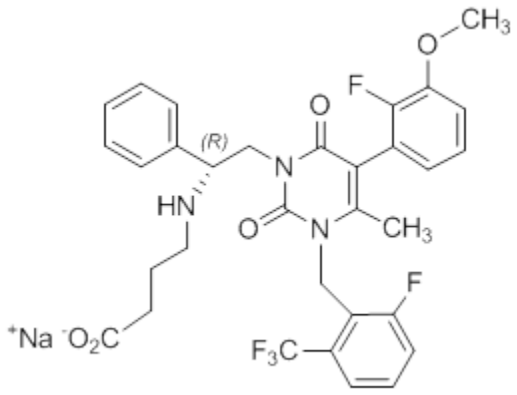
10 OVERDOSAGE

In case of overdose, monitor the patient for any signs or symptoms of adverse reactions and initiate appropriate symptomatic treatment, as needed.

11 DESCRIPTION

ORILISSA (elagolix) tablets for oral administration contain elagolix sodium, the sodium salt of the active moiety elagolix. Elagolix sodium is a nonpeptide small molecule, GnRH receptor antagonist. Elagolix sodium is chemically described as sodium 4-({(1*R*)-2-[5-(2-fluoro-3-methoxyphenyl)-3-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]-1-phenylethyl}amino)butanoate. Elagolix sodium has a molecular formula of $C_{32}H_{29}F_5N_3O_5Na$ and a molecular weight of 653.58. Elagolix free acid has a molecular weight of 631.60.

Elagolix sodium has the following structural formula:



Elagolix sodium is a white to off white to light yellow powder and is freely soluble in water.

ORILISSA 150 mg tablets are light pink, oblong, film-coated tablets with “EL 150” debossed on one side. Each tablet contains 155.2 mg of elagolix sodium (equivalent to 150 mg of elagolix) as the active ingredient and the following inactive ingredients: mannitol, sodium carbonate monohydrate, pregelatinized starch, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and carmine high tint.

ORILISSA 200 mg tablets are light orange, oblong, film-coated tablets with “EL 200” debossed on one side. Each tablet contains 207.0 mg of elagolix sodium (equivalent to 200 mg of

elagolix) as the active ingredient and the following inactive ingredients: mannitol, sodium carbonate monohydrate, pregelatinized starch, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ORILISSA is a GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration of ORILISSA results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased blood concentrations of the ovarian sex hormones, estradiol and progesterone.

12.2 Pharmacodynamics

Effect on Ovulation and Estradiol

In a 3-menstrual cycle study in healthy women, ORILISSA 150 mg once daily and 200 mg twice daily resulted in an ovulation rate of approximately 50% and 32%, respectively. In the Phase 3 trials in women with endometriosis, ORILISSA caused a dose-dependent reduction in median estradiol concentrations to approximately 42 pg/mL for 150 mg once daily regimen and 12 pg/mL for the 200 mg twice daily regimen.

Cardiac Electrophysiology

The effect of elagolix on the QTc interval was evaluated in a randomized, placebo- and positive-controlled, open-label, single-dose, crossover thorough QTc study in 48 healthy adult premenopausal women. Elagolix concentrations in subjects given a single dose of 1200 mg was 17-times higher than the concentration in subjects given elagolix 200 mg twice daily. There was no clinically relevant prolongation of the QTc interval.

12.3 Pharmacokinetics

The pharmacokinetic properties of ORILISSA in healthy subjects are summarized in Table 8. The steady state pharmacokinetic parameters under fasting conditions are summarized in Table 9.

Table 8. Pharmacokinetic Properties of ORILISSA in Healthy Subjects

Absorption	
T_{max} (h)	1.0

Effect of high-fat meal (relative to fasting)	AUC: ↓24%, C_{max}: ↓36%
Distribution	
% Bound to human plasma proteins	80
Blood-to-plasma ratio	0.6
Metabolism	
Metabolism	CYP3A (major) Minor pathways include: CYP2D6, CYP2C8, and uridine glucuronosyl transferases (UGTs)
Elimination	
Major route of elimination	Hepatic metabolism
Terminal phase elimination half-life ($t_{1/2}$) (h)	4-6
% of dose excreted in urine	<3
% of dose excreted in feces	90

Table 9. Mean (%CV) Steady State Pharmacokinetic Parameters of ORILISSA

Pharmacokinetic Parameter (Units)	**150 mg Once Daily N = 6**	**200 mg Twice Daily N = 7**
C_{max} (ng/mL)	574 (29)	774 (68)
AUC_{τ} (ng•hr/mL)	1292 (31)	1725 (57)
CL/F (L/hr)	123 (21)	144 (43)
V_{dss}/F	1674 (94)	881 (38)
R_{ac}	0.98 (7)	0.89 (19)

CV: Coefficient of variation

C_{max}: peak concentration

AUC_{τ}: area under the plasma concentration-time curve during the dosing interval (τ) i.e., 12 hours for twice daily regimen, 24 hours for once daily regimen.

CL/F: oral clearance

V_{dss}/F: apparent volume of distribution at steady state

R_{ac}: drug accumulation ratio

Specific Populations

Renal Impairment

Elagolix exposures (C_{max} and AUC) are not altered by renal impairment. The mean exposures are similar for women with moderate to severe or end stage renal disease (including women on dialysis) compared to women with normal renal function.

Hepatic Impairment

Elagolix exposures (C_{max} and AUC) are similar between women with normal hepatic function and women with mild hepatic impairment. Elagolix exposures in women with moderate and severe hepatic impairment are approximately 3-fold and 7-fold, respectively, higher than exposures from women with normal hepatic function *[see Use in Specific Populations (8.7)]*.

Race/Ethnicity

No clinically meaningful difference in the pharmacokinetics of ORILISSA between White and Black subjects or between Hispanics and others was observed. There is no clinically meaningful difference in the pharmacokinetics of ORILISSA between Japanese and Han Chinese subjects.

Body weight/Body mass index

Body weight or body mass index does not affect the pharmacokinetics of ORILISSA.

Drug Interaction Studies

Drug interaction studies were performed with ORILISSA and other drugs that are likely to be co-administered and with drugs commonly used as probes for pharmacokinetic interactions. Tables 10 and 11 summarize the pharmacokinetic effects when elagolix was co-administered with these drugs.

Table 10. Drug Interactions: Change in Pharmacokinetics of Elagolix in the Presence of Co-administered Drugs

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Elagolix	N	Ratio (90% CI)*	
				C_{max}	AUC
Ketoconazole	400 mg once daily	150 mg single dose	11	1.77 (1.48 – 2.12)	2.20 (1.98 – 2.44)
Rifampin	600 mg single dose	150 mg single dose	12	4.37 (3.62 – 5.28)	5.58 (4.88 – 6.37)
	600 mg once daily			2.00 (1.66 – 2.41)	1.65 (1.45 – 1.89)
CI: Confidence interval					

*ratios for C_{max} and AUC compare co-administration of the medication with elagolix vs. administration of elagolix alone.

No clinically significant changes in elagolix exposures were observed when co-administered with rosuvastatin (20 mg once daily), sertraline (25 mg once daily) or fluconazole (200 mg single dose).

Table 11. Drug Interactions: Change in Pharmacokinetics of Co-administered Drug in the Presence of Elagolix

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Elagolix	N	Ratio (90% CI)*	
				C_{max}	AUC
Digoxin	0.5 mg single dose	200 mg twice daily x 10 days	11	1.71 (1.53 - 1.91)	1.26 (1.17 - 1.35)
Rosuvastatin	20 mg once daily	300 mg twice daily x 7 days	10	0.99 (0.73 – 1.35)	0.60 (0.50 - 0.71)
Midazolam	2 mg single dose	300 mg twice daily x 11 days	20	0.56 (0.51 - 0.62)	0.46 (0.41 - 0.50)
		150 mg once daily x 13 days	11	0.81 (0.74 – 0.89)	0.65 (0.58 - 0.72)
Norethindrone	0.35 mg once daily x 112 days	150 mg once daily x 56 days	32	0.95 (0.86 – 1.05)	0.88 (0.79 – 0.99)
Ethinyl Estradiol	Ethinyl estradiol 35 mcg and triphasic norgestimate 0.18/0.215/0.25 mg once daily	150 mg once daily	21	1.15 (1.07 – 1.25)	1.30 (1.19 - 1.42)
Norelgestromin[a]				0.87 (0.78 – 0.97)	0.85 (0.78 – 0.92)
Norgestrel[a]				0.89 (0.78 – 1.00)	0.92 (0.84 – 1.01)

CI: Confidence interval

*ratios for C_{max} and AUC compare co-administration of the medication with elagolix vs. administration of the medication alone.

[a] metabolite of norgestimate

No clinically significant changes in sertraline or fluconazole exposures were observed when co-administered with elagolix.

12.5 Pharmacogenomics

Disposition of elagolix involves the OATP 1B1 transporter protein. Higher plasma concentrations of elagolix have been observed in groups of patients who have two reduced function alleles of the gene that encodes OATP 1B1 (SLCO1B1 521T>C). The frequency of this SLCO1B1 521 C/C genotype is generally less than 5% in most racial/ethnic groups. Subjects with this genotype are expected to have a 78% mean increase in elagolix concentrations compared to subjects with normal transporter function (i.e., SLCO1B1 521T/T genotype).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies conducted in mice (50, 150, or 500 mg/kg/day) and rats (150, 300, or 800 mg/kg/day) that administered elagolix by the dietary route revealed no increase in tumors in mice at up to 19-fold the MRHD based on AUC. In the rat, there was an increase in thyroid (male and female) and liver (males only) tumors at the high dose (12 to 13-fold the MRHD). The rat tumors were likely species-specific and of negligible relevance to humans.

Elagolix was not genotoxic or mutagenic in a battery of tests, including the *in vitro* bacterial reverse mutation assay, the *in vitro* mammalian cell forward mutation assay at the thymidine kinase (TK+/-) locus in L5178Y mouse lymphoma cells, and the *in vivo* mouse micronucleus assay.

In a fertility study conducted in the rat, there was no effect of elagolix on fertility at any dose (50, 150, or 300 mg/kg/day). Based on AUC, the exposure multiple for the MRHD in women compared to the highest dose of 300 mg/kg/day in female rats is approximately 5-fold. However, because elagolix has low affinity for the GnRH receptor in the rat *[see Use in Specific Populations (8.1)]*, and because effects on fertility are most likely to be mediated via the GnRH receptor, these data have low relevance to humans.

14 CLINICAL STUDIES

The efficacy of ORILISSA 150 mg once daily and 200 mg twice daily for the management of moderate to severe pain associated with endometriosis was demonstrated in two multinational double-blind, placebo-controlled trials in 1686 premenopausal women [Study EM-1 (NCT01620528) and Study EM-2 (NCT01931670)]. The median age of women in the trials was

32 years; 88% were White, 9% were Black or African American and 3% were other races. Each placebo-controlled trial assessed the reduction in endometriosis-associated pain over 6 months of treatment.

Moderate to severe pain associated with endometriosis was required for entry into the trials and was assessed during screening using the composite pelvic signs and symptoms score (CPSSS) and other baseline criteria.

The CPSSS is based on a modified Biberoglu and Behrman scale with five elements: three responses reported by study subjects (dysmenorrhea, dyspareunia, and non-menstrual pelvic pain) and two findings based on investigator assessment during physical examination (rating of pelvic tenderness and induration). Each element is scored from 0 (absent) to 3 (severe) for a maximum total score of 15. A total score of at least 6, with a score of at least 2 for dysmenorrhea and at least 2 for non-menstrual pelvic pain was required to qualify for randomization. Subjects were also required to have non-menstrual pelvic pain for at least four days in the preceding calendar month, defined as 35 days. Other criteria to determine elgibility for randomization included subject responses in a daily electronic diary (Endometriosis Daily Pain Impact Scale, described below) for both dysmenorrhea and non-menstrual pelvic pain in the 35 days prior to randomization.

Dysmenorrhea and Non-Menstrual Pelvic Pain

The co-primary efficacy endpoints were (1) the proportion of subjects whose dysmenorrhea responded to treatment at Month 3 and (2) the proportion of subjects whose pelvic pain not related to menses (also known as non-menstrual pelvic pain) responded to treatment at Month 3. Dysmenorrhea and non-menstrual pelvic pain were evaluated daily using the Endometriosis Daily Pain Impact Scale that asked subjects to rate their pain severity and its impact on daily activities during the prior 24 hours as none, mild, moderate or severe (correlating with a score of 0 to 3, respectively, where higher scores indicated greater severity). Scores at baseline and at each month were averaged over a 35-day interval.

Women were defined as responders if they experienced a reduction in dysmenorrhea and non-menstrual pelvic pain as defined in Table 12 with no increase in analgesic use (nonsteroidal anti-inflammatory drug or opioid) for endometriosis-associated pain. The threshold for defining responders was based on a receiver operating characteristic (ROC) analysis using the patient global impression of change as an anchor. A higher proportion of women treated with ORILISSA 150 mg once daily or 200 mg twice daily were responders for dysmenorrhea and

non-menstrual pelvic pain compared to placebo in a dose-dependent manner at Month 3 *[see Table 12]*.

Table 12. Proportion of Responders† for Dysmenorrhea and Non-Menstrual Pelvic Pain at Month 3 in Studies EM-1 and EM-2, Using the Endometriosis Daily Pain Impact Scale

	Study EM-1			Study EM-2		
	ORILISSA		Placebo	ORILISSA		Placebo
	150 mg Once Daily N=248	200 mg Twice Daily N=244	N=373	150 mg Once Daily N=221	200 mg Twice Daily N=225	N=353
Dysmenorrhea	46%	76%	20%	43%	72%	23%
Difference from placebo	27%**	56%**		21%**	50%**	
Non-Menstrual Pelvic Pain	50%	55%	36%	50%	58%	37%
Difference from placebo	14%**	18%**		13%*	21%**	

† Study EM-1-Dysmenorrhea responder threshold: at least 0.81 point decrease from baseline in dysmenorrhea score; Non-Menstrual Pelvic Pain responder threshold: at least 0.36 point decrease from baseline in Non-Menstrual Pelvic Pain score

Study EM-2 - Dysmenorrhea responder threshold: at least 0.85 point decrease from baseline in dysmenorrhea score; Non-Menstrual Pelvic Pain responder threshold: at least 0.43 point decrease from baseline in Non-Menstrual Pelvic Pain score

*p ≤0.01 for test of difference from placebo

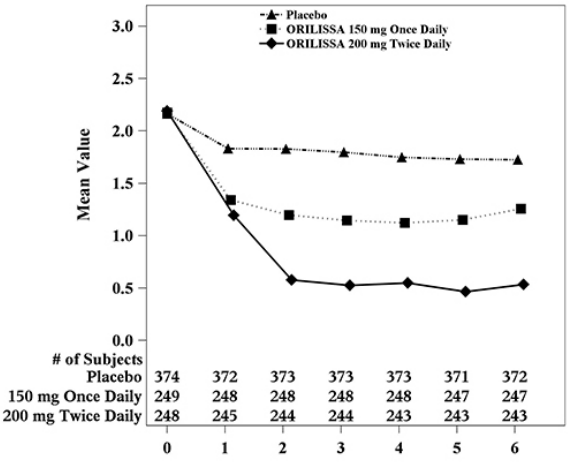
**p≤0.001 for test of difference from placebo

Women in these studies also provided a daily self-assessment of their endometriosis pain using a numeric rating scale (NRS) that asked subjects to rate their endometriosis pain at its worst over the last 24 hours on a scale from 0 (no pain) to 10 (worst pain ever). In Study EM-1, baseline NRS scores were 5.7 for ORILISSA 150 mg once daily, 5.5 for ORILISSA 200 mg twice daily and 5.6 for placebo. In Study EM-2, baseline NRS scores were 5.7 for ORILISSA 150 mg once daily, 5.3 for ORILISSA 200 mg twice daily and 5.6 for placebo. Women taking ORILISSA 150

mg once daily and 200 mg twice daily reported a statistically ($p < 0.001$) significant reduction from baseline in NRS scores compared to placebo at Month 3 in both Studies EM-1 and EM-2 (Study EM-1: 0.7 points for ORILISSA 150 mg once daily and 1.3 points for ORILISSA 200 mg twice daily; Study EM-2: 0.6 points for ORILISSA 150 mg once daily and 1.2 points for ORILISSA 200 mg twice daily).

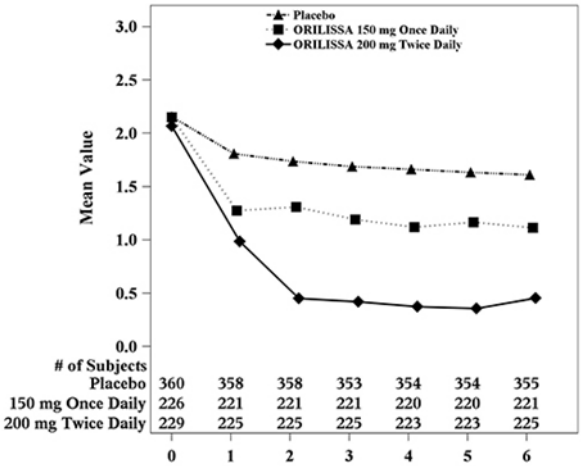
In addition, both ORILISSA treatment groups showed statistically significantly greater mean decreases from baseline compared to placebo in dysmenorrhea and non-menstrual pelvic pain scores at Month 6. Figures 3 through 6 show the mean scores for dysmenorrhea and non-menstrual pelvic pain over time for Study EM-1 and EM-2.

Figure 3. Mean Dysmenorrhea Pain Scores[a] in Study EM-1 Over 6 Months



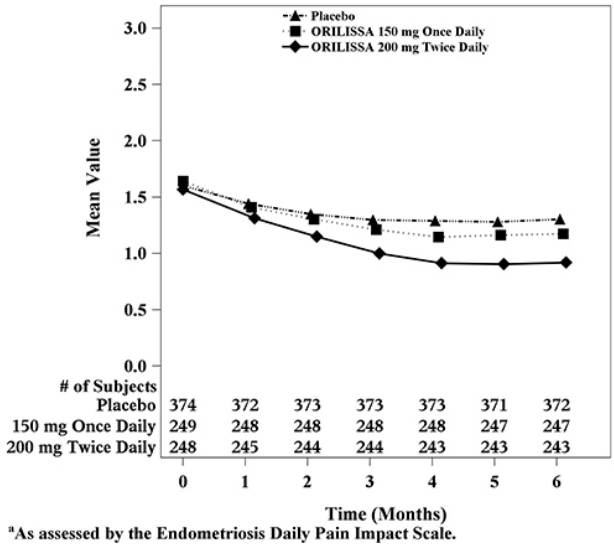
[a]As assessed by the Endometriosis Daily Pain Impact Scale.

Figure 4. Mean Dysmenorrhea Pain Scores[a] in Study EM-2 Over 6 Months



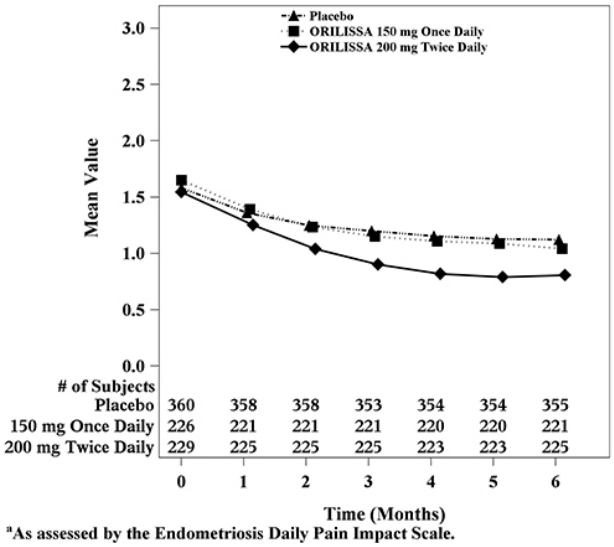
[a]As assessed by the Endometriosis Daily Pain Impact Scale.

Figure 5. Mean Non-Menstrual Pelvic Pain[a] Scores in Study EM-1 Over 6 Months



[a]As assessed by the Endometriosis Daily Pain Impact Scale.

Figure 6. Mean Non-Menstrual Pelvic Pain[a] Scores in Study EM-2 Over 6 Months

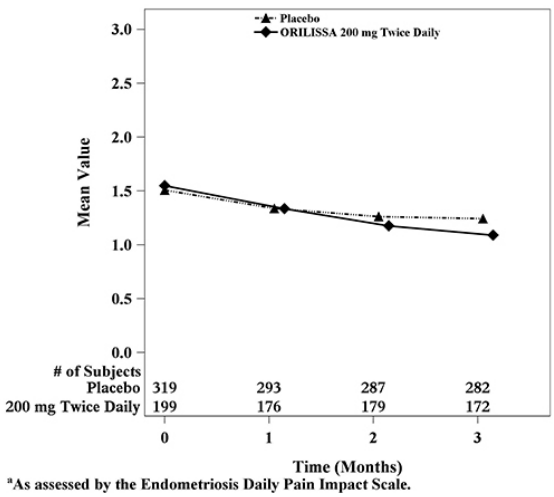


[a]As assessed by the Endometriosis Daily Pain Impact Scale.

Dyspareunia

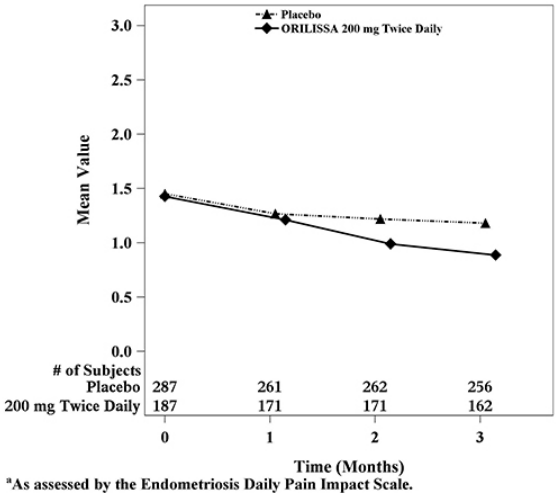
Dyspareunia associated with endometriosis was evaluated as a secondary endpoint using the Endometriosis Daily Pain Impact Scale that asked subjects to rate their pain during sexual intercourse in the prior 24 hours as none, mild, moderate, severe (correlating with a score of 0 to 3, respectively, where higher scores indicated greater severity), or not applicable. In both Studies EM-1 and EM-2, women treated with ORILISSA 200 mg twice daily showed statistically significantly greater reduction in dyspareunia from baseline to Month 3 than women given placebo (Study EM-1: 0.2; Study EM-2: 0.3). Figures 7 and 8 show the mean scores over time for Study EM-1 and EM-2.

Figure 7. Mean Dyspareunia Scores[a] in Study EM-1 Over 3 Months



[a]As assessed by the Endometriosis Daily Pain Impact Scale.

Figure 8. Mean Dyspareunia Scores[a] in Study EM-2 Over 3 Months



[a]As assessed by the Endometriosis Daily Pain Impact Scale.

Use of rescue pain medication

In EM-1 and EM-2, 59% and 60% of patients used an opioid rescue analgesic for pain at baseline. The opioid rescue analgesics used at baseline were predominantly hydrocodone/acetaminophen (HC/APAP) and codeine/APAP at strengths of 5/300-325 mg and 30/300-500 mg. In EM-1, of all patients on an opioid at baseline, 98% and 2% were on HC/APAP and codeine/APAP, respectively. In EM-2, of all patients on an opioid at baseline, 50% were on HC/APAP and 16% were on codeine/APAP.

Other data related to opioid rescue analgesic use are summarized in Table 13.

Table 13. Opioid Rescue Analgesic Use in EM-1 and EM-2

	Study EM-1			Study EM-2		
	ORILISSA 150 mg Once Daily	ORILISSA 200 mg Twice Daily	Placebo	ORILISSA 150 mg Once Daily	ORILISSA 200 mg Twice Daily	Placebo
Tablets per month at baseline (mean±SD)	15 ±24	15 ±25	13 ±21	13 ±29	12 ±26	12 ±21
Tablets per month at baseline [Median (Min, Max)]	4 (0, 184)	4 (0, 195)	4 (0, 146)	4 (0, 236)	3 (0, 214)	4 (0, 152)
Tablets per month at Month 3 (mean±SD)	12 ±29	7 ±18	10 ±17	8 ±22	5 ±14	8 ±15
Tablets per month at Month 3 [Median (Min, Max)]	0 (0, 251)	0 (0, 162)	2 (0, 144)	0 (0, 168)	0 (0, 136)	2 (0, 142)

Tablets per month at Month 6 (mean±SD)	11 ±26	7 ±17	11 ±19	7 ±19	5 ±14	8 ±15
Tablets per month at Month 6 [Median (Min, Max)]	0 (0, 224)	0 (0, 157)	3 (0, 185)	0 (0, 185)	0 (0, 157)	2 (0, 142)
Number and % of patients on any dose of opioid rescue at baseline who were off opioid at Month 3*	46/150 (31%)	59/151 (39%)	36/211 (17%)	44/124 (36%)	68/134 (51%)	54/220 (25%)
Number and % of patients on any dose of opioid rescue at baseline who were off opioid at Month 6*	43/149 (29%)	66/150 (44%)	36/211 (17%)	50/124 (40%)	78/134 (58%)	70/222 (32%)
Number and % of patients not on opioid rescue at baseline who were on any opioid at Month 3^	9/98 (9%)	6/93 (7%)	17/162 (11%)	10/97 (10%)	10/91 (11%)	29/133 (22%)
Number and % of patients not on opioid rescue at baseline who were on any opioid at Month 6^	16/98 (16%)	6/93 (7%)	32/161 (20%)	13/97 (13%)	6/91 (7%)	32/133 (24%)
Min = minimum; Max = maximum; SD = standard deviation Monthly calculations are based on a 35-day interval. *Denominator is the number of subjects on opioid rescue at baseline. ^Denominator is the number of subjects not on opioid rescue at baseline.						

The clinical relevance of these data has not been demonstrated.

16 HOW SUPPLIED/STORAGE AND HANDLING

ORILISSA tablets are available in two strengths: 150 mg and 200 mg, which are equivalent to 155.2 mg and 207.0 mg of elagolix sodium, respectively.

ORILISSA 150 mg tablets are light pink, oblong, film-coated tablets with “EL 150” debossed on one side. ORILISSA 150 mg tablets are packaged in weekly blister packs. Each blister pack contains 7 tablets supplying the drug product for one week. Four blister packs (a total of 28 tablets) are packaged into a carton that provides the drug product for 4 weeks (NDC 0074-0038-28).

ORILISSA 200 mg tablets are light orange, oblong, film-coated tablets with “EL 200” debossed on one side. The 200 mg tablets are packaged in weekly blister packs. Each blister pack contains 14 tablets supplying the drug product for one week. Four blister packs (a total of 56 tablets) are packaged in a carton that provides the drug product for 4 weeks (NDC 0074-0039-56).

Store at 2°C to 30°C (36°F to 86°F).

Dispose unused medication via a take-back option if available. Otherwise, follow FDA instructions for disposing medication in the household trash, www.fda.gov/drugdisposal. Do NOT flush down the toilet.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

- Advise patients on contraceptive options, not to get pregnant while using ORILISSA, to be mindful that menstrual changes could reflect pregnancy and to discontinue ORILISSA if pregnancy occurs *[see Contraindications (4),* and *Warnings and Precautions (5.2)]*.
- Inform patients that estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA.
- Inform patients about the risk of bone loss. Advise adequate intake of calcium and vitamin D *[see Warnings and Precautions (5.1)]*.
- Advise patients to seek immediate medical attention for suicidal ideation and behavior. Instruct patients with new onset or worsening depression, anxiety, or other mood changes to promptly seek medical attention *[see Warnings and Precautions (5.3)]*.
- Counsel patients on signs and symptoms of liver injury *[see Warnings and Precautions (5.4)]*.
- Instruct patients who miss a dose of ORILISSA to take the missed dose on the same day as soon as she remembers and then resume the regular dosing schedule:
    - 150 mg once daily: no more than 1 tablet each day should be taken.
    - 200 mg twice daily: no more than 2 tablets each day should be taken.
- Instruct patients to dispose of unused medication via a take-back option if available or to otherwise follow FDA instructions for disposing of medication in the household trash, www.fda.gov/drugdisposal, and not to flush down the toilet.

Manufactured by
AbbVie Inc.
North Chicago, IL 60064

03-B517 July 2018

SPRIX- ketorolac tromethamine spray, metered
Egalet US Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SPRIX® safely and effectively. See full prescribing information for SPRIX®.

SPRIX® (ketorolac tromethamine) Nasal Spray
Initial U.S. Approval: 1989

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDS) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)**
- **SPRIX® is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**
- **NSAIDS cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**

RECENT MAJOR CHANGES

Indications and Usage (1)	01/2018

INDICATIONS AND USAGE

SPRIX is a nonsteroidal anti-inflammatory drug indicated in adult patients for the short term (up to 5 days) management of moderate to moderately severe pain that requires analgesia at the opioid level. (1)

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. (2.1)
- SPRIX is not an inhaled product. For adult patients < 65 years of age: 31.5 mg (one 15.75 mg spray in each nostril) every 6 to 8 hours. The maximum daily dose is 126 mg. (2.2, 2.3)
- For patients ≥ 65 years of age, renally impaired patients, and patients less than 50 kg (110 lbs): 15.75 mg (one 15.75 mg spray in only one nostril) every 6 to 8 hours. The maximum daily dose is 63 mg. (2.4)
- SPRIX nasal spray should be discarded within 24 hours of taking the first dose, even if the bottle still contains some medication. (2.5)

DOSAGE FORMS AND STRENGTHS

SPRIX (ketorolac tromethamine) Nasal Spray: 15.75 mg of ketorolac tromethamine in each 100 µL spray. Each 1.7 g bottle contains 8 sprays. (3)

CONTRAINDICATIONS

- Known hypersensitivity to ketorolac or any components of the drug product (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)
- Use in patients with active peptic ulcer disease or with recent GI bleeding or perforation (4)
- Use as a prophylactic analgesic before any major surgery (4)
- Use in patients with advanced renal disease or patients at risk for renal failure due to volume depletion (4)
- Use in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding (4)
- Use in labor and delivery (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (5.3)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure. (5.4, 7)
- Heart Failure and Edema: Avoid use of SPRIX in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure. (5.5)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or

hypovolemia. Avoid use of SPRIX in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function. (5.6)

- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs. (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: SPRIX is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity). (5.8)
- Serious Skin Reactions: Discontinue SPRIX at first appearance of skin rash or other signs of hypersensitivity. (5.9)
- Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation. (5.10, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. Do not use SPRIX in patients for whom hemostasis is critical. (5.11, 7)
- Limitations of Use: SPRIX should not be used concomitantly with IM/IV or oral ketorolac, aspirin, or other NSAIDs. (5.15)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2%) in patients treated with SPRIX and occurring at a rate at least twice that of placebo are nasal discomfort, rhinalgia, increased lacrimation, throat irritation, oliguria, rash, bradycardia, decreased urine output, increased ALT and/or AST, hypertension, and rhinitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Egalet US Inc. at 1-800-518-1084 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking SPRIX with drugs that interfere with hemostasis. Concomitant use of SPRIX and analgesic doses of aspirin is not generally recommended. (7)
- ACE inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with SPRIX may diminish the antihypertensive effect of these drugs. Monitor blood pressure. (7)
- ACE Inhibitors and ARBs: Concomitant use with SPRIX in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function. (7)
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects. (7)
- Digoxin: Concomitant use with SPRIX can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels. (7)

USE IN SPECIFIC POPULATIONS

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation. (5.10, 8.1)
Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of SPRIX in women who have difficulties conceiving. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDS) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [*see Warnings and Precautions (5.1)*].**
- **SPRIX® is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [*see Contraindications (4) and Warnings and Precautions (5.1)*].**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDS cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [*see Warnings and Precautions (5.2)*].**

1 INDICATIONS AND USAGE

SPRIX is indicated in adult patients for the short term (up to 5 days) management of moderate to moderately severe pain that requires analgesia at the opioid level.

Limitations of Use

- Sprix is not for use in pediatric patients less than 2 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

The total duration of use of SPRIX alone or sequentially with other formulations of ketorolac (IM/IV or oral) must not exceed 5 days because of the potential for increasing the frequency and severity of adverse reactions associated with the recommended doses [*see Warnings and Precautions (5.15)*].

Do not use SPRIX concomitantly with other formulations of ketorolac or other NSAIDs [*see Warnings and Precautions (5.15)*].

2.2 Administration

SPRIX is not an inhaled product. Do not inhale when administering this product.

Instruct patients to administer as follows:

1. First hold the finger flange with fingers, and remove the clear plastic cover with opposite hand; then remove the blue plastic safety clip. Keep the clear plastic cover; and throw away the blue plastic safety clip.

2. Before using the bottle for the **FIRST** time, activate the pump. To activate the pump, hold the bottle at arm's length away from the body with index finger and middle finger resting on the top of the finger flange and thumb supporting the base.

Press down evenly and release the pump 5 times. Patient may not see a spray the first few times he/she presses down.

The bottle is now ready to use. There is no need to activate the pump again if more doses are used from the bottle.

3. It's important to get the medication to the correct place in the nose so it will be most effective.

- Blow nose gently to clear nostrils.
- Sit up straight or stand. Tilt head slightly forward.
- Insert the tip of the container into your right nostril.
- Point the container away from the center of your nose.
- Hold your breath and spray once into your right nostril, pressing down evenly on both sides.
- Immediately after administration, resume breathing through mouth to reduce expelling the product. Also pinch the nose to help retain the spray if it starts to drip.

If only one spray per dose is prescribed, administration is complete; skip to Step 5 below.

4. If a dose of 2 sprays is prescribed, repeat the process in Step 3 for the left nostril. Again, be sure to point the spray away from the center of nose. Spray once into the left nostril.

5. Replace the clear plastic cover and place the bottle in a cool, dry location out of direct sunlight, such as inside a medication cabinet. Keep out of reach of children.

2.3 Adult Patients < 65 Years of Age

The recommended dose is 31.5 mg SPRIX (one 15.75 mg spray in each nostril) every 6 to 8 hours. The maximum daily dose is 126 mg (four doses).

2.4 Reduced Doses for Special Populations

For patients ≥ 65 years of age, renally impaired patients, and adult patients less than 50 kg (110 lbs), the recommended dose is 15.75 mg SPRIX (**one** 15.75 mg spray in **only one** nostril) every 6 to 8 hours. The maximum daily dose is 63 mg (four doses) [*see Warnings and Precautions (5.2, 5.6)*].

2.5 Discard Used SPRIX Bottle after 24 Hours

Do not use any single SPRIX bottle for more than one day as it will not deliver the intended dose after 24 hours. Therefore, the bottle must be discarded no more than 24 hours after taking the first dose, even if the bottle still contains some liquid.

3 DOSAGE FORMS AND STRENGTHS

SPRIX (ketorolac tromethamine) Nasal spray: 15.75 mg of ketorolac tromethamine in each 100 µL spray. Each 1.7 g bottle contains 8 sprays.

4 CONTRAINDICATIONS

SPRIX is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to ketorolac or any components of the drug product [*see Warning and Precautions (5.7, 5.9)*]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7, 5.8)*]
- In the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*]
- Use in patients with active peptic ulcer disease and in patients with recent gastrointestinal bleeding or perforation [*see Warnings and Precautions (5.2)*]
- Use as a prophylactic analgesic before any major surgery [*see Warnings and Precautions (5.11)*]
- Use in patients with advanced renal disease or patients at risk for renal failure due to volume depletion [*see Warnings and Precautions (5.6)*]
- Use in labor and delivery. Through its prostaglandin synthesis inhibitory effect, ketorolac may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage [*see Use in Specific Populations (8.1)*]
- Use in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, or those for whom hemostasis is critical [*see Warnings and Precautions (5.11), Drug Interactions (7)*]
- Concomitant use with probenecid [*see Drug Interactions (7)*]
- Concomitant use with pentoxifylline [*see Drug Interactions (7)*]

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the

development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as ketorolac, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of SPRIX in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If SPRIX is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

SPRIX is contraindicated in patients with active peptic ulcers and/or GI bleeding and in patients with recent gastrointestinal bleeding or perforation [*see Contraindications (4)*].

NSAIDs, including ketorolac, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, consider alternate therapies other than NSAIDs. Do not use Sprix in those with active GI bleeding.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue SPRIX until a serious GI adverse event is ruled out.

- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].
- Use great care when giving SPRIX to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including ketorolac.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue SPRIX immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including SPRIX, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [*see Drug Interactions (7)*].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of ketorolac may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].

Avoid the use of SPRIX in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If SPRIX is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia

Ketorolac and its metabolites are eliminated primarily by the kidneys. Patients with reduced creatinine clearance will have diminished clearance of the drug [*see Clinical Pharmacology (12.3)*]. SPRIX is contraindicated in patients with advanced renal impairment [*see Contraindications (4)*].

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by

recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of SPRIX in patients with advanced renal disease. The renal effects of SPRIX may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating SPRIX. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of SPRIX [*see Drug Interactions (7)*]. Avoid the use of SPRIX in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If SPRIX is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.7 Anaphylactic Reactions

Ketorolac has been associated with anaphylactic reactions in patients with and without known hypersensitivity to ketorolac and in patients with aspirin-sensitive asthma [*see Contraindications (4) and Warnings and Precautions (5.8)*].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, SPRIX is contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When SPRIX is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions

NSAIDs, including ketorolac, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of SPRIX at the first appearance of skin rash or any other sign of hypersensitivity. SPRIX is contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].

5.10 Premature Closure of Fetal Ductus Arteriosus

Ketorolac may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including SPRIX, in pregnant women starting at 30 weeks of gestation (third trimester) [*see Use in Specific Populations (8.1)*].

5.11 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect upon erythropoiesis. If a patient treated with SPRIX has any signs or symptoms of anemia, monitor hemoglobin or hematocrit. Do not use SPRIX in patients for whom hemostasis is critical [*see Contraindications (4), Drug Interactions (7)*].

NSAIDs, including SPRIX, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].

The concurrent use of ketorolac and therapy that affects hemostasis, including prophylactic low dose

heparin (2500 to 5000 units q12h), warfarin and dextrans, has not been studied extensively, but may also be associated with an increased risk of bleeding. Until data from such studies are available, carefully weigh the benefits against the risks and use such concomitant therapy in these patients only with extreme caution. Monitor patients receiving therapy that affects hemostasis closely.

In clinical trials, serious adverse events related to bleeding were more common in patients treated with SPRIX than placebo. In clinical trials and in postmarketing experience with ketorolac IV and IM dosing, postoperative hematomas and other signs of wound bleeding have been reported in association with peri-operative use. Therefore, use SPRIX with caution in the postoperative setting when hemostasis is critical.

5.12 Masking of Inflammation and Fever

The pharmacological activity of SPRIX in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.13 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [*see Warnings and Precautions (5.2, 5.3, 5.6)*].

5.14 Eye Exposure

Avoid contact of SPRIX with the eyes. If eye contact occurs, wash out the eye with water or saline, and consult a physician if irritation persists for more than an hour.

5.15 Limitations of Use

The total duration of use of SPRIX alone or sequentially with other forms of ketorolac is not to exceed 5 days. SPRIX must not be used concomitantly with other forms of ketorolac or other NSAIDs [*see Dosage and Administration (2.1)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events [*see Warnings and Precautions (5.1)*]
- GI Bleeding, Ulceration and Perforation [*see Warnings and Precautions (5.2)*]
- Hepatotoxicity [*see Warnings and Precautions (5.3)*]
- Hypertension [*see Warnings and Precautions (5.4)*]
- Heart Failure and Edema [*see Warnings and Precautions (5.5)*]
- Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*]
- Anaphylactic Reactions [*see Warnings and Precautions (5.7)*]
- Serious Skin Reactions [*see Warnings and Precautions (5.9)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.11)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to SPRIX in patients enrolled in placebo-controlled efficacy studies of acute pain following major surgery. The studies enrolled 828 patients (183 men, 645 women) ranging from 18 years to over 75 years of age.

The patients in the postoperative pain studies had undergone major abdominal, orthopedic, gynecologic, or other surgery; 455 patients received SPRIX (31.5 mg) three or four times a day for up to 5 days, and 245 patients received placebo. Most patients were receiving concomitant opioids, primarily PCA morphine.

The most frequently reported adverse reactions were related to local symptoms, i.e., nasal discomfort or irritation. These reactions were generally mild and transient in nature.

The most common drug-related adverse events leading to premature discontinuation were nasal discomfort or nasal pain (rhinalgia).

Table 1: Post-Operative Patients with Adverse Reactions Observed at a Rate of 2% or More and at Least Twice the Incidence of the Placebo Group.

	SPRIX (N = 455)	Placebo (N = 245)
Nasal discomfort	15%	2%
Rhinalgia	13%	<1%
Lacrimation increased	5%	0%
Throat irritation	4%	<1%
Oliguria	3%	1%
Rash	3%	<1%
Bradycardia	2%	<1%
Urine output decreased	2%	<1%
ALT and/or AST increased	2%	1%
Hypertension	2%	1%
Rhinitis	2%	<1%

In controlled clinical trials in major surgery, primarily knee and hip replacements and abdominal hysterectomies, seven patients (N=455, 1.5%) treated with SPRIX experienced serious adverse events of bleeding (4 patients) or hematoma (3 patients) at the operative site versus one patient (N=245, 0.4%) treated with placebo (hematoma). Six of the seven patients treated with SPRIX underwent a surgical procedure and/or blood transfusion and the placebo patient subsequently required a blood transfusion.

Adverse Reactions Reported in Clinical Trials with Other Dosage Forms of Ketorolac or Other NSAIDs

Adverse reaction rates increase with higher doses of ketorolac. It is necessary to remain alert for the severe complications of treatment with ketorolac, such as GI ulceration, bleeding, and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions, and liver failure. These complications can be serious in certain patients for whom ketorolac is indicated, especially when the drug is used inappropriately.

In patients taking ketorolac or other NSAIDs in clinical trials, the most frequently reported adverse experiences in approximately 1% to 10% of patients are:

Gastrointestinal (GI) experiences including:		
abdominal pain	constipation/diarrhea	dyspepsia
flatulence	GI fullness	GI ulcers (gastric/duodenal)
gross bleeding/perforation	heartburn	nausea*
stomatitis	vomiting	
Other experiences:		
abnormal renal function	anemia	dizziness
drowsiness	edema	elevated liver enzymes
headache*	hypertension	increased bleeding time
injection site pain	pruritus	purpura
rash	tinnitus	sweating

**Incidence greater than 10%*

Additional adverse experiences reported occasionally (<1% in patients taking ketorolac or other

NSAIDs in clinical trials) include:

Body as a Whole: fever, infection, sepsis

Cardiovascular System: congestive heart failure, palpitation, pallor, tachycardia, syncope

Digestive System: anorexia, dry mouth, eructation, esophagitis, excessive thirst, gastritis, glossitis, hematemesis, hepatitis, increased appetite, jaundice, melena, rectal bleeding

Hemic and Lymphatic: ecchymosis, eosinophilia, epistaxis, leukopenia, thrombocytopenia

Metabolic and Nutritional: weight change

Nervous System: abnormal dreams, abnormal thinking, anxiety, asthenia, confusion, depression, euphoria, extrapyramidal symptoms, hallucinations, hyperkinesis, inability to concentrate, insomnia, nervousness, paresthesia, somnolence, stupor, tremors, vertigo, malaise

Respiratory: asthma, dyspnea, pulmonary edema, rhinitis

Special Senses: abnormal taste, abnormal vision, blurred vision, hearing loss

Urogenital: cystitis, dysuria, hematuria, increased urinary frequency, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure, urinary retention

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ketorolac or other NSAIDs. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Other observed reactions (reported from postmarketing experience in patients taking ketorolac or other NSAIDs) are:

Body as a Whole: angioedema, death, hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, tongue edema, myalgia

Cardiovascular: arrhythmia, bradycardia, chest pain, flushing, hypotension, myocardial infarction, vasculitis

Dermatologic: exfoliative dermatitis, erythema multiforme, Lyell's syndrome, bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis

Gastrointestinal: acute pancreatitis, liver failure, ulcerative stomatitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn’s disease)

Hemic and Lymphatic: agranulocytosis, aplastic anemia, hemolytic anemia, lymphadenopathy, pancytopenia, postoperative wound hemorrhage (rarely requiring blood transfusion)

Metabolic and Nutritional: hyperglycemia, hyperkalemia, hyponatremia

Nervous System: aseptic meningitis, convulsions, coma, psychosis

Respiratory: bronchospasm, respiratory depression, pneumonia

Special Senses: conjunctivitis

Urogenital: flank pain with or without hematuria and/or azotemia, hemolytic uremic syndrome

7 DRUG INTERACTIONS

See Table 2 for clinically significant drug interactions with ketorolac.

Table 2: Clinically Significant Drug Interactions with Ketorolac

Drugs that Interfere with Hemostasis	
Clinical Impact:	• Ketorolac and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of ketorolac and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone [*see Clinical Pharmacology (12.3)*].

	• Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone. • When ketorolac is administered concurrently with pentoxifylline, there is an increased risk of bleeding.
Intervention:	Monitor patients with concomitant use of SPRIX with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.11)*]. Concomitant use of SPRIX and pentoxifylline is contraindicated [*see Contraindications (4) and Warnings and Precautions (5.11)*].
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.2)*].
Intervention:	Concomitant use of SPRIX and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.11)*]. SPRIX is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of SPRIX and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of SPRIX and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis
Intervention:	During concomitant use of SPRIX with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [*see Warnings and Precautions (5.6)*].
Digoxin	
Clinical Impact:	The concomitant use of ketorolac with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of SPRIX and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal

	clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of SPRIX and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of SPRIX and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of SPRIX and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of SPRIX and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of ketorolac with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)*].
Intervention:	The concomitant use of ketorolac with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of SPRIX and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of SPRIX and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Probenecid	
Clinical Impact:	Concomitant administration of oral ketorolac and probenecid results in increased half-life and systemic exposure. [*see Clinical Pharmacology (12.3)*].
Intervention:	Concomitant use of SPRIX and probenecid is contraindicated.
Antiepileptic Drugs	
Clinical Impact:	Sporadic cases of seizures have been reported during concomitant use of ketorolac and antiepileptic drugs (phenytoin, carbamazepine).
Intervention:	During concomitant use of SPRIX and antiepileptic drugs, monitor patients for seizures.
Psychoactive Drugs	
Clinical Impact:	Hallucinations have been reported when ketorolac was used in patients taking psychoactive drugs (fluoxetine, thiothixene, alprazolam).
Intervention:	During concomitant use of SPRIX and psychoactive drugs, monitor patients for hallucinations.
Nondepolarizing Muscle Relaxants	
Clinical Impact:	In postmarketing experience there have been reports of a possible interaction between ketorolac and nondepolarizing muscle relaxants that resulted in apnea. The concurrent use of ketorolac with muscle relaxants has not been formally studied.
Intervention:	During concomitant use of SPRIX and nondepolarizing muscle relaxants, monitor patients for apnea.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation.

Risk Summary

Use of NSAIDs, including SPRIX, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including SPRIX, in pregnant women starting at 30 weeks of gestation (third trimester).

There are no adequate and well-controlled studies of SPRIX in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. In animal reproduction studies in rabbits and rats tested at 0.6 and 1.5 times the human systemic exposure, respectively, at the recommended maximum IN dose of 31.5 mg four times a day, there was no evidence of teratogenicity or other adverse developmental outcomes (see Data). Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as ketorolac, resulted in increased pre- and post-implantation loss.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of SPRIX during labor or delivery. In animal studies, NSAIDs, including ketorolac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

There are no adequate and well-controlled studies of SPRIX in pregnant women.

Animal Data

Reproduction studies have been performed during organogenesis using daily oral doses of ketorolac tromethamine at 3.6 mg/kg (0.6 times the human systemic exposure at the recommended maximum IN dose of 31.5 mg qid, based on area-under-the-plasma-concentration curve [AUC]) in rabbits and at 10 mg/kg (1.5 times the human AUC) in rats. These studies did not reveal evidence of teratogenicity or other adverse developmental outcomes. However, because animal dosing was limited by maternal toxicity, these studies do not adequately assess ketorolac's potential to cause adverse developmental outcomes in humans.

8.2 Lactation

Risk Summary

Ketorolac is excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SPRIX and any potential adverse effects on the breastfed infant from the SPRIX or from the underlying maternal condition.

Clinical Considerations

Exercise caution when administering SPRIX to a nursing woman. Available information has not shown any specific adverse events in nursing infants; however, instruct patients to contact their infant's health care provider if they note any adverse events.

Data

Limited data from one published study involving ten nursing mothers 2-6 days postpartum showed low levels of ketorolac in breast milk. Levels were undetectable (less than 5 ng/mL) in 4 of the patients. After a single administration of 10 mg ketorolac, the maximum milk concentration observed was 7.3

ng/mL, and the maximum milk to plasma ratio was 0.037. After 1 day of dosing (10 mg every 6 hours), the maximum milk concentration was 7.9 ng/mL, and the maximum milk-to-plasma ratio was 0.025. Assuming a daily intake of 400-1000 mL of human milk per day and a maternal body weight of 60 kg, the calculated maximum daily infant exposure was 0.00263 mg/kg/day, which is 0.4% of the maternal weight adjusted dose.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including SPRIX, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including SPRIX, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Sprix is not for use in pediatric patients less than 2 years of age. The safety and effectiveness of ketorolac in pediatric patients 17 years of age and younger have not been established.

8.5 Geriatric Use

Exercise caution when treating the elderly (65 years and older) with SPRIX. Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Dosage and Administration (2.4), Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.13), Clinical Pharmacology (12.3)*]. After observing the response to initial therapy with SPRIX, adjust the dose and frequency to suit an individual patient's needs.

Ketorolac and its metabolites are known to be substantially excreted by the kidneys, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, use caution in this patient population, and it may be useful to monitor renal function [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)*].

There has been no experience with overdosage of SPRIX. In controlled overdosage studies with IM ketorolac injection, daily doses of 360 mg given for five days (approximately 3 times the maximum daily dose of SPRIX) caused abdominal pain and peptic ulcers, which healed after discontinuation of dosing. Single overdoses of ketorolac tromethamine have been variously associated with abdominal pain, nausea, vomiting, hyperventilation, peptic ulcers and/or erosive gastritis, and renal dysfunction.

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

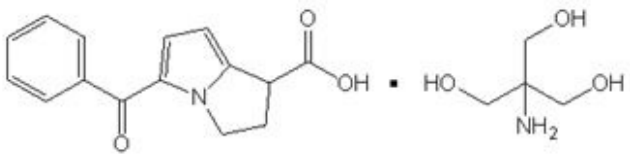
For additional information about overdosage treatment contact a poison control center (1-800-222-

1222).

11 DESCRIPTION

SPRIX (ketorolac tromethamine) Nasal Spray is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs, available as a clear, colorless to yellow solution packaged in a glass vial with a snap on spray pump that delivers 15.75 mg ketorolac tromethamine per spray and is intended for intranasal administration. The chemical name is (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). The molecular weight is 376.41.

Its molecular formula is $C_{19}H_{24}N_2O_6$($C_{15}H_{13}NO_3$•$C_4H_{11}NO_3$), and it has the following chemical structure.



Ketorolac tromethamine is highly water-soluble, allowing its formulation in an aqueous nasal spray product at pH 7.2.

The inactive ingredients in SPRIX include: edetate disodium (EDTA), monobasic potassium phosphate, sodium hydroxide, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ketorolac has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of SPRIX, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2), an early component of the arachidonic acid cascade, resulting in the reduced synthesis of prostaglandins, thromboxanes, and prostacyclin.

Ketorolac is a potent inhibitor of prostaglandin synthesis *in vitro*. Ketorolac concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because ketorolac is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.3 Pharmacokinetics

The half-lives of ketorolac by the IN and IM routes were similar. The bioavailability of ketorolac by the IN route of administration of a 31.5 mg dose was approximately 60% compared to IM administration. (See Table 3).

Table 3: Pharmacokinetic Parameters of Ketorolac Tromethamine after Intramuscular (IM) and Intranasal (IN) Administration

Ketorolac Tromethamine	C_{max} (SD) ng/mL	t_{max} (range) hours	$AUC_{0-\infty}$ (SD) ng•h/mL	$T_{½}$ (SD) hours
30 mg IM (1.0 mL of a 30 mg/mL solution)	2382.2 (432.7)	0.75 (0.25-1.03)	11152.8 (4260.1)	4.80 (1.18)
31.5 mg IN (SPRIX) (2 x 100 µL of a 15% w/w solution)	1805.8 (882.8)	0.75 (0.50-2.00)	7477.3 (3654.4)	5.24 (1.33)
15 mg IM (0.5 mL of a 30 mg/mL solution)	1163.4 (279.9)	0.75 (0.25-1.50)	5196.3 (2076.7)	5.00 (1.72)

C_{max} = maximum plasma concentration; t_{max} = time of C_{max}; $AUC_{0-\infty}$ = complete area under the concentration-time curve; $T_{½}$ = half-life; SD = standard deviation. All values are means, except t_{max}, for which medians are reported.

Absorption

In a study in which SPRIX (31.5 mg) was administered to healthy volunteers four times daily for 5 days, the C_{max}, t_{max}, and AUC values following the final dose were comparable to those obtained in the single-dose study. Accumulation of ketorolac has not been studied in special populations, geriatric, pediatric, renal failure or hepatic disease patients.

Distribution

Scintigraphic assessment of drug disposition of ketorolac following SPRIX intranasal dosing demonstrated that most of the ketorolac was deposited in the nasal cavity and pharynx, with less than 20% deposited in the esophagus and stomach, and zero or negligible deposition in the lungs (<0.5%).

The mean apparent volume (Vβ) of ketorolac tromethamine following complete distribution was approximately 13 liters. This parameter was determined from single-dose data. The ketorolac tromethamine racemate has been shown to be highly protein bound (99.2%). Nevertheless, plasma concentrations as high as 10 mcg/mL will only occupy approximately 5% of the albumin binding sites. Thus, the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin, and tolbutamide did not alter ketorolac protein binding. *In vitro* studies indicate that, at therapeutic concentrations of salicylate (300 mcg/mL), the binding of ketorolac was reduced from approximately 99.2% to 97.5%, representing a potential twofold increase in unbound ketorolac plasma levels.

The *in vitro* binding of warfarin to plasma proteins is only slightly reduced by ketorolac (99.5% control vs. 99.3%) when ketorolac plasma concentrations reach 5 to 10 mcg/mL.

Ketorolac tromethamine is excreted in human milk.

Elimination

Metabolism

Ketorolac tromethamine is largely metabolized in the liver. The metabolic products are hydroxylated and conjugated forms of the parent drug. The products of metabolism, and some unchanged drug, are excreted in the urine. There is no evidence in animal or human studies that ketorolac induces or inhibits hepatic enzymes capable of metabolizing itself or other drugs.

Excretion

The principal route of elimination of ketorolac and its metabolites is renal. About 92% of a given dose is found in the urine, approximately 40% as metabolites and 60% as unchanged ketorolac. Approximately 6% of a dose is excreted in the feces. A single-dose study with 10 mg ketorolac tromethamine (n = 9) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer and that the clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S- form in humans.

The half-life of the ketorolac tromethamine S-enantiomer was approximately 2.5 hours (SD ± 0.4) compared with 5 hours (SD ± 1.7) for the R-enantiomer. In other studies, the half-life for the racemate has been reported to lie within the range of 5 to 6 hours.

Specific Populations

Geriatric: A single-dose study was conducted to compare the pharmacokinetics of SPRIX (31.5 mg) in subjects ≥ age 65 to the pharmacokinetics in subjects < age 65. Exposure to ketorolac was increased by 23% for the ≥ 65 population as compared to subjects < 65. Peak concentrations of 2028 and 1840 ng/mL were observed for the elderly and nonelderly adult populations, respectively, at 0.75 h after dosing. In the elderly population a longer terminal half-life was observed as compared to the nonelderly adults (4.5 h vs. 3.3 h, respectively).

Race: Pharmacokinetic differences due to race have not been identified.

Hepatic Impairment: There was no significant difference in estimates of half-life, AUC_{∞} and C_{max} in 7 patients with liver disease compared to healthy volunteers.

Renal Impairment: Based on single-dose data only, the mean half-life of ketorolac tromethamine in renally impaired patients is between 6 and 19 hours, and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total ketorolac tromethamine clearance in the elderly and populations with renal impairment (r = 0.5).

In patients with renal disease, the AUC_{∞} of each enantiomer increased by approximately 100% compared with healthy volunteers. The volume of distribution doubles for the S-enantiomer and increases by 1/5th for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction. The AUC_{∞}-ratio of the ketorolac tromethamine enantiomers in healthy subjects and patients remained similar, indicating there was no selective excretion of either enantiomer in patients compared to healthy subjects.

Allergic Rhinitis: Comparison of the pharmacokinetics of SPRIX in subjects with allergic rhinitis to data from a previous study in healthy subjects showed no differences that would be of clinical consequence for the efficacy or safety of SPRIX.

Drug Interaction Studies

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 2 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].

Other Nasal Spray Products: A study was conducted in subjects with symptomatic allergic rhinitis to assess the effects of the commonly used nasal spray products oxymetazoline hydrochloride and fluticasone propionate on the pharmacokinetics of SPRIX. Subjects received a single dose of oxymetazoline nasal spray followed by a single dose (31.5 mg) of SPRIX 30 min later. Subjects also received fluticasone nasal spray (200 mcg as 2 x 50 mcg in each nostril) for seven days, with a single dose (31.5 mg) of SPRIX on the 7^{th} day. Administration of these common intranasal products had no effect of clinical significance on the rate or extent of ketorolac absorption.

Probenecid: Concomitant administration of oral ketorolac and probenecid resulted in decreased clearance and volume of distribution of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately threefold from 5.4 to 17.8 mcg/h/mL), and terminal half-life increased approximately twofold from 6.6 to 15.1 hours [*see Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

An 18-month study in mice with oral doses of ketorolac at 2 mg/kg/day (approximately 1.3 times the human systemic exposure at the recommended maximum IN dose of 31.5 mg four times a day, based on area-under-the-plasma-concentration curve [AUC]), and a 24-month study in rats at 5 mg/kg/day (approximately 0.8 times the human AUC) showed no evidence of tumorigenicity.

Mutagenesis

Ketorolac was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, or in forward mutation assays. Ketorolac did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 µg/mL and at higher concentrations, ketorolac increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility

Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (approximately 1.3 times the human AUC) and 16 mg/kg (approximately 2.4 times the human AUC) of ketorolac,

respectively.

14 CLINICAL STUDIES

14.1 Postoperative Pain

The effect of SPRIX on acute pain was evaluated in two multi-center, randomized, double-blind, placebo-controlled studies.

In a study of adults who had undergone elective abdominal or orthopedic surgery, 300 patients were randomized and treated with SPRIX or placebo administered every 8 hours and morphine administered via patient controlled analgesia on an as needed basis. Efficacy was demonstrated as a statistically significant greater reduction in the summed pain intensity difference over 48 hours in patients who received SPRIX as compared to those receiving placebo. The clinical relevance of this is reflected in the finding that patients treated with SPRIX required 36% less morphine over 48 hours than patients treated with placebo.

In a study of adults who had undergone elective abdominal surgery, 321 patients were randomized and treated with SPRIX or placebo administered every 6 hours and morphine administered via patient controlled analgesia on an as needed basis. Efficacy was demonstrated as a statistically significant greater reduction in the summed pain intensity difference over 48 hours in patients who received SPRIX as compared to those receiving placebo. The clinical relevance of this is reflected in the finding that patients treated with SPRIX required 26% less morphine over 48 hours than patients treated with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPRIX (ketorolac tromethamine) Nasal Spray, 15.75 mg/spray, are single-day preservative-free spray bottles, supplied as:

NDC 69344-144-43 Carton containing 5 single-day nasal spray bottles
NDC 69344-144-53 Carton containing 1 single-day nasal spray bottle

Each single-day nasal spray bottle contains a sufficient quantity of solution to deliver 8 sprays for a total of 126 mg of ketorolac tromethamine. Each spray delivers 15.75 mg of ketorolac tromethamine. The delivery system is designed to administer precisely metered doses of 100 µL per spray.

Storage

Protect from light and freezing. Store unopened SPRIX between 2°C to 8°C (36°F to 46°F). During use, keep containers of SPRIX Nasal Spray at controlled room temperature, between 15°C to 30°C (59°F to 86°F), out of direct sunlight. Bottles of SPRIX should be discarded within 24 hours of priming.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) that accompanies each prescription dispensed. Instruct all patients to read and closely follow the FDA-approved SPRIX Patient Instructions to ensure proper administration of SPRIX. When prescribing SPRIX, inform patients or their caregivers of the potential risks of ketorolac treatment, instruct patients to seek medical advice if they develop treatment-related adverse events, advise patients not to give SPRIX to other family members, and advise patients to discard any unused drug. Inform patients, families, or their caregivers of the following information before initiating therapy with SPRIX and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [*see Warnings and Precautions (5.1)*].

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [*see Contraindications (4), Warnings and Precautions (5.2)*].

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop SPRIX and seek immediate medical therapy [*see Warnings and Precautions (5.3)*].

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [*see Warnings and Precautions (5.5)*].

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat) Instruct patients to seek immediate emergency help if these occur [*see Contraindications (4) and Warnings and Precautions (5.7)*].

Serious Skin Reactions

Advise patients to stop SPRIX immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9)*].

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including SPRIX, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*].

Fetal Toxicity

Inform pregnant women to avoid use of SPRIX and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*].

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of SPRIX with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [*see Warnings and Precautions (5.2) and Drug Interactions (7)*]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with SPRIX until they talk to their healthcare provider [*see Drug Interactions (7)*].

Renal Effects

SPRIX is eliminated by the kidneys. Advise patients to maintain adequate fluid intake and request medical advice if urine output decreases significantly [*see Contraindications (4), Warnings and Precautions (5.6)*].

Limitations of Use

Instruct patients not to use SPRIX for more than 5 days. Use of SPRIX alone or in combination with any other ketorolac product for more than 5 days increases the risk for serious complications including GI bleeding and renal injury [*see Dosage and Administration (2)*].

Single-Day Container

Instruct patients not to use any single bottle of SPRIX for more than one day [*see Dosage and Administration (2.5)*].

Nasal Discomfort

Advise patients that they may experience transient, mild to moderate nasal irritation or discomfort upon dosing.

Manufactured for and Distributed by:

Egalet US Inc.
Wayne, PA 19087

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LBL # 101.02

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?
NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."
Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

The risk of getting an ulcer or bleeding increases with:

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

NSAIDs should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?
NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?
Do not take NSAIDs:

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. **You should not take NSAIDs after 29 weeks of pregnancy.**
- are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Do not start taking any new medicine without talking to your healthcare provider first.

What are the possible side effects of NSAIDs?
NSAIDs can cause serious side effects, including:
See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?"

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.
These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your

healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.
If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

Manufactured for: Egalet US Inc., Wayne, PA 19087
Distributed by: Egalet US Inc., Wayne, PA 19087
For more information, go to www.sprix.com or call 1-800-518-1084.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued or Revised: May/2016

Instructions for Use
SPRIX® (spriks)
(ketorolac tromethamine)
Nasal Spray

Read this Instructions for Use before you start using SPRIX and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

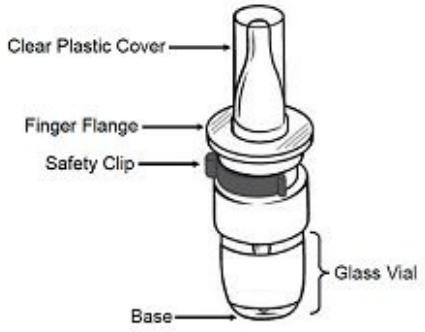
Important information:
- **SPRIX is for use in your nose only. Do not breathe in (inhale) SPRIX.**
- Each SPRIX bottle has enough pain medicine for 1 day.
- Throw away each SPRIX bottle within 24 hours of taking your first dose, even if the bottle still contains unused medicine.

Your healthcare provider has prescribed SPRIX to treat moderate to severe pain.
- Use SPRIX exactly as your healthcare provider tells you to use it.
- Your healthcare provider will tell you how many sprays you should use each time you use SPRIX.
- Do not use SPRIX for more than 5 days. If you still have pain after 5 days, contact your healthcare provider.
- Do not use SPRIX more than every 6 hours.
- It is important that you drink plenty of fluids while you are using SPRIX. Tell your healthcare provider if you urinate less while using SPRIX.

You may have discomfort or irritation in your nose when using SPRIX. This usually lasts for a short time. Do not breathe in (inhale) SPRIX while spraying.

Using SPRIX Nasal Spray

Parts of your SPRIX bottle



Follow the instructions below to use SPRIX.

Before you use SPRIX for the first time, you will need to prime the bottle.

Priming SPRIX:

Step 1. Hold the finger flange with your fingers **(see Figure A)**, and remove the clear plastic cover with your opposite hand. Keep the clear plastic cover for later. Remove and throw away the blue plastic safety clip.

Figure A

If the clear plastic cover is improperly removed, the tip of the bottle may be pulled off of the glass vial. If this happens, place the tip back onto the glass vial by lining it up carefully and gently pushing it back on until it is back in the correct position **(see Figure B)**. The SPRIX bottle should work properly again.

Figure B

Step 2. Hold the SPRIX bottle upright at arm's length away from you with your index finger and middle finger resting on the top of the finger flange and your thumb supporting the base **(see Figure C)**.

Press down on the finger flange and release the pump 5 times. You may not see a spray the first few times you press down.

Now the pump is primed and ready to use. You do not need to prime the pump again if you use more doses from this bottle.

Figure C

Step 3. Blow your nose to clear your nostrils.

Step 4. Sit up straight or stand.

Step 5. Keep your head tilted downward toward your toes.

Step 6. Place the tip of the SPRIX bottle into your right nostril.

Step 7. Hold the SPRIX bottle upright and aim the tip toward the back of your nose **(see Figure D)**.

Figure D

Step 8. Hold your breath and spray 1 time into your right nostril, pressing down on both sides of the finger flange **(see Figure D)**.

Step 9. Breathe in gently through your mouth after you use SPRIX. You may also pinch your nose to help keep the medicine in your nose.

Step 10. If your healthcare provider has prescribed only 1 spray per dose for you, you have now finished your dose, skip to Step 12 below.

Step 11. If your healthcare provider has prescribed 2 sprays for you, repeat steps 3 - 9 above for your left nostril. Be sure to point the spray away from the center of your nose. Spray 1 time into your left nostril.

Step 12. When you are finished using SPRIX, put the clear plastic cover back on the SPRIX bottle.

How should I store SPRIX?

- Store unopened SPRIX bottles between 36°F to 46°F (2°C to 8°C).
- Keep opened bottles of SPRIX at room temperature.
- Keep SPRIX out of direct sunlight.
- Do not freeze SPRIX.
- SPRIX does not contain a preservative. Throw away each SPRIX bottle within 24 hours of taking your first dose, even if the bottle still contains unused medicine.

Keep SPRIX and all medicines out of the reach of children.

General information about the safe and effective use of SPRIX.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not give SPRIX to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about SPRIX that is written for health professionals.

What are the ingredients in SPRIX?

Active ingredient: ketorolac tromethamine
Inactive ingredient: edetate disodium (EDTA), monobasic potassium phosphate, sodium hydroxide, and water for injection

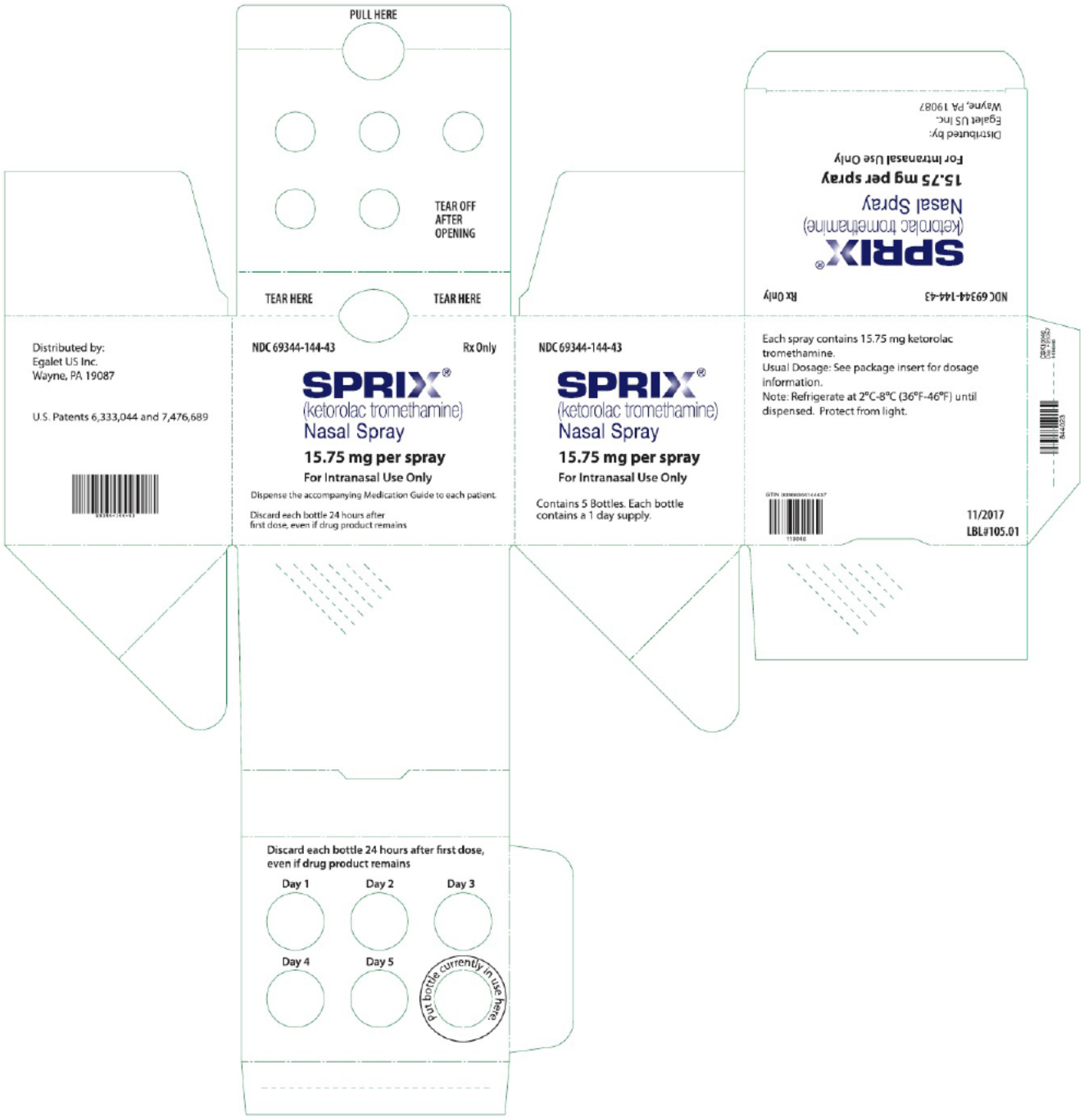
This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by:
Egalet US Inc.
Wayne, PA 19087

LBL # 102.02
Revised: 01/2018

PRINCIPAL DISPLAY PANEL - NDC 69344-144-63 - Vial Label

PRINCIPAL DISPLAY PANEL - NDC 69344-144-43 - Carton Label



SPRIX

ketorolac tromethamine spray, metered

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69344 144
Route of Administration	NASAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
KETOROLAC TROMETHAMINE (UNII: 4EVE5946BQ) (KETOROLAC UNII:YZI5105V0L)	KETOROLAC TROMETHAMINE	15 75 mg

Inactive Ingredients

Ingredient Name	Strength
EDETATE DISODIUM (UNII: 7FLD91C86K)	
POTASSIUM PHOSPHATE, MONOBASIC (UNII: 4J9FJ0HL51)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69344 144 43	5 in 1 CARTON	04/26/2011	
1	NDC:69344 144 53	1 in 1 CARTON		
1	NDC:69344 144 63	8 in 1 BOTTLE, SPRAY; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022382	04/26/2011	

Labeler - Egale US Inc. (079581441)

Revised: 1/2018

Egalet US Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYTIGA safely and effectively. See full prescribing information for ZYTIGA.

ZYTIGA® (abiraterone acetate) tablets
for oral use
Initial U.S. Approval: 2011

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	02/2018
Dosage and Administration (2)	02/2018
Warnings and Precautions (5)	02/2018

----------INDICATIONS AND USAGE----------

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with

- metastatic castration-resistant prostate cancer (CRPC). (1)
- metastatic high-risk castration-sensitive prostate cancer (CSPC). (1)

----------DOSAGE AND ADMINISTRATION----------

Metastatic castration-resistant prostate cancer:

- ZYTIGA 1,000 mg orally once daily with prednisone 5 mg orally **twice** daily. (2.1)

Metastatic castration-sensitive prostate cancer:

- ZYTIGA 1,000 mg orally once daily with prednisone 5 mg orally **once** daily. (2.2)

Patients receiving ZYTIGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. ZYTIGA must be taken on an empty stomach with water at least 1 hour before or 2 hours after a meal. Do not crush or chew tablets. (2.3)

Dose Modification:

- For patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the ZYTIGA starting dose to 250 mg once daily. (2.4)
- For patients who develop hepatotoxicity during treatment, hold ZYTIGA until recovery. Retreatment may be initiated at a reduced dose. ZYTIGA should be discontinued if patients develop severe hepatotoxicity. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- Film-Coated Tablet 500 mg (3)
- Film-Coated Tablet 250 mg (3)
- Uncoated Tablet 250 mg (3)

----------CONTRAINDICATIONS----------

- Pregnancy. (4, 8.1)

----------WARNINGS AND PRECAUTIONS----------

- Mineralocorticoid excess: Closely monitor patients with cardiovascular disease. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly. (5.1)
- Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations. (5.2)
- Hepatotoxicity: Can be severe and fatal. Monitor liver function and modify, interrupt, or discontinue ZYTIGA dosing as recommended. (5.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥10%) are fatigue, arthralgia, hypertension, nausea, edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory infection, cough, and headache. (6.1)

The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, and hypokalemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- CYP3A4 Inducers: Avoid concomitant strong CYP3A4 inducers during ZYTIGA treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency. (2.5, 7.1)
- CYP2D6 Substrates: Avoid co-administration of ZYTIGA with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Females and Males of Reproductive Potential: Advise males with female partners of reproductive potential to use effective contraception. (8.3)
- Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYTIGA is indicated in combination with prednisone for the treatment of patients with

- Metastatic castration-resistant prostate cancer (CRPC)
- Metastatic high-risk castration-sensitive prostate cancer (CSPC)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose for metastatic CRPC

The recommended dose of ZYTIGA is 1,000 mg (two 500 mg tablets or four 250 mg tablets) orally once daily with prednisone 5 mg orally **twice** daily.

2.2 Recommended Dose for metastatic high-risk CSPC

The recommended dose of ZYTIGA is 1,000 mg (two 500 mg tablets or four 250 mg tablets) orally once daily with prednisone 5 mg administered orally **once** daily.

2.3 Important Administration Instructions

Patients receiving ZYTIGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. ZYTIGA must be taken on an empty stomach, either one hour before or two hours after a meal *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole with water. Do not crush or chew tablets.

2.4 Dose Modification Guidelines in Hepatic Impairment and Hepatotoxicity

Hepatic Impairment

In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. In patients with moderate hepatic impairment monitor ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5X upper limit of normal (ULN) or total bilirubin greater than 3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA and do not re-treat patients with ZYTIGA *[see Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)]*.

Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C).

Hepatotoxicity

For patients who develop hepatotoxicity during treatment with ZYTIGA (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with ZYTIGA *[see Warnings and Precautions (5.3)]*. Treatment may be restarted at a reduced dose of 750 mg

once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with ZYTIGA.

Permanently discontinue ZYTIGA for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation *[see Warnings and Precautions (5.3)]*.

2.5 Dose Modification Guidelines for Strong CYP3A4 Inducers

Avoid concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during ZYTIGA treatment.

If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency to twice a day only during the co-administration period (e.g., from 1,000 mg once daily to 1,000 mg twice a day). Reduce the dose back to the previous dose and frequency, if the concomitant strong CYP3A4 inducer is discontinued *[see Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets (500 mg): purple, oval-shaped, film-coated tablets debossed with "AA" one side and "500" on the other side.

Tablets (250 mg): pink, oval-shaped, film-coated tablets debossed with "AA250" on one side.

Tablets (250 mg): white to off-white, oval-shaped tablets debossed with "AA250" on one side.

4 CONTRAINDICATIONS

Pregnancy

ZYTIGA can cause fetal harm and potential loss of pregnancy *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Clinical Pharmacology (12.1)]*. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

In the combined data from 4 placebo-controlled trials using prednisone 5 mg twice daily in combination with 1000 mg abiraterone acetate daily, grades 3-4 hypokalemia were detected in 4% of patients on the ZYTIGA arm and 2% of patients on the placebo arm. Grades 3-4 hypertension were observed in 2% of patients each arm and grades 3-4 fluid retention in 1% of patients each arm.

In LATITUDE (a randomized placebo-controlled, multicenter clinical trial), which used prednisone 5 mg daily in combination with 1000 mg abiraterone acetate daily, grades 3-4 hypokalemia were detected in 10% of patients on the ZYTIGA arm and 1% of patients on the placebo arm, grades 3-4 hypertension were observed in 20% of patients on the ZYTIGA arm and 10% of patients on the placebo arm. Grades 3-4 fluid retention occurred in 1% of patients each arm *[see Adverse Reactions (6)]*.

Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in COU-AA-301) or NYHA Class II to IV heart failure (in COU-AA-302 and LATITUDE) has not been established because these patients were excluded from these randomized clinical trials *[see Clinical Studies (14)]*.

5.2 Adrenocortical Insufficiency

Adrenal insufficiency occurred in 0.3% of 2230 patients taking ZYTIGA and in 0.1% of 1763 patients taking placebo in the combined data of the 5 randomized, placebo-controlled clinical studies. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress.

Monitor patients for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions (5.1)]*.

5.3 Hepatotoxicity

In postmarketing experience, there have been ZYTIGA-associated severe hepatic toxicity, including fulminant hepatitis, acute liver failure and deaths *[see Adverse Reactions (6.2)]*.

In the combined data of 5 randomized clinical trials, grade 3-4 ALT or AST increases (at least 5X ULN) were reported in 6% of 2230 patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to ALT and AST increases or abnormal hepatic function occurred in 1.1% of 2230 patients taking ZYTIGA. In these clinical trials, no deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function.

Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.4)]*.

Permanently discontinue ZYTIGA for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation *[see Dosage and Administration (2.4)]*.

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess *[see Warnings and Precautions (5.1)]*.
- Adrenocortical Insufficiency *[see Warnings and Precautions (5.2)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized placebo-controlled, multicenter clinical trials (COU-AA-301 and COU-AA-302) enrolled patients who had metastatic CRPC in which ZYTIGA was administered orally at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to patients on the control arm. A third randomized placebo-controlled, multicenter clinical trial (LATITUDE) enrolled patients who had metastatic high-risk CSPC in which ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg once daily. Placebos were administered to patients in the control arm. Additionally, two other randomized, placebo-controlled trials were conducted in patients with metastatic CRPC. The safety data pooled from 2230 patients in the 5 randomized controlled trials constitute the basis for the data presented in the Warnings and Precautions, Grade 1-4 adverse reactions, and Grade 1-4 laboratory abnormalities. In all trials, a gonadotropin-releasing hormone (GnRH) analog or prior orchiectomy was required in both arms.

In the pooled data, median treatment duration was 11 months (0.1, 43) for ZYTIGA-treated patients and 7.2 months (0.1, 43) for placebo-treated patients. The most common adverse reactions (≥10%) that occurred more commonly (>2%) in the ZYTIGA arm were fatigue, arthralgia, hypertension, nausea, edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory infection, cough, and headache. The most common laboratory abnormalities (>20%) that occurred more commonly (≥2%) in the ZYTIGA arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, and hypokalemia. Grades 3-4 adverse events were reported for 53% of patients in the ZYTIGA arm and 46% of patients in the placebo arm. Treatment discontinuation was reported in 14% of patients in the ZYTIGA arm and 13% of patients in the placebo arm. The common adverse

events (≥1%) resulting in discontinuation of ZYTIGA and prednisone were hepatotoxicity and cardiac disorders.

Deaths associated with treatment-emergent adverse events were reported for 7.5% of patients in the ZYTIGA arm and 6.6% of patients in the placebo arm. Of the patients in the ZYTIGA arm, the most common cause of death was disease progression (3.3%). Other reported causes of death in ≥5 patients included pneumonia, cardio-respiratory arrest, death (no additional information), and general physical health deterioration.

COU-AA-301: Metastatic CRPC Following Chemotherapy

COU-AA-301 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥2.5X ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT >5X ULN.

Table 1 shows adverse reactions on the ZYTIGA arm in COU-AA-301 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA with prednisone was 8 months.

Table 1: Adverse Reactions due to ZYTIGA in COU-AA-301

	ZYTIGA with Prednisone (N=791)		**Placebo with Prednisone (N=394)**	
System/Organ Class	All Grades[1]	Grade 3-4	All Grades	Grade 3-4
Adverse reaction	%	%	%	%
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort[2]	30	4.2	23	4.1
Muscle discomfort[3]	26	3.0	23	2.3
General disorders				
Edema[4]	27	1.9	18	0.8
Vascular disorders				
Hot flush	19	0.3	17	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	18	0.6	14	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	12	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	11	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Injury, poisoning and procedural complications				
Fractures[5]	5.9	1.4	2.3	0

Cardiac disorders				
Arrhythmia[6]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[7]	3.8	0.5	2.8	0
Cardiac failure[8]	2.3	1.9	1.0	0.3

[1] Adverse events graded according to CTCAE version 3.0.
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness.
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness.
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema.
[5] Includes all fractures with the exception of pathological fracture.
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia.
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased.

Table 2 shows laboratory abnormalities of interest from COU-AA-301.

Table 2: Laboratory Abnormalities of Interest in COU-AA-301

	ZYTIGA with Prednisone (N=791)		**Placebo with Prednisone (N=394)**	
Laboratory Abnormality	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hypertriglyceridemia	63	0.4	53	0
High AST	31	2.1	36	1.5
Hypokalemia	28	5.3	20	1.0
Hypophosphatemia	24	7.2	16	5.8
High ALT	11	1.4	10	0.8
High Total Bilirubin	6.6	0.1	4.6	0

COU-AA-302: Metastatic CRPC Prior to Chemotherapy

COU-AA-302 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥2.5X ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in COU-AA-302 that occurred in ≥5% of patients with a ≥2% absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA with prednisone was 13.8 months.

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in COU-AA-302

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=542) All Grades[1] %	 Grade 3-4 %	Placebo with Prednisone (N=540) All Grades %	 Grade 3-4 %
General disorders				
Fatigue	39	2.2	34	1.7
Edema[2]	25	0.4	21	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort[3]	30	2.0	25	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23	0.4	19	0.6
Diarrhea	22	0.9	18	0.9
Dyspepsia	11	0.0	5.0	0.2
Vascular disorders				
Hot flush	22	0.2	18	0.0
Hypertension	22	3.9	13	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17	0.0	14	0.2
Dyspnea	12	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	14	0.2	11	0.0
Injury, poisoning and procedural complications				
Contusion	13	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	13	0.0	8.0	0.0
Nasopharyngitis	11	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

[1] Adverse events graded according to CTCAE version 3.0.
[2] Includes terms Edema peripheral, Pitting edema, and Generalized edema.
[3] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness.

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebo in COU-AA-302.

Table 4: Laboratory Abnormalities in >15% of Patients in the ZYTIGA Arm of COU-AA-302

Laboratory Abnormality	ZYTIGA with Prednisone (N=542) Grade 1-4 %	 Grade 3-4 %	Placebo with Prednisone (N=540) Grade 1-4 %	 Grade 3-4 %
Hematology				
Lymphopenia	38	8.7	32	7.4

Chemistry				
Hyperglycemia[1]	57	6.5	51	5.2
High ALT	42	6.1	29	0.7
High AST	37	3.1	29	1.1
Hypernatremia	33	0.4	25	0.2
Hypokalemia	17	2.8	10	1.7

[1] Based on non-fasting blood draws

LATITUDE: Patients with Metastatic High-risk CSPC

LATITUDE enrolled 1199 patients with newly-diagnosed metastatic, high-risk CSPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥2.5X ULN or if they had liver metastases. All the patients received GnRH analogs or had prior bilateral orchiectomy during the trial. The median duration of treatment with ZYTIGA and prednisone was 24 months.

Table 5 shows adverse reactions on the ZYTIGA arm that occurred in ≥5% of patients with a ≥2% absolute increase in frequency compared to those on the placebos arm.

Table 5: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in LATITUDE[1]

	ZYTIGA with Prednisone (N=597)		**Placebos (N=602)**	
System/Organ Class	All Grades[2]	Grade 3-4	All Grades	Grade 3-4
Adverse reaction	%	%	%	%
Vascular disorders				
Hypertension	37	20	13	10
Hot flush	15	0.0	13	0.2
Metabolism and nutrition disorders				
Hypokalemia	20	10	3.7	1.3
Investigations				
Alanine aminotransferase increased[3]	16	5.5	13	1.3
Aspartate aminotransferase increased[3]	15	4.4	11	1.5
Infections and infestations				
Urinary tract infection	7.0	1.0	3.7	0.8
Upper respiratory tract infection	6.7	0.2	4.7	0.2
Nervous system disorders				
Headache	7.5	0.3	5.0	0.2
Respiratory, Thoracic and Mediastinal Disorders				
Cough[4]	6.5	0.0	3.2	0

[1] All patients were receiving an GnRH agonist or had undergone orchiectomy.
[2] Adverse events graded according to CTCAE version 4.0
[3] Reported as an adverse event or reaction
[4] Including cough, productive cough, upper airway cough syndrome

Table 6 shows laboratory abnormalities that occurred in >15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebos.

Table 6: Laboratory Abnormalities in >15% of Patients in the ZYTIGA Arm of LATITUDE

	ZYTIGA with Prednisone (N=597)		**Placebos (N=602)**	
Laboratory Abnormality	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Hematology				
Lymphopenia	20	4.1	14	1.8
Chemistry				
Hypokalemia	30	9.6	6.7	1.3
Elevated ALT	46	6.4	45	1.3
Elevated total bilirubin	16	0.2	6.2	0.2

Cardiovascular Adverse Reactions

In the combined data of 5 randomized, placebo-controlled clinical studies, cardiac failure occurred more commonly in patients on the ZYTIGA arm compared to patients on the placebo arm (2.6% versus 0.9%). Grade 3-4 cardiac failure occurred in 1.3% of patients taking ZYTIGA and led to 5 treatment discontinuations and 4 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and two deaths due to cardiac failure in the placebo group.

In the same combined data, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and three patients with sudden death in the ZYTIGA arms and five deaths in the placebo arms. There were 7 (0.3%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 2 (0.1%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 3 deaths in the ZYTIGA arms.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of ZYTIGA with prednisone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory, Thoracic and Mediastinal Disorders: non-infectious pneumonitis.

Musculoskeletal and Connective Tissue Disorders: myopathy, including rhabdomyolysis.

Hepatobiliary Disorders: fulminant hepatitis, including acute hepatic failure and death.

7 DRUG INTERACTIONS

7.1 Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4.

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency *[see Dosage and Administration (2.5)* and *Clinical Pharmacology (12.3)]*.

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone *[see Clinical Pharmacology (12.3)]*.

7.2 Effects of Abiraterone on Drug Metabolizing Enzymes

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, consider a dose reduction of the concomitant CYP2D6 substrate drug *[see Clinical Pharmacology (12.3)]*.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, ZYTIGA is contraindicated for use in pregnant women because the drug can cause fetal harm and potential loss of pregnancy. ZYTIGA is not indicated for use in females.

There are no human data on the use of ZYTIGA in pregnant women. In animal reproduction studies, oral administration of abiraterone acetate to pregnant rats during organogenesis caused adverse developmental effects at maternal exposures approximately ≥ 0.03 times the human exposure (AUC) at the recommended dose *(see Data).*

Data

Animal Data

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥10 mg/kg/day, decreased fetal ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

8.2 Lactation

Risk Summary

ZYTIGA is not indicated for use in women. There is no information available on the presence of abiraterone acetate in human milk, or on the effects on the breastfed child or milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animal reproduction studies and its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 weeks after the final dose of ZYTIGA *[see Use in Specific Populations (8.1)]*.

Infertility

Based on animal studies, ZYTIGA may impair reproductive function and fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of ZYTIGA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients receiving ZYTIGA in randomized clinical trials, 70% of patients were 65 years and over and 27% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

The pharmacokinetics of abiraterone were examined in subjects with baseline mild (N=8) or moderate (N=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (N=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 7-fold and the fraction of free drug increased 2-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)]*.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required *[see Dosage and Administration (2.4), Warnings and Precautions (5.3),* and *Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

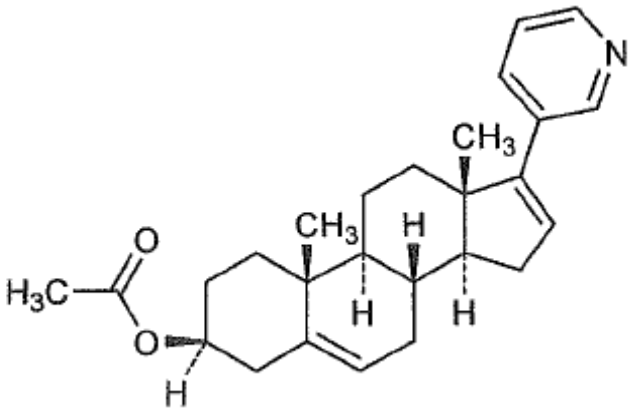
Human experience of overdose with ZYTIGA is limited.

There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

11 DESCRIPTION

Abiraterone acetate, the active ingredient of ZYTIGA is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). Each ZYTIGA tablet

contains either 250 mg or 500 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl) androsta-5,16-dien-3-yl acetate and its structure is:



Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

ZYTIGA tablets are available in 500 mg film-coated tablets, 250 mg film-coated tablets and 250 mg uncoated tablets with the following inactive ingredients:

- 500 mg film-coated tablets: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, silicified microcrystalline cellulose, and sodium lauryl sulfate. The coating, Opadry® II Purple, contains iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

- 250 mg film-coated tablets: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate. The coating, Opadry® II Beige, contains iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

- 250 mg uncoated tablets: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abiraterone acetate (ZYTIGA) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals *[see Warnings and Precautions (5.1)]*.

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

ZYTIGA decreased serum testosterone and other androgens in patients in the placebo-controlled clinical trial. It is not necessary to monitor the effect of ZYTIGA on serum testosterone levels.

Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

12.3 Pharmacokinetics

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects and in patients with metastatic CRPC. *In vivo*, abiraterone acetate is converted to abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (<0.2 ng/mL) in >99% of the analyzed samples.

Absorption

Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1,000 mg dose of abiraterone acetate.

At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of C_{max} were 226 ± 178 ng/mL and of AUC were 993 ± 639 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg. However, the

exposure was not significantly increased when the dose was doubled from 1,000 to 2,000 mg (8% increase in the mean AUC).

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. In healthy subjects abiraterone C_{max} and $AUC_{0-\infty}$ were approximately 7- and 5-fold higher, respectively, when a single dose of abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal compared to overnight fasting. Abiraterone $AUC_{0-\infty}$ was approximately 7-fold or 1.6-fold higher, respectively, when a single dose of abiraterone acetate was administered 2 hours after or 1 hour before a medium fat meal (25% fat, 491 calories) compared to overnight fasting.

Systemic exposures of abiraterone in patients with metastatic CRPC, after repeated dosing of abiraterone acetate were similar when abiraterone acetate was taken with low-fat meals for 7 days and increased approximately 2-fold when taken with high-fat meals for 7 days compared to when taken at least 2 hours after a meal and at least 1 hour before a meal for 7 days.

Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in increased and highly variable exposures. Therefore, ZYTIGA must be taken on an empty stomach, either one hour before or two hours after a meal. The tablets should be swallowed whole with water *[see Dosage and Administration (2.3)]*.

Distribution and Protein Binding

Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean ± SD) is 19,669 ± 13,358 L. *In vitro* studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp) and that abiraterone acetate is an inhibitor of P-gp.

Metabolism

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity (the esterases have not been identified) and is not CYP mediated. The two main circulating metabolites of abiraterone in human plasma are abiraterone sulphate (inactive) and N-oxide abiraterone sulphate (inactive), which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate and SULT2A1 is involved in the formation of abiraterone sulphate.

Excretion

In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean ± SD) is 12 ± 5 hours. Following oral administration of ^{14}C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in urine. The major compounds present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Patients with Hepatic Impairment

The pharmacokinetics of abiraterone was examined in subjects with baseline mild (N=8) or moderate (N=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. Systemic exposure to abiraterone after a single oral 1,000 mg dose given under fasting conditions increased approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (N=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 7-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function. In addition, the mean protein binding was found to be lower in the severe hepatic impairment group compared to the normal hepatic function group, which resulted in a two-fold increase in the fraction of free drug in patients with severe hepatic impairment *[see Dosage and Administration (2.4)* and *Use in Specific Populations (8.6)]*.

Patients with Renal Impairment

The pharmacokinetics of abiraterone were examined in patients with end-stage renal disease (ESRD) on a stable hemodialysis schedule (N=8) and in matched control subjects with normal renal function (N=8). In the ESRD cohort of the trial, a single 1,000 mg ZYTIGA dose was given under fasting conditions 1 hour after dialysis, and samples for pharmacokinetic analysis were collected up to 96 hours post dose. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis, compared to subjects with normal renal function *[see Use in Specific Populations (8.7)]*.

Drug Interactions

In vitro studies with human hepatic microsomes showed that abiraterone has the potential to inhibit CYP1A2, CYP2D6, CYP2C8 and to a lesser extent CYP2C9, CYP2C19 and CYP3A4/5.

In an *in vivo* drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold *[see Drug Interactions (7.2)]*.

In a clinical study to determine the effects of abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily) on a single 100 mg dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

Abiraterone is a substrate of CYP3A4, *in vitro*. In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer (rifampin, 600 mg daily for 6 days) followed by a single dose of abiraterone acetate 1,000 mg, the mean plasma AUC_{∞} of abiraterone was decreased by 55% *[see Drug Interactions (7.1)]*.

In a separate clinical pharmacokinetic interaction study of healthy subjects, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone *[see Drug Interactions (7.1)]*.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate *[see Drug Interactions (7.2)]*.

In vitro, abiraterone and its major metabolites were shown to inhibit the hepatic uptake transporter OATP1B1. There are no clinical data available to confirm transporter based interaction.

12.6 QT Prolongation

In a multi-center, open-label, single-arm trial, 33 patients with metastatic CRPC received ZYTIGA orally at a dose of 1,000 mg once daily at least 1 hour before or 2 hours after a meal in combination with prednisone 5 mg orally twice daily. Assessments up to Cycle 2 Day 2 showed no large changes in the QTc interval (i.e., >20 ms) from baseline. However, small increases in the QTc interval (i.e., <10 ms) due to abiraterone acetate cannot be excluded due to study design limitations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

A two-year carcinogenicity study was conducted in rats at oral abiraterone acetate doses of 5, 15, and 50 mg/kg/day for males and 15, 50, and 150 mg/kg/day for females. Abiraterone acetate increased the combined incidence of interstitial cell adenomas and carcinomas in the testes at all

dose levels tested. This finding is considered to be related to the pharmacological activity of abiraterone. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Abiraterone acetate was not carcinogenic in female rats at exposure levels up to 0.8 times the human clinical exposure based on AUC. Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse.

Abiraterone acetate and abiraterone was not mutagenic in an *in vitro* microbial mutagenesis (Ames) assay or clastogenic in an *in vitro* cytogenetic assay using primary human lymphocytes or an *in vivo* rat micronucleus assay.

In repeat-dose toxicity studies in male rats (13- and 26-weeks) and monkeys (39-weeks), atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at ≥50 mg/kg/day in rats and ≥250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone. These effects were observed in rats at systemic exposures similar to humans and in monkeys at exposures approximately 0.6 times the AUC in humans.

In a fertility study in male rats, reduced organ weights of the reproductive system, sperm counts, sperm motility, altered sperm morphology and decreased fertility were observed in animals dosed for 4 weeks at ≥30 mg/kg/day orally. Mating of untreated females with males that received 30 mg/kg/day oral abiraterone acetate resulted in a reduced number of corpora lutea, implantations and live embryos and an increased incidence of pre-implantation loss. Effects on male rats were reversible after 16 weeks from the last abiraterone acetate administration.

In a fertility study in female rats, animals dosed orally for 2 weeks until day 7 of pregnancy at ≥30 mg/kg/day had an increased incidence of irregular or extended estrous cycles and pre-implantation loss (300 mg/kg/day). There were no differences in mating, fertility, and litter parameters in female rats that received abiraterone acetate. Effects on female rats were reversible after 4 weeks from the last abiraterone acetate administration.

The dose of 30 mg/kg/day in rats is approximately 0.3 times the recommended dose of 1,000 mg/day based on body surface area.

In 13- and 26-week studies in rats and 13- and 39-week studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone acetate at approximately one half the human clinical exposure based on AUC. As a result, decreases in organ weights and toxicities were observed in the male and female reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. The changes in the reproductive organs are consistent with the antiandrogenic pharmacological activity of abiraterone acetate.

13.2 Animal Toxicology and/or Pharmacology

A dose-dependent increase in cataracts was observed in rats after daily oral abiraterone acetate administration for 26 weeks starting at ≥50 mg/kg/day (similar to the human clinical exposure based on AUC). In a 39-week monkey study with daily oral abiraterone acetate administration, no cataracts were observed at higher doses (2 times greater than the clinical exposure based on AUC).

14 CLINICAL STUDIES

The efficacy and safety of ZYTIGA with prednisone was established in three randomized placebo-controlled international clinical studies. All patients in these studies received a GnRH analog or had prior bilateral orchiectomy. Patients with prior ketoconazole treatment for prostate cancer and a history of adrenal gland or pituitary disorders were excluded from these trials. Concurrent use of spironolactone was not allowed during the study period.

COU-AA-301 (NCT00638690): Patients with metastatic CRPC who had received prior docetaxel chemotherapy

A total of 1195 patients were randomized 2:1 to receive either ZYTIGA orally at a dose of 1,000 mg once daily in combination with prednisone 5 mg orally twice daily (N=797) or placebo once daily plus prednisone 5 mg orally twice daily (N=398). Patients randomized to either arm were to continue treatment until disease progression (defined as a 25% increase in PSA over the patient's baseline/nadir together with protocol-defined radiographic progression and symptomatic or clinical progression), initiation of new treatment, unacceptable toxicity or withdrawal.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 39-95) and the racial distribution was 93% Caucasian, 3.6% Black, 1.7% Asian, and 1.6% Other. Eighty-nine percent of patients enrolled had an ECOG performance status score of 0-1 and 45% had a Brief Pain Inventory-Short Form score of ≥4 (patient's reported worst pain over the previous 24 hours). Ninety percent of patients had metastases in bone and 30% had visceral involvement. Seventy percent of patients had radiographic evidence of disease progression and 30% had PSA-only progression. Seventy percent of patients had previously received one cytotoxic chemotherapy regimen and 30% received two regimens.

The protocol pre-specified interim analysis was conducted after 552 deaths and showed a statistically significant improvement in overall survival (OS) in patients treated with ZYTIGA with prednisone compared to patients in the placebo with prednisone arm (Table 9 and Figure 1). An updated survival analysis was conducted when 775 deaths (97% of the planned number of

deaths for final analysis) were observed. Results from this analysis were consistent with those from the interim analysis (Table 7).

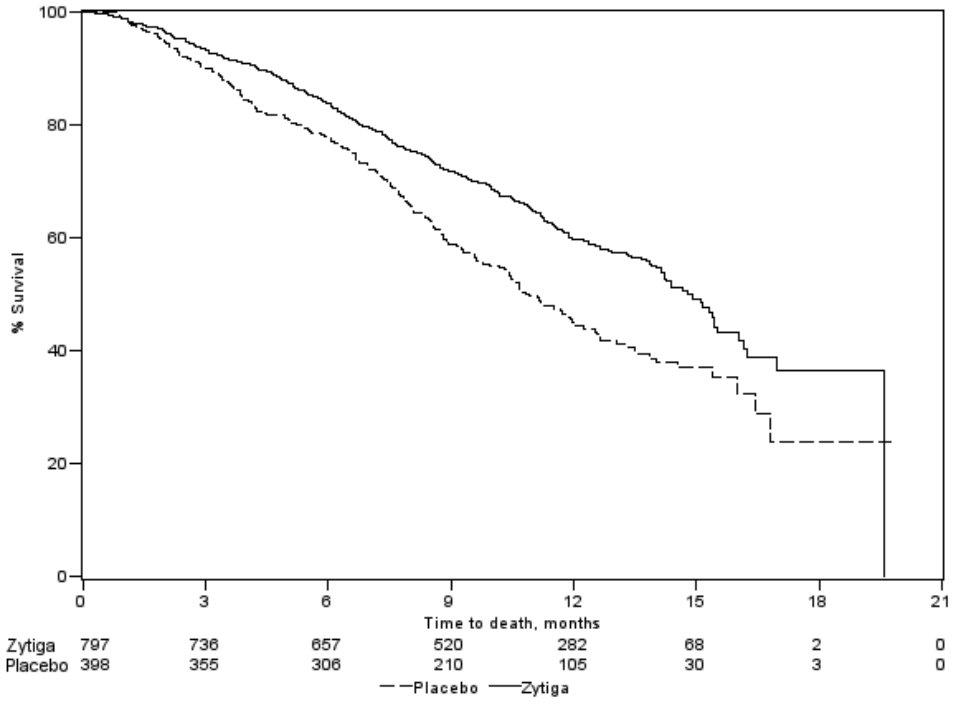
Table 7: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in COU-AA-301 (Intent-to-Treat Analysis)

	ZYTIGA with Prednisone (N=797)	Placebo with Prednisone (N=398)
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p-value[1]	<0.0001	
Hazard ratio (95% CI)[2]	0.646 (0.543, 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median survival (months) (95% CI)	15.8 (14.8, 17.0)	11.2 (10.4, 13.1)
Hazard ratio (95% CI)[2]	0.740 (0.638, 0.859)	

[1] p-value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs. 2), pain score (absent vs. present), number of prior chemotherapy regimens (1 vs. 2), and type of disease progression (PSA only vs. radiographic).

[2] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA with prednisone.

Figure 1: Kaplan-Meier Overall Survival Curves in COU-AA-301 (Intent-to-Treat Analysis)



COU-AA-302 (NCT00887198): Patients with metastatic CRPC who had not received prior cytotoxic chemotherapy

In COU-AA-302, 1088 patients were randomized 1:1 to receive either ZYTIGA orally at a dose of 1,000 mg once daily (N=546) or Placebo orally once daily (N=542). Both arms were given concomitant prednisone 5 mg twice daily. Patients continued treatment until radiographic or clinical (cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or ECOG performance status decline to 3 or more) disease progression, unacceptable toxicity or withdrawal. Patients with moderate or severe pain, opiate use for cancer pain, or visceral organ metastases were excluded.

Patient demographics were balanced between the treatment arms. The median age was 70 years. The racial distribution of patients treated with ZYTIGA was 95% Caucasian, 2.8% Black, 0.7% Asian and 1.1% Other. The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). Baseline pain assessment was 0-1 (asymptomatic) in 66% of patients and 2-3 (mildly symptomatic) in 26% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours).

Radiographic progression-free survival was assessed with the use of sequential imaging studies and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Working Group 2 criteria) and/or modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria for progression of soft tissue lesions. Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

The planned final analysis for OS, conducted after 741 deaths (median follow up of 49 months) demonstrated a statistically significant OS improvement in patients treated with ZYTIGA with prednisone compared to those treated with placebo with prednisone (Table 8 and Figure 2). Sixty-five percent of patients on the ZYTIGA arm and 78% of patients on the placebo arm used subsequent therapies that may prolong OS in metastatic CRPC. ZYTIGA was used as a subsequent therapy in 13% of patients on the ZYTIGA arm and 44% of patients on the placebo arm.

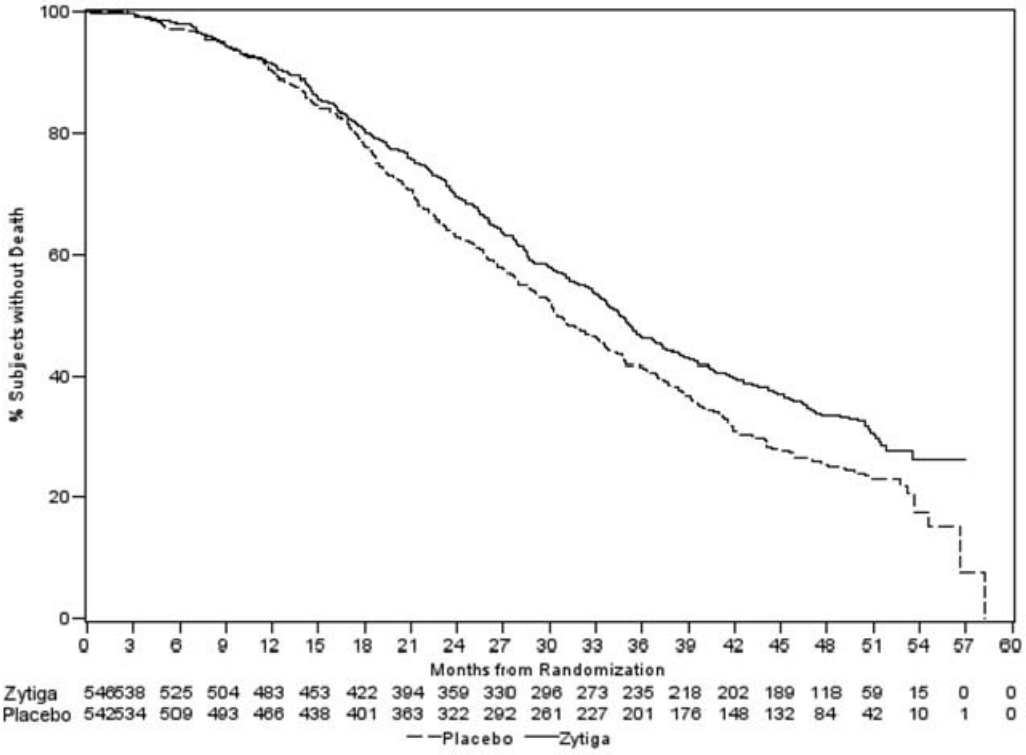
Table 8: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in COU-AA-302 (Intent-to-Treat Analysis)

Overall Survival	ZYTIGA with Prednisone (N=546)	Placebo with Prednisone (N=542)
Deaths	354 (65%)	387 (71%)
Median survival (months) (95% CI)	34.7 (32.7, 36.8)	30.3 (28.7, 33.3)
p-value[1]	0.0033	
Hazard ratio[2] (95% CI)	0.81 (0.70, 0.93)	

[1] p-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).

[2] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA with prednisone.

Figure 2: Kaplan Meier Overall Survival Curves in COU-AA-302



At the pre-specified rPFS analysis, 150 (28%) patients treated with ZYTIGA with prednisone and 251 (46%) patients treated with placebo with prednisone had radiographic progression. A significant difference in rPFS between treatment groups was observed (Table 9 and Figure 3).

Table 9: Radiographic Progression-free Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in COU-AA-302 (Intent-to-Treat Analysis)

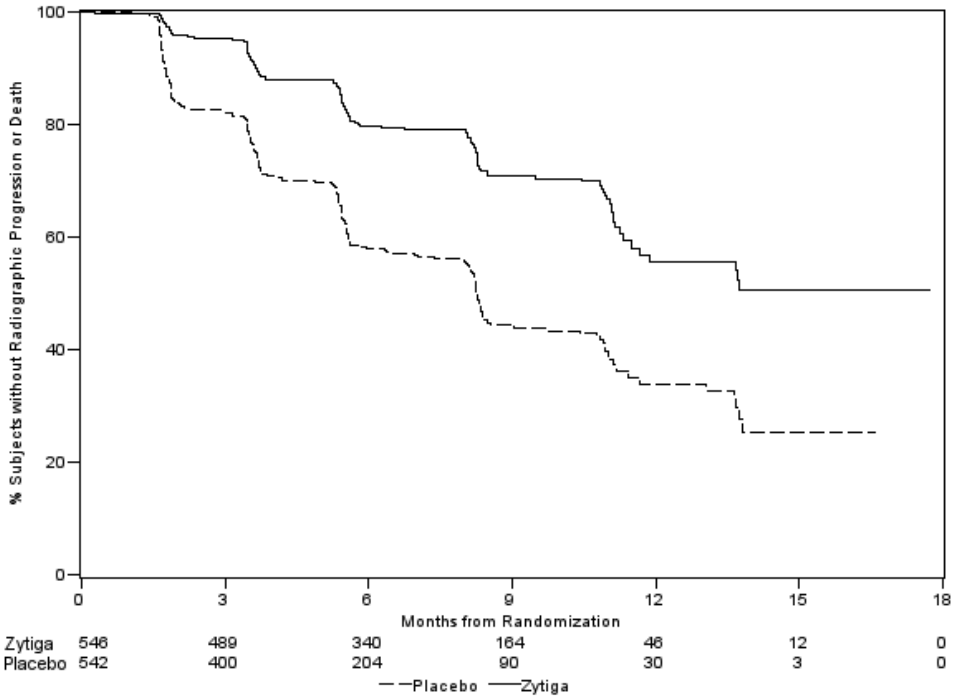
Radiographic Progression-free Survival	ZYTIGA with Prednisone (N=546)	Placebo with Prednisone (N=542)
Progression or death	150 (28%)	251 (46%)
Median rPFS (months) (95% CI)	NR (11.66, NR)	8.28 (8.12, 8.54)
p-value[1]	<0.0001	
Hazard ratio[2] (95% CI)	0.425 (0.347, 0.522)	

NR=Not reached.

[1] p-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).

[2] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA with prednisone.

Figure 3: Kaplan Meier Curves of Radiographic Progression-free Survival in COU-AA-302 (Intent-to-Treat Analysis)



The primary efficacy analyses are supported by the following prospectively defined endpoints. The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients in the ZYTIGA arm and 16.8 months for patients in the placebo arm (HR=0.580; 95% CI: [0.487, 0.691], $p < 0.0001$).

The median time to opiate use for prostate cancer pain was not reached for patients receiving ZYTIGA and was 23.7 months for patients receiving placebo (HR=0.686; 95% CI: [0.566, 0.833], p=0.0001). The time to opiate use result was supported by a delay in patient reported pain progression favoring the ZYTIGA arm.

LATITUDE (NCT01715285): Patients with metastatic high-risk CSPC

In LATITUDE, 1199 patients with metastatic high-risk CSPC were randomized 1:1 to receive either ZYTIGA orally at a dose of 1,000 mg once daily with prednisone 5 mg once daily (N=597) or placebos orally once daily (N=602). High-risk disease was defined as having at least two of three risk factors at baseline: a total Gleason score of ≥8, presence of ≥3 lesions on bone scan, and evidence of measurable visceral metastases. Patients with significant cardiac, adrenal, or hepatic dysfunction were excluded. Patients continued treatment until radiographic or clinical disease progression, unacceptable toxicity, withdrawal or death. Clinical progression was defined as the need for cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or ECOG performance status decline ≥3.

Patient demographics were balanced between the treatment arms. The median age was 67 years. The racial distribution of patients treated with ZYTIGA was 69% Caucasian, 2.5% Black, 21% Asian, and 8.1% Other. The ECOG performance status was 0 for 55%, 1 for 42%, and 2 for 3.5% of patients. Baseline pain assessment was 0-1 (asymptomatic) in 50% of patients, 2-3 (mildly symptomatic) in 23% of patients, and ≥4 in 28% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours).

A major efficacy outcome was overall survival. The pre-specified interim analysis was conducted after 406 deaths and showed a statistically significant improvement in OS in patients on ZYTIGA with prednisone compared to those on placebos (see Table 10 and Figure 4). Twenty-one percent of patients on the ZYTIGA arm and 41% of patients on the placebo arm received subsequent therapies that may prolong OS in metastatic CRPC, including cytotoxic chemotherapy, abiraterone acetate, enzalutamide, and systemic radiotherapy.

Table 10: Overall Survival of Patients Treated with Either ZYTIGA in Combination with Prednisone or Placebos in LATITUDE (Intent-to-Treat Analysis)

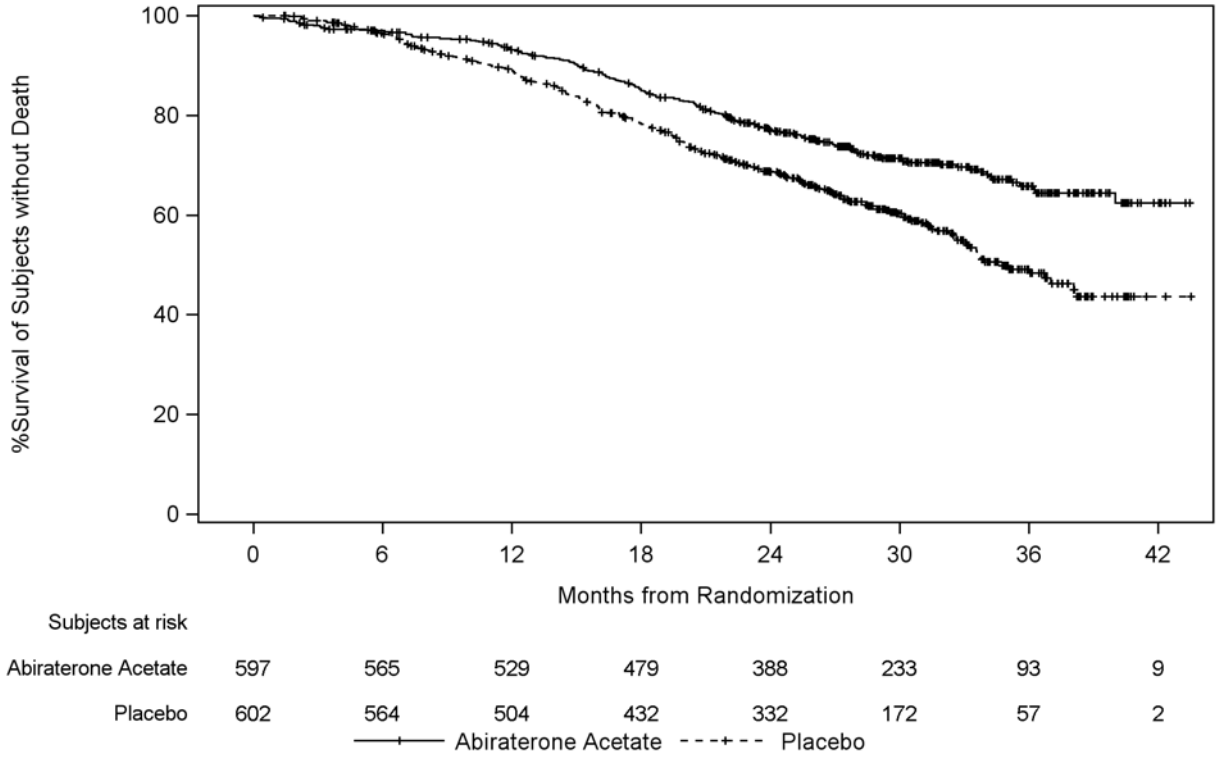
Overall Survival	ZYTIGA with Prednisone (N=597)	Placebos (N=602)
Deaths	169 (28%)	237 (39%)
Median survival (months) (95% CI)	NE	34.7 (33.1, NE)
p-value[1]	< 0.0001	
Hazard ratio[2] (95% CI)	0.621 (0.509, 0.756)	

NE=Not estimable.

[1] p value is from log-rank test stratified by ECOG PS score (0/1 or 2) and visceral (absent or present)

[2] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA with prednisone.

Figure 4: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population in LATITUDE



The major efficacy outcome was supported by a statistically significant delay in time to initiation of chemotherapy for patients in the ZYTIGA arm compared to those in the placebos arm. The median time to initiation of chemotherapy was not reached for patients on ZYTIGA with prednisone and was 38.9 months for patients on placebos (HR = 0.44; 95% CI: [0.35, 0.56], $p < 0.0001$).

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYTIGA® (abiraterone acetate) Tablets are available in the strengths and packages listed below:

- **ZYTIGA® 500 mg film-coated Tablets**
  Purple, oval-shaped tablets debossed with "AA" one side and "500" on the other side.
  NDC 57894-195-06 60 tablets available in high-density polyethylene bottles
- **ZYTIGA® 250 mg film-coated Tablets**
  Pink, oval-shaped tablets debossed with "AA250" on one side.
  NDC 57894-184-12 120 tablets available in high-density polyethylene bottles
- **ZYTIGA® 250 mg uncoated Tablets**
  White to off-white, oval-shaped tablets debossed with "AA250" on one side.
  NDC 57894-150-12 120 tablets available in high-density polyethylene bottles

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

Keep out of reach of children.

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Women who are pregnant or women who may be pregnant should not handle ZYTIGA 250 mg uncoated tablets or other ZYTIGA tablets if broken, crushed, or damaged without protection, e.g., gloves *[see Use in Specific Populations (8.1)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Hypertension, Hypokalemia, and Fluid Retention

- Inform patients that ZYTIGA is associated with hypertension, hypokalemia, and peripheral edema. Advise patients to report symptoms of hypertension, hypokalemia, or edema to their healthcare provider *[see Warnings and Precautions (5.1)]*.

Adrenocortical Insufficiency

- Inform patients that ZYTIGA with prednisone is associated with adrenal insufficiency. Advise patients to report symptoms of adrenocortical insufficiency to their healthcare provider *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

- Inform patients that ZYTIGA is associated with severe hepatotoxicity. Inform patients that their liver function will be monitored using blood tests. Advise patients to immediately report symptoms of hepatotoxicity to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Dosing and Administration

- Inform patients that ZYTIGA is taken once daily with prednisone (once or twice daily according to their healthcare provider's instructions) and to not interrupt or stop either of these medications without consulting their healthcare provider.
- Inform patients receiving GnRH therapy that they need to maintain this treatment during the course of treatment with ZYTIGA.
- Instruct patients to take ZYTIGA on an empty stomach, either one hour before or two hours after a meal. ZYTIGA taken with food causes increased exposure and may result in adverse reactions. Instruct patients to swallow tablets whole with water and not to crush or chew the tablets *[see Dosage and Administration (2.3)]*.

- Inform patients that if they miss a dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, inform patients to contact their healthcare provider *[see Dosage and Administration (2.3)]*.

Fetal Toxicity

- Inform patients that ZYTIGA may harm a developing fetus. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 weeks after the final dose of ZYTIGA *[see Use in Specific Populations (8.1)]*.
- Women who are pregnant or women who may be pregnant should not handle ZYTIGA 250 mg uncoated tablets or other ZYTIGA tablets if broken, crushed, or damaged without protection, e.g., gloves *[see Use in Specific Populations (8.1) and How Supplied/Storage and Handling (16)]*.

Infertility

- Advise male patients that ZYTIGA may impair fertility *[see Use in Specific Populations (8.3)]*.

500 mg Tablets
Manufactured by:

Patheon France S.A.S.

Bourgoin Jallieu, France

250 mg Tablets
Manufactured by:
Patheon Inc.

Mississauga, Canada

Manufactured for:

Janssen Biotech, Inc.

Horsham, PA 19044

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