# CLINICAL REVIEW

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| Application Type | NDA |
| Application Number(s) | 20-239/S-023 |
| Priority or Standard | Standard |
| Submit Date(s) | 30 March 2010 |
| Received Date(s) | 31 March 2010 |
| PDUFA Goal Date | 30 April 2011 |
| Division / Office | ODE III/DGIEP (HFD-180) |
| Reviewer Name(s) | Karyn L. Berry, MD, MPH |
| Review Completion Date | 05 April 2011 |
| Established Name | Granisetron |
| (Proposed) Trade Name | Kytril |
| Therapeutic Class | 5-$HT_3$ receptor antagonist |
| Applicant | Hoffman-La Roche |
| Formulation(s) | Intravenous |
| Dosing Regimen | Administered as a 30 second I.V. infusion delivered (b) (4) |
| Indication(s) | Prevention of postoperative nausea and vomiting (PONV) |
| Intended Population(s) | Pediatric (aged 2 to 16 years) |

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

Based on my review of the clinical data, I recommend that the Kytril I.V. label be updated to include a description of the clinical trial including adverse reactions and the limitations that prevent interpretation of the safety and efficacy data. (b) (4)

I also concur with recommendations from the Division of Medication Error, Prevention and Analysis (DMEPA), the Division of Drug Marketing, Advertising, and Communications (DDMAC) and the Division of Risk Management (DRISK) on conversion of the Kytril I.V. label to the PLR format.

## 1.2 Risk Benefit Assessment

The Applicant conducted trial ML16633 to fulfill a Pediatric Research Equity Act (PREA) commitment. A single exploratory study, ML16633, was submitted to evaluate the use of Kytril 20 mcg/kg I.V. and 40 mcg/kg I.V. in providing total control of PONV (no nausea, no vomiting and no use of rescue medication) in the first 2 hours after surgery in pediatric patients aged 2 to 16 years who were undergoing outpatient tonsillectomy or adenotonsillectomy. A key secondary efficacy endpoint was the proportion of patients with total control during the 24 hours following surgery. Total control of PONV during the first 2 hours after surgery was observed in 85.7% and 90.4% in the 20 mcg/kg and 40 mcg/kg dose groups respectively. Total control of PONV during the 24 hours after surgery was observed in 65.7% and 61.6% in the 20 mcg/kg and 40 mcg/kg dose groups respectively. There were however a number of limitations related to the design of Protocol ML16633 that affected the overall adequacy of this trial. The most significant is the lack of an active comparator.

Safety issues were also identified during the review of this submission. They included prolongation of QT interval and the use of higher Kytril I.V. doses than what is currently approved. QT prolongation was seen at both the 20 mcg/kg and 40 mcg/kg dose levels. Five patients experienced an increase of ≥ 60 msec in QTcF. In addition, there were two patients whose QTcF was ≥ 500 msec.

In the absence of an active comparator and lack of a dose response, the data is inconclusive and not adequate to determine the most effective dose of Kytril I.V. for the prevention of PONV in the pediatric population.

(b) (4)

The safety and efficacy of Kytril I.V. in the prevention of PONV in pediatric patients were not established in this clinical trial and the label should reflect this.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommendations for postmarket risk evaluation and mitigation strategies.

### 1.4 Recommendations for Postmarket Requirements and Commitments

The safety and efficacy of Kytril I.V. for the prevention of PONV in the pediatric population has not been adequately studied. In addition, pharmacokinetics (PK) in pediatric surgical patients has not been studied. ECG changes, including QT interval prolongation, which are class effects of 5-$HT_3$ receptor antagonist, were observed in this trial. These effects may be of particular concern in patients with co-morbidities or receiving drugs that are known to prolong the QT interval and warrant additional evaluation. The QT effect of Kytril I.V. should be assessed with a thorough QT (tQT) trial.

This reviewer recommends the following:

Postmarket Requirement:

- A thorough QT (tQT) trial to assess the QT effect of Kytril I.V.

Postmarket Commitment:

- An adequate and well controlled clinical trial in pediatric patients aged 0 to 16 that is designed to evaluate PK, safety and efficacy (b) (4) of Kytril I.V. (b) (4) compared to an active control.

## 2 Introduction and Regulatory Background

PONV is defined as nausea and/or vomiting that occurs within 24 hours after surgery. PONV are complications which cause discomfort and distress for both patients and their families. PONV occurs more frequently in children than in adults [1]. In the pediatric

1 Rose JB, Watcha MF. Postoperative nausea and vomiting in paediatric patients. Br J Anaesth 1999; 83:104-117.

population, the occurrence of PONV increases with age, having an incidence of 5% in infants and a peak incidence of 34% to 50% in school-aged children [1]. Persistent postoperative vomiting can cause tension on sutures and potential dehiscence, pulmonary aspiration of gastric contents, dehydration, and electrolyte imbalance, all leading to delayed discharge or unplanned hospitalization and increased utilization of resources.

In children, tonsillectomy and adenotonsillectomy are among the most common surgical procedures and are associated with an incidence of PONV ranging from 50% to 89% [2]. Factors that increase the risk of PONV in children include age, history of motion sickness or previous postoperative emesis, certain types of surgical procedures, duration of surgery, certain anesthetic medications, postoperative pain, opioid analgesics, and anxiety [1].

Two 5-$HT_3$ receptor antagonists (ondansetron and dolasetron) have been approved to reduce the incidence of PONV in children. Other antiemetic drugs including anticholinergics, antihistamines, benzamides, butyrophenones, and phenothiazines have been evaluated for the prevention of PONV in children. However, undesirable side effects such as excessive sedation, dysphoria, and extrapyramidal symptoms limit the use of these drugs [3].

A review of the literature indicates that granisetron I.V., has been studied at various doses (10 mcg/kg to 100 mcg/kg) for the prevention of PONV in the pediatric population. There is no current consensus on the preferred granisetron dose for the prevention of PONV in pediatric patients. The Applicant stated that this Phase 4 pediatric trial (ML 16633) was designed to 1) estimate the effectiveness of granisetron 20 mcg/kg and 40 mcg/kg in preventing PONV and 2) evaluate safety, with primary concern during the 2 hour interval following extubation (end of surgery).

PREA

Two PREA requirements were established with approval of NDA 20-239/S-008 for the prevention of PONV in adults (August 16, 2002). This application is submitted as a response to PREA requirement #2. The original PREA requirements were:

1. Deferred pediatric study for the treatment of postoperative nausea and vomiting in pediatric patients aged 2 to 16 years.

2 Aouad MT, Siddik SS. The effect of dexamethasone on postoperative vomiting after tonsillectomy. Anesth Analg 2001;92:636-40.

3 Watcha MF, White PF. Postoperative Nausea and Vomiting, its etiology, treatment and prevention-Review article. Anesthesiology 1992; 77:162-184.

2. Deferred pediatric study for the prevention of postoperative nausea and vomiting in pediatric patients aged 2 to 16 years.

In January 2007, the Applicant was granted a waiver for conducting pediatric studies for the treatment of PONV in patients aged 2 to 16 years. The Applicant was released from this requirement based upon the Division's concurrence that 1) there are currently other available treatments for this condition and 2) the similarity of responses between adults and children as evidenced from prior studies.

A Pediatric Review Committee (PeRC) meeting held on November 17, 2010 determined that the submitted pediatric trial fulfilled the PREA requirement for the prevention of PONV.

Labeling supplements
On February 5, 2009, the Applicant submitted prior approval labeling supplements (NDA 20239/S-021; (b) (4); NDA 20239/S-007) to revise the label based on a comprehensive assessment of clinical events, including spontaneous reports that may indicate QT prolongation in patients who received Kytril I.V. in protocol ML16633. On October 7, 2009, after a review by the QT-Interdisciplinary Review Team (IRT) and the Office of Surveillance and Epidemiology (OSE), the Kytril labels were updated to include information on QT prolongation in the PRECAUTIONS, Drug Interactions, ADVERSE REACTIONS and Postmarketing Experiences sections of the label.

## 2.1 Product Information

(b) (4) Trade Name: Kytril Injection

(b) (4) Indication: Prevention of PONV in pediatric patients.

(b) (4) Age Group: Pediatric (aged 2 to 16 years)

Pharmacologic Class: 5-$HT_3$ receptor antagonist

Route of Administration, Description, and Formulation: Administered as a 30 second I.V. infusion delivered (b) (4))

(b) (4) Treatment Regimen: The Applicant has not proposed a treatment regimen.

Current Indications and Dosing of Kytril I.V.:

Kytril (granisetron hydrochloride) injection, a selective 5-$HT_3$ receptor antagonist, is an anti-nauseant and antiemetic agent. It is indicated for:

- The prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high dose cisplatin.

- The prevention and treatment of post-operative nausea and vomiting in adults.

The recommended dosages for Kytril I.V. for the prevention of CINV in adults and pediatric patients aged 2 to 16 years is 10 mcg/kg administered intravenously within 30 minutes before the initiation of chemotherapy and only on the day(s) chemotherapy is given. Pediatric patients under aged 2 years have not been studied.

The recommended dose of Kytril I.V. for the prevention of PONV in adults is 1 mg, administered intravenously over 30 seconds, before induction of anesthesia or immediately before reversal of anesthesia.

The recommended dose of Kytril I.V. for the treatment of PONV after surgery in adults is 1 mg administered over 30 seconds.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently two 5-HT3 receptor antagonist drugs (ondansetron and dolasetron) that are FDA approved for the prevention of post operative nausea and vomiting in the pediatric population.

**Table 1: 5-HT3 receptor antagonist for the prevention of PONV in the pediatric population**

| Drug | Formulation/Strength | NDA#/Approval Date | PONV Pediatric Labeling/Dose |
|---|---|---|---|
| Zofran (ondansetron) | I.V. 2 mg/mL | N20-007 (1/4/91) | 1 month -12yrs (≤ 40 kg- 0.1 mg/kg; > 40 kg- 4mg) |
| | Injection Pre-mixed 32 mg/50 mL | N20-403 (1/31/95) | |
| Anzemet (dolasetron) | I.V. 20 mg/mL | N20-624 (9/11/97) | 2 yrs – 16 yrs (0.35mg/kg up to a max of 12.5 mg) |
| | Tablet 50 mg & 100 mg | N20-623 (9/11/97) | 2 yrs – 16 yrs (1.2mg/kg up to a max of 100 mg) |

Reviewer's table

Other antiemetic drugs used for the prevention of postoperative nausea and vomiting in children include dexamethasone, dimenhydrinate, perphenazine, and droperidol [4].

## 2.3 Availability of Proposed Active Ingredient in the United States

Granisetron is available in injectable, oral tablets, oral solution and transdermal formulations. It is indicated for the prevention of chemotherapy induced nausea and vomiting (CINV), the prevention of radiation induced nausea and vomiting (RINV) and PONV.

Granisetron Injection (10 mcg/kg) was approved for use in the United States for the prevention of CINV in pediatric and adult patients in December 1993. Granisetron Tablets were approved in March 1995 for the prevention of CINV in adult patients, and in July 1999 it was approved for the prevention of adult RINV. In June 2001, Granisetron Oral Solution was approved for the prevention of CINV and RINV in adult patients. In August 2002, Granisetron Injection was approved for the prevention and treatment of post operative nausea and vomiting in adult patients. Transdermal granisetron was approved in September 2008 for prevention of acute onset CINV in adults receiving moderately emetogenic chemotherapy and highly emetogenic chemotherapy.

**Table 2: Granisetron Approved Indications**

| Granisetron Formulation | Chemotherapy Induced Nausea and Vomiting | Radiation Therapy Induced Nausea and Vomiting | Post Operative Nausea and Vomiting (adults only) | Dose | Approved Age |
|---|---|---|---|---|---|
| Injection | December 1993 | NA | August 2002 | 10 mcg/kg (1 mg/ml) | Pediatric (prevention of CINV only) & Adult |
| Tablets | March 1995 | July 1999 | NA | 2 mg tab PO QD or 1 mg tab PO BID | Adult |
| Oral Solution | June 2001 | June 2001 | NA | (2 mg/10 ml) 10 ml QD or 5 ml BID | Adult |
| Transdermal | September 2008 | NA | NA | Apply 1 patch for up to 7days | Adult |

4 Kovac AL. Management of postoperative nausea and vomiting in children. Pediatr Drugs 2007;9(1):47-69.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Although 5-HT3 receptor antagonists are generally perceived as safe, they have been associated with severe cardiovascular adverse events, such as QT prolongation and cardiac arrhythmias. To date, there has not been a thorough QT trial for Kytril I.V.

In the UK, Kytril I.V. is indicated for the prevention or treatment of CINV for adults and children of an unspecified age range and for the prevention and treatment of PONV in adults only. The recommended intravenous dose for both prevention and treatment of CINV in children is a single dose of 40 mcg/kg body weight (up to 3mg).

In December 2010, the FDA contraindicated the use of dolasetron I.V. in adults and children for the prevention of CINV due to serious cardiac arrhythmias, i.e. prolonged QT interval. The European Medicines Agency (EMEA) has contraindicated the use of dolasetron in pediatric patients because of serious cardiovascular events associated with its use.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Drug development occurred under IND 31,707. Below is a summary of regulatory guidance and advice provided by the Agency.

April 21, 2005
The proposed pediatric study (Protocol ML 16633A) was submitted by the Applicant to the FDA to satisfy the PREA post-marketing commitment for the adult PONV indication.

May 12, 2005 (Advice letter)
The FDA recommended including in the protocol two blood draws (pre-surgery and 24 hours post surgery) form each patient for hematology and blood chemistry assessment.

July 6, 2005
The Applicant submitted results of a feasibility study with 10 investigators participating in the trial that indicated that patients would not return to the hospital/clinic for the 24 hour post surgery blood draw. The investigators also believed that parents would not allow their children to be subjected to another blood draw subsequent to release from the hospital/clinic. Based on these results, the Applicant proposed that the second blood draw be obtained just prior to discharge from the hospital/clinic.

July 22, 2005 (Advice Letter)
The FDA presented five recommendations to the proposed protocol. These recommendations were:

1. Use an approved active comparator or, as an alternative, demonstrate the 40 mcg/kg dose level to be clinically and statistically superior to the 20 mcg/kg dose level.

2. Define specific oral antiemetics to be used as rescue therapy.

3. Include "total control" (no nausea, vomiting and no rescue therapy) for the 0-2 hours and 0-24 hours time period as a primary efficacy endpoint.

4. An alternative to using "total control" as a primary endpoint would be to include a 24-hour "no-vomiting" assessment as part of the primary endpoint.

5. Justify the use of granisetron I.V. (10 mcg/kg) as rescue therapy.

October 31, 2005 (Advice letter)
The FDA agreed to pre- and post-operative blood draws, with the post-operative blood draw occurring just prior to leaving the hospital/clinic. The Applicant was also reminded of the recommendations in the Agency's letter dated July 22, 2005

December 22, 2005
The Applicant submitted correspondence agreeing to amend the protocol based on Agency recommendations for #2 and #5 (see July 22, 2005). Regarding recommendation #1, the Applicant stated that evaluating granisetron in a head-to-head comparison with an active comparator (i.e. 5-HT3 antagonist approved for pediatric PONV prevention) would require a very large sample size and would therefore cause delays in study conduct and subsequently in the availability of safety and efficacy information. Regarding recommendations #3 and #4, the Applicant responded that they agreed with 1) deleting the primary endpoint of no vomiting from 0 to 2 hours, 2) adding the primary endpoint of total control (no vomiting, no nausea, no use of rescue mediation) from 0 to 2 hours, 3) adding the secondary endpoint of no vomiting from 0 to 2 hours and 4) adding the secondary endpoint of total control from 0 to 24 hours. The Applicant stated that capturing total control data in the 0 to 24 hour period would possibly be compromised by limitations of symptom reporting by parents/legal guardian and therefore did not agree with adding total control from 0 to 24 hours as a primary endpoint. The Applicant maintained total control from 0 to 24 hours as a secondary endpoint.

May 10, 2006 (Advice letter)
The Division responded to the Applicant's submission of December 2005. Regarding recommendation 1, the FDA reiterated to the Applicant the recommendation that the protocol utilize an approved active comparator. This was based on the FDA's concern that if the efficacy results of both the 20 mcg/kg and the 40 mcg/kg doses were similar, it would be impossible to determine if both dose levels of granisetron were equally effective or equally ineffective. The Agency recommended that one path forward would be to add a relevant historical control. The Agency found the Applicant's proposals for recommendations #3 and #4 acceptable. The FDA also recommended collecting pre- and post-dosing ECGs to address concerns about QT issues in this class of drugs.

### 2.6 Other Relevant Background Information

A written request (WR) was issued to the Applicant in December 2002 for granisetron I.V. PK studies in pediatric surgical patients. (b) (4)
On August 24, 2005, a meeting was held with PdIT and the Division to discuss whether the WR should be referred to the Foundation for the NIH (FNIH) under Section 4 of the Best Pharmaceuticals for Children Act (BPCA). It was determined by the Division and PdIT that there was not an adequate public health benefit to warrant referral to FNIH.

The Applicant submitted an email to the Division on November 15, 2010 in which they stated that they are "no longer selling or distributing any version of Kytril."

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission is acceptable.

### 3.2 Compliance with Good Clinical Practices

According to the Applicant, the clinical trial was conducted in accordance with the US Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRBs (21 CFR 56) and the obligations of clinical investigators (21 CFR 312). This trial was also conducted in accordance with US Title 21 CFR on Good Clinical Practices (GCPs) which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization and the Food and Drug Administration.

No clinical site inspections were requested from the Division of Scientific Investigations (DSI).

### 3.3 Financial Disclosures

The Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Applicant also certified that each clinical investigator had no proprietary interest in this product or significant equity in the Applicant as defined by 21 CFR 54.2(b). As defined by 21 CFR 54.2(f), the Applicant certified that no clinical investigator was the recipient of any significant payments of any other sorts.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

No new data was submitted by the Applicant

## 4.2 Clinical Microbiology

No new data was submitted by the Applicant

## 4.3 Preclinical Pharmacology/Toxicology

No new data was submitted by the Applicant

## 4.4 Clinical Pharmacology

No new data was submitted by the Applicant.

### 4.4.1 Mechanism of Action

No new data was submitted by the Applicant.

### 4.4.2 Pharmacodynamics

No pediatric pharmacodynamic (PD) studies were conducted for this submission.

### 4.4.3 Pharmacokinetics

No pediatric pharmacokinetic (PK) studies were conducted for this submission.

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

**Table 3: Clinical Trial**

| Trial Code<br><br>Number of trial centers<br><br>Location(s) | Trial design | Trial Objective(s) | Test Product(s); Dosage Regimen; Route of Administration | Number of patients | Subjects/Patients | Treatment/ Duration | Primary Efficacy Endpoint(s) |
|---|---|---|---|---|---|---|---|
| ML 16633<br><br>8 trial centers<br><br>USA | Prospective, randomized, double-blind, parallel-group | Primary:<br>Estimate effectiveness of two dose levels in preventing PONV during the 2 hr following extubation<br><br>Secondary:<br>Estimate effectiveness of the two dose level during 24 hr following extubation<br><br>Exploratory:<br>Pre-post dose QT intervals and Chem-21 lab assessment | Granisetron 20 mcg I.V. & 40 mcg/kg I.V. | Planned: 170<br>Enrolled: 171<br>Treated: 157<br>79 in 20mcg/kg<br>78 in 40mcg/kg | Children aged 2 to 16 yrs with an American Society of Anesthesiologists physical status classification of 1 to 3 who were undergoing elective surgery for tonsillectomy or adenotonsillectomy | Granisetron 20 or 40 mcg/kg body weight, delivered in a single 5-mL 30-sec IV infusion approximately 15 min prior to extubation | Proportion of subjects with total control of PONV (no vomiting, no nausea, & no rescue medication) during the 2-hr following the time of extubation |

## 5.2 Review Strategy

A review of the clinical trial was performed using the Applicant's submitted data. The trial was reviewed by the medical reviewer and compared to the results reported in the Applicant's safety and efficacy reports and with the drug's established safety profile.

Other sources of clinical data consulted in this review include:

- Electronic submission of the medical section of the NDA (including narratives and case report forms)
- Electronic submitted data sets
- Literature review

## 5.3 Discussion of Individual Studies/Clinical Trials

The Applicant conducted and submitted one clinical trial study report.

Protocol Synopsis: – Protocol Number: ML16633

Study Title: Intravenous granisetron (Kytril) in the prevention of post-operative nausea and vomiting (PONV) in pediatric subjects undergoing tonsillectomy or adenotonsillectomy

Name of investigational product: Kytril (Granisetron) I.V.

Indication studied: Prevention of PONV in pediatric patients

Study sponsor: Roche

Protocol No.: ML16633

Study Period: April 16, 2007 to December 20, 2007

Clinical Phase: Phase 4

Investigators: This trial was conducted at 8 centers in the United States. A total of 170 patients aged 2 to 16 years (85 per treatment group) were planned. 171 patients were enrolled and 157 were treated (79 in the 20 mcg/kg group and 78 in the 40 mcg/kg group).

Study Objectives: The primary efficacy objective was to evaluate the effectiveness of two dose levels of I.V. granisetron (20 mcg/kg and 40 mcg/kg) in preventing PONV, defined as total control (i.e. no nausea, no vomiting, and no use of rescue medication) during the 2-hour interval following the time of extubation (end of surgery) in children aged 2 to 16 years.

The primary efficacy objective was clarified with Amendment B (January 26, 2007).

The secondary efficacy objective was to evaluate the effectiveness of two dose levels of I.V. granisetron (20 and 40 micrograms/kg) in preventing PONV during the 24-hour interval following the time of extubation (end of surgery) in children aged 2 to 16 years, based on specified secondary endpoints.

The exploratory objectives were to describe QT intervals (as determined by 12 lead ECGs) and Chem 21 laboratory assessments in study subjects before and after dosing.

The safety objective was to examine the safety profile of granisetron I.V. in children undergoing tonsillectomy or adenotonsillectomy.

Study Design:
This was a prospective, multicenter, randomized, double-blind study of two dose levels of granisetron in children undergoing elective surgery for tonsillectomy or adenotonsillectomy.

The study consisted of a ≤ 14-day screening period, baseline assessments performed on the day of surgery, a 24-hour treatment evaluation period following extubation (end of surgery), and a safety follow-up contact 15 days after surgery. After screening and confirmation of eligibility, study subjects were randomized to receive granisetron 20 mcg/kg or 40 mcg/kg as a single 30-second I.V. injection approximately 15 minutes prior to the time of extubation (end of surgery). Prior to surgery, vital signs, Chem-21 laboratory tests, a urine pregnancy test for females of childbearing potential if indicated, and 12-lead ECG were assessed. Subjects were monitored for occurrence of vomiting, complaints of nausea, use of rescue medication, and other adverse events during the study, with postoperative monitoring occurring at 2 hours after extubation, immediately prior to discharge from the post-anesthesia care unit (PACU), and by telephone at 24 hours after extubation. Chem-21 laboratory tests and vital signs were assessed immediately prior to PACU discharge. Subjects were contacted 15 days after the 24-hour treatment evaluation period for adverse events.

Protocol Amendments: The original protocol (version A) was amended three times, on 26 January 2007 (Version B), 8 May 2007 (Version C), and 2 July 2007 (Version D).

Amendment B (26 January 2007) consisted of changes to the primary, secondary, and exploratory objectives and endpoints, changes to the use of rescue treatment, the addition of laboratory and ECG assessments, and a number of clarifications.

Amendment C (8 May 2007) consisted of a correction to the intraoperative and post-operative doses of I.V. hydromorphone to be given as PACU analgesia.

Amendment D (2 July 2007) consisted of clarification noting that intraoperative neuromuscular blockade was optional and that study subjects who received it would also receive a neuromuscular blockade reversal agent.

Study Population:
The target population included children aged 2 to 16 years with an American Society of Anesthesiologists (ASA) physical status classification of 1 to 3 who were undergoing elective surgery for tonsillectomy or adenotonsillectomy that required general anesthesia and endotracheal intubation.

Additional Inclusion criteria:

- Male or female
- Scheduled for hospital admission for ≤ 24 hours
- Willing and able to be under medical supervision for at least 2 hours postoperatively
- Willing and able (or have parents/legal guardians willing and able) to undergo telephone contact for follow-up 24 hours after hospital discharge
- Have parent(s) or legal guardian(s) willing and able to sign the informed consent

form
- For capable subjects, willing to sign the assent form

Exclusion criteria:

- Received a prohibited medication within the 24 hours prior to surgery or were scheduled to receive such drugs during surgery or within the 24 hours following surgery (except as rescue medication)
- Had a known allergy or other contraindication to the use of granisetron or any of its components
- Had a known allergy to any 5-$HT_3$ receptor antagonist
- Were allergic to any of the intraoperative medications
- Experienced retching or vomiting in the 24 hours prior to anesthesia
- Had a history of motion sickness or PONV
- Had any of the following medical conditions:
    - Congenital heart disease
    - Juvenile-onset diabetes mellitus
    - Congenital endocrine, kidney, or metabolic disorder
    - Active or previously treated brain tumor (benign or malignant)
    - Gastrointestinal dysmotility or gastrointestinal reflux
    - Central nervous system dysfunction
    - Recurrent seizures or seizure disorder
    - Migraines
    - Symptomatology suggestive of clinically significant obstructive sleep apnea
- Body weight > 70 kg and/or greater than the $95^{th}$ percentile for their respective age
- Pregnant or breast feeding
- Scheduled to undergo additional concurrent medical/surgical procedures (e.g., myringotomy, bronchoscopy)
- Unwilling or unable to comply with the protocol
- Received an active investigational drug within 30 days of study entry or were currently participating in a study and/or receiving an investigational product

Trial Medication:
All subjects were to receive a single 30-second I.V. infusion of 5 mL granisetron solution approximately 15 minutes prior to the time of extubation (end of surgery). Subjects were randomized to one of two granisetron doses:
- Granisetron 20 mcg/kg
- Granisetron 40 mcg/kg

Granisetron was to be diluted in normal saline according to subject's body weight. The maximum allowable granisetron dose of 3 mg was removed with Amendment B.

Trial Assessments and Procedures:

Screening Procedures

Informed consent and assent were obtained before any study assessment and preferably prior to the actual day of surgery. Screening assessments for determining eligibility and for safety were to be completed within 14 days prior to surgery, and all eligibility criteria were to be verified on the day of and prior to surgery. An Eligibility Screening Form documenting fulfillment of the entry criteria for each subject considered for the study was to be completed by the investigator and forwarded to Roche, whether or not the subject was subsequently included.

During screening, demographic data (gender, date of birth, race, diagnosis, and type of surgery) were collected along with a complete medication and medical history and a history of motion sickness and/or PONV. A physical examination was performed, body height and weight measured, and vital signs (blood pressure, pulse, respiratory rate, and body temperature) recorded.

Eligible subjects were required to fast as per ASA guidelines. Final checking of evaluability criteria and assessments of vital signs were performed prior to anesthesia on the day of surgery. Female subjects of childbearing potential were to have a urine pregnancy test performed if clinically indicated.

Surgery Treatment Evaluation Period and Follow-up

Anesthesia was to be induced and I.V. access established. A pre-operative blood draw for Chem-21 laboratory assessments and 12-lead ECG were performed. A single dose of study drug (granisetron 20 or 40 mcg/kg) was to be administered as a 30-second I.V. infusion approximately 15 minutes prior to the time of extubation (end of surgery). All subjects were to be intubated, and at the end of surgery, gastric contents were to be suctioned. Prior to discontinuation of I.V. access and anesthesia reversal, postoperative 12-lead ECG and blood draw for Chem-21 laboratory assessments were to be performed. Subjects were required to remain under medical supervision for at least 2 hours after surgery and were evaluated for 24 hours after the time of extubation (end of surgery).

During the 24-hour treatment evaluation period, the onset time of each vomiting (including retching) episode and complaint of nausea was to be recorded. Vomiting at the time of extubation was not considered prophylaxis failure. Any episodes of vomiting or complaints of nausea that occurred from extubation up to 2 hours after extubation were to be recorded on the CRF by study staff at the 2-hour assessment. Any occurrences from the 2-hour assessment up to PACU discharge were to be recorded at the PACU discharge assessment along with the time of PACU discharge. The time of hospital discharge was also to be recorded. A follow-up interview was to be conducted by telephone approximately 24 hours after the time of extubation to record the time and

frequency of any nausea, vomiting, and/or adverse event occurring from PACU discharge up to the end of the 24-hour treatment evaluation period. Subjects who experienced symptoms of PONV after extubation were to be managed at the discretion of the investigator using an antiemetic agent other than a 5-$HT_3$ receptor antagonist. Any rescue medication used from the time of extubation up to 24 hours after extubation were to be recorded (name, dose, route, and time of administration). A follow-up telephone call to the subject was to be made 15 days after the end of the treatment evaluation period to record any adverse events.

Subjects were monitored for 24 hours after the time of extubation (end of surgery) for complaints of nausea, occurrences of vomiting (including retching), and use of rescue medication. Each episode of nausea or vomiting was to be recorded with the time of the episode. Also to be recorded were the name, dose, route, and time of administration of all rescue medication.

- Vomiting/retching: Vomiting was defined as the expulsion of stomach contents. Retching was defined as an involuntary attempt to vomit that was not productive of stomach contents. Vomiting and/or retching separated by less than a 5-minute interval were counted as a single vomiting episode.

- Nausea: Nausea was defined as a relatively unpleasant sensation associated with flushing, tachycardia, and an awareness of the urge to vomit. Nausea separated by less than a 5-minute interval was counted as a single complaint of nausea.

Primary Efficacy Endpoint:
The primary efficacy endpoint was the proportion of subjects with total control of PONV (i.e., no vomiting, no nausea, and no use of rescue medication) during the 2-hour interval following the time of extubation (end of surgery). The endpoint was changed from evaluating no vomiting to evaluating total control with Amendment B to the protocol.

The Applicant was not able to provide clarification on how nausea was assessed in younger children.

Secondary Efficacy Endpoint:
Secondary efficacy endpoints included:

- Proportion of subjects with total control of PONV (i.e., no vomiting, no nausea, no use of rescue medication) during the 24 hours following the time of extubation (end of surgery) (changed from no vomiting only with Amendment B)
- Proportion of subjects with no vomiting during the 2-hour interval following the time of extubation (end of surgery) (added with Amendment B)
- Proportion of subjects with vomiting from the time of extubation until PACU

discharge (added with Amendment B)
- Proportion of subjects with no vomiting during the 24 hours following the time of extubation (end of surgery) (added with Amendment B)
- Time to first vomiting episode following the time of extubation
- Proportion of subjects with no complaints of nausea during the 2-hour interval following the time of extubation (end of surgery) (added with Amendment B)
- Proportion of subjects with no complaints of nausea from the time of extubation until PACU discharge (added with Amendment B)
- Proportion of subjects with no complaints of nausea during the 24 hours following the time of extubation (end of surgery)
- Proportion of subjects requiring rescue medication from the time of extubation until PACU discharge (changed with Amendment B)
- Time to first use of rescue medication from the time of extubation until PACU discharge (changed with Amendment B)

The Applicant indicated that secondary efficacy endpoints were added to the protocol with Amendment B to support the secondary objective. The secondary endpoint regarding the resolution of symptoms following granisetron rescue medication was removed with Amendment B because granisetron 10 mcg/kg was no longer included as rescue medication.

Exploratory Endpoints:
The exploratory endpoints, added with Amendment B, were safety endpoints and included:

- QT intervals as determined by 12-lead ECG before and after dosing
- Chem-21 laboratory assessments before and after dosing

Safety Endpoints:
Safety endpoints included: monitoring for clinical adverse events, including Serious Adverse Events (SAEs), clinical laboratory tests (Chem-21 panel), 12-lead ECG, measurement of vital signs and physical examination.

Statistical Hypothesis and Analysis Populations:
The Applicant stated that there was no formal hypothesis for this exploratory trial.

The Applicant defined three analysis populations:

- Evaluable population: included all randomized subjects who received their single dose of study treatment and had a post dose assessment of nausea, vomiting, or use of rescue medication in the 24 hours following extubation.

- Safety population**:** included all randomized subjects who received their single dose of study treatment.

- All-subjects population: included all subjects enrolled in the study, whether or not they were randomized.

All analyses of efficacy were based on the evaluable population. Results for the primary efficacy endpoint (proportion of subjects with total control of PONV during the 2 hours following extubation) and other binary efficacy measures (secondary efficacy endpoints based on proportions) were summarized as proportions with the two-sided 95% Clopper-Pearson confidence interval for the proportion for each treatment group.

The pre- and post dose heart rate and PR, QRS, and QT intervals as determined by 12-lead ECG, the corrected QT intervals (QTc), and the changes from baseline (from pre to postdose) were summarized for each treatment group. PR, QRS, and QT intervals were read from the ECG tracing. RR and QTc were derived from the reported heart rate and QT interval,

*Medical Reviewer's comments: This is not an adequate/well designed clinical trial protocol. The Applicant did not use an active control or placebo arm which limits the ability to interpret the data. The Applicant did not conduct a dose finding study and the doses used in the clinical trial, 20 mcg/kg and 40 mcg/kg, are higher than what is currently approved for Kytril I.V. Nausea is a component of the primary efficacy endpoint, but the Applicant was unable to provide clarification on how nausea was assessed in younger children.*

# 6 Review of Efficacy

## ***Efficacy Summary***

The Applicant submitted a prospective, multicenter, randomized, double-blind, parallel group trial that compared the effectiveness of two doses (20 mcg/kg and 40 mcg/kg) of Kytril I.V. in the prevention of PONV in pediatric surgical patients aged 2 to 16. The primary efficacy endpoint was the proportion of patients with total control during the 2 hours following extubation. A key secondary efficacy endpoint was the proportion of patients with total control during the 24 hours following surgery. Total control of PONV during the first 2 hours after surgery was observed in 85.7% and 90.4% in the 20 mcg/kg and 40 mcg/kg dose groups respectively. Total control of PONV during the 24 hours after surgery was observed in 65.7% and 61.6% in the 20 mcg/kg and 40 mcg/kg dose groups respectively.

In this reviewer's assessment, the design of this trial was not adequate to determine the most effective dose of Kytril I.V. for the prevention of PONV in the pediatric population. There was no difference between the rates of total control of PONV between the two

doses of granisetron (20 mcg/kg and 40 mcg/kg) studied. Key issues with the clinical trial design include the absence of a placebo or active comparator and inadequacy of dose finding. The Applicant has not formally demonstrated efficacy of the doses studied.

## 6.1 Indication

The Applicant did not propose a new indication for Kytril I.V. based on the results of the clinical trial. The Applicant proposes to add the results of the clinical trial to the drug label.

### 6.1.1 Methods

The clinical data from trial ML1633 were reviewed to determine whether a clinical benefit was demonstrated in pediatric patients undergoing tonsillectomy or adenotonsillectomy.

### 6.1.2 Demographics

**Table 4: Demographics of Evaluable Population**

| **Demographic Characteristics** | **Kytril 20 mcg/kg (N = 70)** | **Kytril 40 mcg/kg (N = 73)** |
|---|---|---|
| **Age (Yrs)** | | |
| Mean | 6 | 6.2 |
| **Weight (kg)** | | |
| Mean | 24.89 | 25.09 |
| Range | 11.1 – 67.7 | 11.4 – 58.0 |
| **Race (%)** | | |
| White | 74 | 72 |
| Black | 13 | 11 |
| American Indian or Alaskan Native | 6 | 4 |
| **Sex (%)** | | |
| Male | 69 | 41 |
| Female | 31 | 59 |

*Medical Reviewer's comments:*
*The two treatment groups were balanced except for a higher proportion of males in the 20 mcg/kg dose group (69%) and a higher proportion of females in the 40 mcg/kg dose group (59%).*

6.1.3 Subject Disposition

A total of 171 pediatric subjects undergoing elective tonsillectomy or adenotonsillectomy were randomized into the study at eight centers in the United States. Fourteen subjects did not receive study treatment. The remaining 157 subjects (79 and 78 in the granisetron 20 and 40-mcg/kg dose groups, respectively) received study drug approximately 15 min before extubation (end of surgery).

Of those subjects who received study treatment, two (in the 20 mcg/kg dose group) did not complete the 24-hour follow-up, and 10 (five in each dose group) did not complete the 15-day follow-up.

A total of 14 randomized subjects were withdrawn from the study prior to receiving study treatment. Five of these subjects violated an entry criterion (nausea/vomiting or prohibited medication within 24 hours prior to surgery, incorrect surgery). Three subjects refused treatment/did not cooperate/withdrew consent, and others were not treated because of a safety concern or a problem with providing study drug. Ten of the subjects who received study treatment (five in each dose group) did not complete the 15-day follow-up. In all cases, the subject/guardian could not be reached by telephone, because the telephone was disconnected, not answered, or the message was not returned.

**Table 5: Summary of Subject Disposition**

| Status | Kytril 20 mcg/kg N = 87 | Kytril 40 mcg/kg N = 84 |
|---|---|---|
| Not treated | 8 | 6 |
| Reason not treated | | |
| Violation of selection criteria at entry | 3 | 2 |
| Did not cooperate/refused treatment | 1 | 1 |
| Other protocol violation | 0 | 0 |
| Withdrew consent | 1 | 0 |
| Administrative/other | 3 | 2 |
| Adverse event/intercurrent illness | 0 | 1 |
| Treated | 79 | 78 |
| Evaluable | 70 | 73 |
| Not evaluable | 9 | 5 |

| | | |
|---|---|---|
| Reason | | |
| Subject had planned secondary operative procedure | 5 | 0 |
| Subject received NSAIDS | 1 | 5 |
| Subject's weight > 95$^{th}$ percentile for their age | 2 | 0 |
| Subject had hx of migraines | 1 | 0 |

Applicant's table

6.1.4 Analysis of Primary Endpoint(s)

Total control of PONV during the first 2 hours after surgery was observed in most subjects (85.7% and 90.4% in the 20- and 40-mcg/kg dose groups, respectively), with a trend for a larger proportion with the higher granisetron dose (treatment difference of 4.7%).

**Table 6: Proportion of subjects of TC (no nausea, no vomiting and no use of rescue medication) during the two hours following extubation**

| | Kytril 20 mcg/kg N = 70 | Kytril 40 mcg/kg N = 73 | Difference |
|---|---|---|---|
| **Proportion of subjects with TC (0-2 hrs)** | | | |
| n | 60 | 66 | |
| % | 85.7 | 90.4 | 4.7 |
| 95% CI | 0.75 – 0.93 | 0.81 – 0.96 | -0.09 – 0.23 |

*Medical Reviewer's comments:*
*The results demonstrate that the majority of patients in both treatment dose groups (20 mcg/kg and 40 mcg/kg) had total control of PONV during the first 2 hours after surgery. There were a number of limitations related to the design of Protocol ML16633 that affected the overall adequacy of this trial. These include: the lack of an active control or placebo, the use of the literature as the sole basis for dose finding and the Applicant's inability to describe how the nausea component of the total control endpoint was measured, especially in younger children.*

*There are limitations in the ability to assess nausea as a component of the primary endpoint in a pediatric population. Although the Division recommended that the Applicant consider including a component of nausea in the primary endpoint since the indication is "PONV", nausea is difficult to assess in young children. In children post-operative vomiting (POV) is more commonly studied than post-operative nausea. The Applicant was unable to provide information on how nausea was assessed in young children. In multiple advice letters, the Division recommended that the Applicant utilize an active control to assess efficacy. While the Division did not comment on the*

*Applicant's use of the literature to determine the study drug doses (20 mcg/kg and 40 mcg/kg), these doses are potentially higher than what is currently approved in the US.*

6.1.5 Analysis of Secondary Endpoints(s)

Key secondary endpoints that were analyzed include:

- Proportion of subjects with TC over a 24 hour period post-operative

- Vomiting episodes (including retching) during the 2 hours after extubation, from extubation to PACU discharge and over 24 hours following extubation was also a key secondary efficacy endpoint that was analyzed.

Over the 24 hours following extubation, total control was similar in the two dose groups (65.7% and 61.6% respectively) with a higher proportion of total control in the 20 mcg/kg dose group. Over the 24 hours following extubation, most subjects in the 20- and 40-mcg/kg dose groups had no vomiting (70.0% and 68.5%, respectively) and no complaints of nausea (80.0% and 84.9%).

**Table 7: Proportion of subjects with TC over a 24 hour period post-operative**

| | **Kytril 20 mcg/kg N = 70** | **Kytril 40 mcg/kg N = 73** | **Difference** |
|---|---|---|---|
| **Proportion of subjects with TC (0-24 hrs)** | | | |
| n | 46 | 45 | |
| % | 65.7 | 61.6 | -4.1 |
| 95% CI | 0.53 – 0.77 | 0.50 – 0.73 | -0.20 – 0.12 |

**Table 8: Proportion of subjects with no vomiting (evaluable population)**

| | **Kytril 20 mcg/kg N = 70** | **Kytril 40 mcg/kg N = 73** | **Difference** |
|---|---|---|---|
| **Proportion of subjects with no vomiting (0-2 hrs)** | | | |
| n | 61 | 69 | |
| % | 87.1 | 94.5 | 7.4 |
| 95% CI | 0.77 – 0.94 | 0.87 – 0.98 | -0.4 – 0.29 |
| | | | |
| | | | |
| **Proportion of subjects with no vomiting (0-24 hrs)** | | | |
| n | 49 | 50 | |
| % | 70.0 | 68.5 | -1.50 |
| 95% CI | 0.58 – 0.80 | 0.57 – 0.79 | -0.18 – 0.15 |

*Medical Reviewer's comments:*
*Over 24 hours, the proportions of subjects with total control were similar in the two treatment groups and less than observed at 2 hours. The majority of patients in both treatment dose groups had no vomiting during the 2 hours post-surgery (87.1% and 94.5% of patients in the 20- and 40-mcg/kg dose groups, respectively). Over the 24 hours following extubation, the proportion of patients with no vomiting episodes was similar for both dose groups (70.0% and 68.5% of patients in the 20- and 40-mcg/kg dose groups, respectively).*

*The Applicant noted that these secondary endpoints were exploratory and that no hierarchical structure was considered in the analysis.*

**Table 9: Combined Primary and Secondary Efficacy Results**

| | Granisetron 20µg/kg N = 70 | Granisetron 40µg/kg N = 73 | Difference[a] |
|---|---|---|---|
| **Proportion of Patients With Total Control** | | | |
| (0-2 hr) | | | |
| n | 60 | 66 | |
| (%) | (85.7) | (90.4) | 4.7 |
| 95% Confidence Interval[b] | | | -0.09, 0.23 |
| (0-24 hr) | | | |
| n | 46 | 45 | |
| (%) | (65.7) | (61.6) | -4.1 |
| 95% Confidence Interval[b] | | | -0.20, 0.12 |
| **Proportion of Patients With No Vomiting** | | | |
| (0-2 hr) | | | |
| n | 61 | 69 | |
| (%) | 87.1 | 94.5 | 7.40 |
| 95% Confidence Interval[b] | | | -0.04, 0.29 |
| (0-PACU Discharge) | | | |
| n | 64 | 70 | |
| (%) | (91.4) | (95.9) | 4.50 |
| 95% Confidence Interval[b] | | | -0.08, 0.25 |
| (0-24 hr) | | | |
| n | 49 | 50 | |
| (%) | (70.0) | (68.5) | -1.50 |
| 95% Confidence Interval[b] | | | -0.18, 0.15 |
| **Proportion of Patients With No Nausea** | | | |
| (0-2 hr) | | | |
| n | 62 | 69 | |
| (%) | (88.6) | (94.5) | 5.9 |
| 95% Confidence Interval[b] | | | -0.06, 0.27 |
| (0-PACU Discharge) | | | |
| n | 64 | 71 | |
| (%) | (91.4) | (97.3) | 5.9 |
| 95% Confidence Interval[b] | | | -0.04, 0.29 |
| (0-24 hr) | | | |
| n | 56 | 62 | |
| (%) | (80.0) | (84.9) | 4.9 |
| 95% Confidence Interval[b] | | | -0.10, 0.23 |
| **Proportion of Patients With No Rescue Medication Use** | | | |
| (0-PACU Discharge) | | | |
| n | 66 | 71 | |
| (%) | (94.2) | (97.2) | 2.97 |
| 95% Confidence Interval[b] | | | -0.09, 0.23 |

Note: **Total control** is defined as no nausea, no vomiting, and no use of rescue medication.
a Difference in percentages is granisetron 40 µg/kg minus granisetron 20 µg/kg.
b 95% confidence interval for within-group proportion.

Sponsor's table

6.1.6 Other Endpoints

None

6.1.7 Subpopulations

The primary and secondary endpoints were reviewed by age groups (2 years to 6 years, 7 years to 11 years and 12 years to 16 years) and gender. Some of the subgroups have small sample size which limits analysis.

**Table 10: Proportion of Subjects with Total Control by age groups (Evaluable population)**

| | **Kytril 20 mcg/kg N = 51** | **Kytril 40 mcg/kg N = 47** | **Overall** | |
|---|---|---|---|---|
| | | | **Kytril 20 mcg/kg** | **Kytril 40 mcg/kg** |
| **Proportion of subjects with TC (0-2 hrs)** | 2 years – 6 years | | | |
| **n** | 42 | 45 | | |
| **%** | 82.4 | 95.7 | 85.7 | 90.4 |
| | | | | |
| **Proportion of subjects with TC (0-24 hrs)** | | | | |
| **n** | 32 | 31 | | |
| **%** | 62.7 | 66.0 | 65.7 | 61.6 |
| | | | | |
| | **Kytril 20 mcg/kg N = 13** | **Kytril 40 mcg/kg N = 20** | | |
| **Proportion of subjects with TC (0-2 hrs)** | 7 years – 11 years | | | |
| **n** | 13 | 16 | | |
| **%** | 100 | 80 | 85.7 | 90.4 |
| | | | | |
| **Proportion of subjects with TC (0-24 hrs)** | | | | |
| **n** | 9 | 11 | | |
| **%** | 69.2 | 55 | 65.7 | 61.6 |
| | | | | |
| | **Kytril 20 mcg/kg N = 6** | **Kytril 40 mcg/kg N = 6** | | |
| **Proportion of subjects with TC (0-2 hrs)** | 12 years – 16 years | | | |
| **n** | 5 | 5 | | |
| **%** | 83.3 | 83.3 | 85.7 | 90.4 |
| | | | | |
| **Proportion of subjects with TC (0-24 hrs)** | | | | |
| **n** | 5 | 3 | | |
| **%** | 83.3 | 50 | 65.7 | 61.6 |

**Table 11: Proportion of Subjects with Total Control by gender (Evaluable population)**

| | Kytril 20 mcg/kg N = 22 | Kytril 40 mcg/kg N = 43 | Overall | |
|---|---|---|---|---|
| | | | Kytril 20 mcg/kg | Kytril 40 mcg/kg |
| **Proportion of subjects with TC (0-2 hrs)** | Females | | | |
| **n** | 20 | 38 | | |
| **%** | 90.9 | 88.4 | 85.7 | 90.4 |
| | | | | |
| **Proportion of subjects with TC (0-24 hrs)** | | | | |
| **n** | 15 | 26 | | |
| **%** | 68.2 | 60.5 | 65.7 | 61.6 |
| | | | | |
| | **Kytril 20 mcg/kg N = 48** | **Kytril 40 mcg/kg N = 30** | | |
| **Proportion of subjects with TC (0-2 hrs)** | Males | | | |
| **n** | 40 | 28 | | |
| **%** | 83.3 | 93.3 | 85.7 | 90.4 |
| | | | | |
| **Proportion of subjects with TC (0-24 hrs)** | | | | |
| **n** | 31 | 19 | | |
| **%** | 64.6 | 63.3 | 65.7 | 61.6 |

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No dosing recommendations can be made based on the results of the clinical trial.

The Applicant based the trial drug doses on results seen in the literature. The Applicant notes that in the literature, Kytril I.V. doses from 10 mcg/kg to 80 mcg/kg have been studied for the prevention of PONV in the pediatric population. The Applicant assessed that the most efficacious dose in the literature was 40 mcg/kg.

*Medical Reviewer's comments: Upon review of the literature, multiple doses of Kytril I.V. have been studied, but it is unclear what the most appropriate dose would be for prevention of PONV in the pediatric population. Studies from the literature have demonstrated that doses lower than 40 mcg/kg, such as 10 mcg/kg, may be effective in preventing pediatric PONV. A lower dose such as 10 mcg/kg should also be studied to accurately assess the most appropriate dose for this indication. See Table 18 in 9.1.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Effects on the endpoint of total control declined over time (from assessment at 2 hours after surgery to 24 hours after surgery) for both the 20 mcg/kg dose and the 40 mcg/kg dose (See Table 9).

### 6.1.10 Additional Efficacy Issues/Analyses

The efficacy results of the Kytril I.V. trial were compared with the Zofran I.V. placebo controlled trial (S3A-380) which was conducted to assess the safety and efficacy of Zofran I.V. for the prevention of PONV in a pediatric population.

Trial ML16633 (Kytril I.V.) and Trial S3A-380 (Zofran I.V.) differed in a number of key areas, including the number of patients enrolled, inclusion criteria and efficacy parameters studied. The Kytril trial enrolled 171 patients aged 2-16 years and the Zofran trial enrolled 433 patients aged 2-12 years. Patients in the Kytril trial underwent either tonsillectomy or adenotonsillectomy. Patients in the Zofran trial underwent either strabismus surgery, tonsillectomy (with or without adenoidectomy), herniorrhaphy or orchidopexy. The Kytril trial efficacy parameters were total control (no nausea, no vomiting, and no use of rescue medications). The efficacy parameter for the Zofran trial was complete response (no emetic episodes, no rescue and no withdrawal) and the number of emetic episodes. See Table 12

**Table 12: Summary of efficacy parameters for Zofran and Kytril trials**

| | Historical Study (S3A-380) | | ML16633 | |
|---|---|---|---|---|
| **Efficacy parameters** | **Placebo I.V.** | **Zofran I.V.** | **Kytril 20 mcg/kg** | **Kytril 40 mcg/kg** |
| ***Complete response 0-2 hrs** | 70% (148/211) | 89% (185/208) | | |
| ***Complete response 0-24 hrs** | 39% (82/210) | 68% (140/205) | | |
| **#Total control 0-2 hrs** | | | 83.7% (60/70) | 90.4% (66/73) |
| **#Total control 0-24 hrs** | | | 65.7% (46/70) | 61.6 (45/73) |
| **Number of emetic episodes 0-24 hrs** | N=210<br>**0 39%**<br>1 10%<br>2 6%<br>3 5%<br>4 5%<br>>4 6% | N=205<br>**0 68%**<br>1 18%<br>2 2%<br>3 2%<br>4 <1%<br>>4 1% | | |
| **No vomiting 0-24 hrs** | | | **70%** (49/70) | **68.5%** (50/73) |

*Complete response- no emetic episodes, rescue or withdrawal
#Total control – no nausea, no vomiting, & no use of rescue medications
Reviewer's table

*Medical Reviewer's comments:*
*Results for the primary (total control from 0 to 2 hours) and key secondary (total control from 0 to 24 hours and vomiting) efficacy endpoints in the Kytril trial were observed to be greater than placebo results seen in the Zofran historical trial. The differences in the clinical trials limit the ability of the Zofran trial to serve as an historical control.*

# 7 Review of Safety

## ***Safety Summary***

There were no deaths reported in this trial. 8 patients experienced a serious adverse reactions (SAEs) and the most common AEs reported were gastrointestinal related which has been observed in other granisetron clinical trials. None of the SAEs were considered by the Applicant to be related to the use of Kytril I.V. QT prolongation was observed during the trial. One subject in each dose group had a post dose QTcF of > 500 ms. Five subjects (3 in the 20 mcg/kg group and 2 in the 40 mcg/kg group) had a ≥

60 ms increase in the QTcF. No subject had both a ≥ 500 ms QTcF and a ≥ 60 ms increase in QTcF. This is of concern since higher Kytril I.V. doses were studied as compared to dosages currently approved. A thorough QT trial is needed to assess the observed QT prolongation.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from trial ML16633.

### 7.1.2 Categorization of Adverse Events

Adverse reactions were classified by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from one trial was submitted and reviewed.

## 7.2 Adequacy of Safety Assessments

All patients who received a dose of the study drug were included in the safety analysis population.

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

An adequate number of subjects were exposed to the drug, including adequate numbers of demographic subsets.

**Table 13: Demographics - Safety Population**

| Demographic Characteristics | Kytril 20 mcg/kg (N = 79) | Kytril 40 mcg/kg (N = 78) |
|---|---|---|
| **Age (Yrs)** | | |
| Mean<br>Range | 5.9<br>2-16 | 6.1<br>2-16 |
| **Race (%)** | | |
| White | 77.2 | 66 |
| Black | 11.4 | 11.5 |
| Asian | 1.3 | 5.1 |
| American Indian or Alaskan Native | 5.1 | 3.9 |
| **Sex (%)** | | |
| Male | 68.5 | 42.3 |
| Female | 31.7 | 55 |

7.2.2 Explorations for Dose Response

7.2.3 Special Animal and/or In Vitro Testing

No new non-clinical data were submitted in support of this application.

7.2.4 Routine Clinical Testing

The protocol defined clinical testing and safety assessments were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

None submitted

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

None

## 7.3 Major Safety Results

### 7.3.1 Deaths

The Applicant reported no deaths in the clinical trial.

### 7.3.2 Nonfatal Serious Adverse Events

Data sources used in the review of individual cases included: Case Report Forms (CRFs) and the Applicant's narrative summaries.

Eight of the 157 treated subjects (six and two in the 20- and 40-mcg/kg dose groups, respectively) experienced a treatment-emergent serious adverse event up to 15 days after the treatment evaluation period. Three subjects had post-procedural hemorrhage, two had dehydration, two reduced oral intake, and other serious adverse events (migraine, tonsillar hemorrhage, oxygen saturation decrease, procedural pain) were experienced by a single subject each. Two subjects had more than one serious event. All of the serious adverse events were considered by the investigator to be unrelated to study treatment and all except the case of migraine resolved without sequelae by the end of the reporting period.

**Table 14: Serious Adverse Events**

| Subject # | Age (yrs) | Sex | Dose | Time (days) | Adverse event |
|---|---|---|---|---|---|
| 57872/3102 | 3 | F | 20 mcg/kg | 2 | Mod dehydration |
| 57882/3316 | 15 | Male | 20 mcg/kg | 1 | Tonsillar hemorrhage |
| | | | | 2 | migraine |
| 57885/3225 | 2 | Male | 20 mcg/kg | 3 | Reduced oral intake |
| 142864/2053 | 3 | Female | 20 mcg/kg | 6 | Dehydration |
| 142864/2062 | 10 | Male | 20 mcg/kg | 2 | Post-procedural hemorrhage |
| 142864/2064 | 5 | Male | 20 mcg/kg | 1 | Post-procedural hemorrhage |
| 57872/2001 | 3 | Male | 40 mcg/kg | 2 | Post-procedural hemorrhage |
| 57885/3220 | 7 | Male | 40 mcg/kg | 1 | Oxygen saturation decreased |

| | | | | | |
|---|---|---|---|---|---|
| | | | | 2 | Procedural pain |
| | | | | 2 | Oral intake reduced |

*Medical Reviewer's comments: After review of the SAEs case report forms (CRFs), this reviewer agrees with the Applicant's assessment that the the SAEs are likely related to complications linked to the surgical procedure and not the study drug.*

7.3.3 Dropouts and/or Discontinuations

The Applicant reported that no patients were withdrawn from the trial because of a treatment emergent adverse event.

7.3.4 Significant Adverse Events

Overall, 34 (22%) subjects in the study had a reported adverse event, but only two had severe events (dehydration, migraine and tonsillar hemorrhage) and one patient in the 40 mcg/kg treatment dose group experienced two adverse events ( flatulence and abdominal pain) that were considered by the investigator to be related to study treatment.

**Table 15: Overview of all Treatment emergent Adverse events Safety Population**

| | **Kytril 20 mcg/kg N= 79** | **Kytril 40 mcg/kg N= 78** | **All subjects N= 157** |
|---|---|---|---|
| All treatment emergent adverse events | 18 (23%) | 16 (21%) | 34 (22%) |
| Severe AEs | 2 (3%) | 0 | 2 (1%) |
| Related AEs | 0 | 2 (3%) | 2 (1%) |
| Serious AEs | 6 (8%) | 2 (3%) | 8 (5%) |
| Deaths | 0 | 0 | 0 |
| Withdrawals due to an AEs | 0 | 0 | 0 |

*Medical Reviewer's comments: The incidence of AEs was similar in the two treatment groups (23% and 21% in the 20 mcg/kg and 40 mcg/kg dose groups).*

7.3.5 Submission Specific Primary Safety Concerns

The doses of Kytril I.V.used in the prevention PONV trial are higher than the recommended doses for the prevention of CINV in adults and children (10mcg/kg) and are higher in some pediatric patients than the recommended dose in adults for the prevention of PONV (1 mg). A primary safety concern is the potential for increased risk

of cardiac arrhythmias, especially QT interval prolongation, related to the increased dose

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Commonly reported AEs included vomiting and abdominal pain. The most common AE in any treatment group was vomiting.

**Table 16: Treatment emergent AEs (≥ 3%) Safety Population**

| System organ class<br>Preferred term | Kytril 20 mcg/kg (N=79) | | Kytril 40 mcg/kg (N=78) | | All Patients (N=157) | |
|---|---|---|---|---|---|---|
| **Number (%) of patients with at least one AE** | 18 (23) | | 16 (21) | | 34 (22) | |
| **Total Number of AEs** | 26 | | 21 | | 47 | |
| | n | % | n | % | n | % |
| **Gastrointestinal disorders** | | | | | | |
| Vomiting | 6 | 8 | 4 | 5 | 10 | 6 |
| Abdominal pain upper | 2 | 3 | 1 | 1 | 3 | 2 |
| **Injury, poisoning, & procedural complications** | | | | | | |
| Post procedural hemorrhage | 4 | 5 | 2 | 3 | 6 | 4 |
| **Investigations** | | | | | | |
| Oxygen saturation decreased | 1 | 1 | 2 | 3 | 3 | 2 |
| **Metabolism and nutrition disorders** | | | | | | |
| Dehydration | 4 | 5 | 0 | 0 | 4 | 3 |
| **Respiratory, thoracic, and mediastinal disorders** | | | | | | |
| Tonsillar hemorrhage | 2 | 3 | 0 | 0 | 2 | 1 |

Modified Applicant's table

Medical Reviewer's comments:
*The incidence of common AEs was similar across treatment groups. The Gastrointestinal AEs noted in the above tables are known to be associated with granisetron I.V.*

### 7.4.2 Laboratory Findings

The protocol defined clinical testing and safety assessments were adequate.

The pre- and post dosing Chem-21 laboratory assessments were exploratory safety

endpoints analyzed on the safety population. For most laboratory variables, mean changes from baseline (predose) to just prior to PACU discharge (post dose) were minimal and not clinically relevant, including AST and ALT concentrations. Mean fasting blood glucose increased from predose to post-dose in both treatment groups (increases of 1.41 and 1.52 mmol/L in the 20- and 40-mcg/kg dose groups, respectively). This increase resulted in post dose values that were above the investigator's normal range in about 54% of subjects who had normal pre-dose values in each dose group. No relationship between the increase in fasting blood glucose and the granisetron dose was observed.

### 7.4.3 Vital Signs

The protocol defined vital sign testing and safety assessments were adequate.

Mean systolic blood pressure and pulse rate increased from screening to PACU discharge to a similar extent in both treatment groups (mean increases of 8 mmHg and 16 bpm in the overall study population). Most of the increase in systolic blood pressure occurred after anesthesia was induced, and much of the increase in pulse rate occurred by the baseline assessment, prior to granisetron administration. Both increases were similar in the two dose groups. No clinically relevant change in diastolic blood pressure, respiration rate, or body temperature could be attributed to granisetron administration.

### 7.4.4 Electrocardiograms (ECGs)

The protocol defined ECG testing and safety assessments were not linked to PK data.

### 7.4.5 Special Safety Studies/Clinical Trials

The Applicant conducted an assessment for QT prolongation on all patients in trial ML16633. Pre and post-dose QT intervals were exploratory safety endpoints analyzed on the safety population. Standard 12 –lead ECGs were performed prior to surgery after the induction of anesthesia and insertion of I.V. access (pre-dose) and again at the end of surgery after the administration of study treatment and just prior to reversal of anesthesia. The exact time of the ECG within this framework was dependent on the situation in the operating room and varied between patients.

The Applicant reported that ECG variables demonstrated a 9.2 ms mean increase from baseline in QT interval in the 40 mcg/kg dose group. An increase in mean heart rate was observed in the 20 mcg/kg dose group (+8.0 bpm), but little change was observed in the 40 mcg/kg group. After correcting for heart rate, the post-dose QTcF was increased from baseline in both dose groups (15.0 and 16.0 ms in the 20 mcg/kg and 40 mcg/kg dose groups, respectively), which resulted in a > 500 ms post-dose QTcF in one subject in each group and a ≥ 60 ms increase in the QTcF in five subjects (3 in the 20

mcg/kg group and 2 in the 40 mcg/kg group). No subject had both a ≥ 500 ms QTcF and a ≥ 60 ms increase in QTcF.

- Subject 122528/3444 (20 mcg/kg) was an 11-year-old white female who had a 37-ms increase from predose to postdose in QTcF (471 to 508 ms) with a 20-bpm increase in heart rate (61 to 81 bpm). Her raw QT intervals were 468 ms (predose) and 460 ms (postdose). During this period, concomitant medications were sevoflurane/nitrous oxide/oxygen, dexamethasone, morphine sulfate, and bupivacaine with epinephrine.

- Subject 142864/2055 (40 mcg/kg) was a 10-year-old white male who had a 10-ms increase from predose to post dose in QTcF (492 to 502 ms) with a 20-bpm increase in heart rate (90 to 110 bpm). His raw QT intervals were 430 ms (predose) and 410 ms (post dose). During this period, concomitant medications were lidocaine, propofol, sevoflurane/nitrous oxide/oxygen, dexamethasone, and morphine.

**Table 17: Proportions of Subjects with a QTc Interval > 450 ms and with an Increase in QTc Interval ≥ 30 ms by Time Category, Safety Population**

| Scheduled Time | Criteria | Granisetron 20 µg/kg N = 79 | | Granisetron 40 ug/kg 40 µg/kg N = 78 | |
|---|---|---|---|---|---|
| Pre-dose | QTcB > 450 ms | 44 | (57.1) | 42 | (54.5) |
| | QTcB > 480 ms | 8 | (10.4) | 14 | (18.2) |
| | QTcB > 500 ms | 2 | (2.6) | 5 | (6.5) |
| | n | 77 | | 77 | |
| | QTcF > 450 ms | 6 | (7.8) | 7 | (9.1) |
| | QTcF > 480 ms | 0 | (0.0) | 1 | (1.3) |
| | QTcF > 500 ms | 0 | (0.0) | 0 | (0.0) |
| | n | 77 | | 77 | |
| Post-dose | QTcB > 450 ms | 65 | (83.3) | 65 | (84.4) |
| | QTcB > 480 ms | 26 | (33.3) | 26 | (33.8) |
| | QTcB > 500 ms | 8 | (10.3) | 11 | (14.3) |
| | n | 78 | | 77 | |
| | QTcF > 450 ms | 15 | (19.2) | 12 | (15.6) |
| | QTcF > 480 ms | 1 | (1.3) | 1 | (1.3) |
| | QTcF > 500 ms | 1 | (1.3) | 1 | (1.3) |
| | n | 78 | | 77 | |
| | QTcB increase >= 30ms | 28 | (36.4) | 25 | (32.9) |
| | QTcB increase >= 60ms | 6 | (7.8) | 4 | (5.3) |
| | n | 77 | | 76 | |
| | QTcF increase >= 30ms | 20 | (26.0) | 18 | (23.7) |
| | QTcF increase >= 60ms | 3 | (3.9) | 2 | (2.6) |
| | n | 77 | | 76 | |

n = number with QTc assessment at the relevant time point(s) and is the denominator for the percentages.
QTcB = Bazett's correction, QTcF = Fridericia's correction

Sponsor's table

*Medical Reviewer's comments:*
*A consult was requested from the QT Interdisciplinary Review Team (IRT) to review the final study report. The QT IRT determined that the results of the study were confounded by lack of a placebo control, concomitant medications and the post-operative state. The label was also reviewed and recommendations were made by the QT IRT to include the following: "An adequate QT assessment has not been conducted, but QT prolongation has been reported with Kytril. In patients with pre-existing arrhythmias or cardiac conduction disorders, this might lead to clinical consequences, particularly in patients with cardiac co-morbidities, on cardio-toxic chemotherapy, with concomitant electrolyte abnormalities or concomitant medications that prolong the QT interval." The QT IRT recommended that the QT effect of granisetron would be best characterized with a thorough QT trial and this medical reviewer agrees with their recommendation.*

7.4.6 Immunogenicity

None

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

The incidence of observed AEs was similar across both the 20 mcg/kg treatment group and the 40 mcg/kg treatment group.

### 7.5.2 Time Dependency for Adverse Events

Since Kytril I.V. for the prevention of PONV is intended for single administration limited use, evaluation of time dependency was not performed.

### 7.5.3 Drug-Demographic Interactions

In the 2 to 6 year age range, the total number of patients with at least one AE was 11 (20%) in the 20 mcg/kg dose group and 13 (27%) in the 40 mcg/kg dose group. The total number of AEs was 16 in each dose group.

In the 7 to 11 year age range, the total number of patients with at least one AE was 6 (35%) in the 20 mcg/kg dose group and 2 (9%) in the 40 mcg/kg dose group. The total number of AEs was 7 in the 20 mcg/kg group and 4 in the 40 mcg/kg group.

In the 12 to 16 year age range, the total number of patients with at least one AE was 1 (17%) in both dose groups. The total number of AEs was 3 in the 20 mcg/kg group and 1 in the 40 mcg/kg group.

### 7.5.4 Drug-Disease Interactions

No studies were conducted to investigate.

### 7.5.5 Drug-Drug Interactions

No studies were conducted to specifically investigate the potential for Kytril I.V. to cause or result in drug-drug interactions.

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not conducted.

#### 7.6.2 Human Reproduction and Pregnancy Data

No studies were conducted.

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

No studies were conducted.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Kytril I.V. for the prevention of PONV is administered in a controlled setting as a single dose. The Applicant did not report any cases of drug overdose in the pediatric clinical trial. Granisetron is not considered to have drug abuse potential.

### 7.7 Additional Submissions / Safety Issues

None

## 8 Postmarket Experience

In July 2009, a review was conducted by the Office of Surveillance and Epidemiology (OSE) to update cases of selected cardiovascular (CV) events (e.g. arrhythmias, torsades des pointes, heart block, myocardial infarction [MI]) associated with granisetron use since their previous review of May 2006. A search of AERS from May 2006 to June 2009 identified 32 reports of CV events. Twenty cases were excluded because they did not meet the case definition.

The remaining 11 cases ranged in age from 52 to 85 years with a mean of 66 years. Six cases occurred in females, four in males and one case did not state gender. The source for all but one case was foreign. Granisetron formulations were: oral (1) (dose not provided); intravenous (10) [0.2 mg [1], 1 mg [1], 3 mg [3], 3 mL [1], dose not provided [4]. The reported events were bradycardia (1), QT prolongation (1), syncope (2), asystole (1), cardiac/cardio respiratory arrest (2), ventricular fibrillation (1), MI (3), chest discomfort/pain (2), dyspnea (1), tachycardia (1), shock (1), increased troponin (2), myocardial ischemia 91), coronary artery spasm (1). Eight patients received concomitant medications that were labeled for CV adverse events. Two cases were

fatal. Most of the cases were reportedly poorly documented and therefore it was difficult to make determinations regarding safety.

# 9 Appendices

## 9.1 Literature Review/References

## Table 18: Literature review

| Article<br><br>Publication Date | Trial design | Trial Objective(s) | Treatment | Number of patients | Primary Endpoint(s) | Endpoint Results |
|---|---|---|---|---|---|---|
| The safety and efficacy of granisetron in PONV in pediatric patients undergoing tonsillectomy<br><br>Carnahan et.al. 1997 | Randomized, DB, placebo | Examine the safety & efficacy of granisetron in the prevention of POV in children undergoing tonsillectomy | Study drug-granisetron 10 mcg/kg IV<br><br>Placebo – saline solution IV | 54 patients ( ages 2 – 8 yrs)<br>28 patients given study drug<br>26 given placebo | Episodes of vomiting were assessed 1) upon admission to the PACU; 2) until D/C from the hosp and 3) after D/C from hosp (via tele day after surg) | Granisetron<br>Vomiting reduced for both granisetron grps ($p< 0.01$)<br>Incidence of vomiting:<br>In-hosp- 17.8%<br>Post D/C – 14%<br><br>Placebo<br>Incidence of vomiting:<br>In-hosp – 69%<br>Post D/C- 61.5% |
| Granisetron reduces POV in children: a dose-ranging study<br><br>Fujii et. al.<br>1999 | Randomized, DB, placebo controlled | To determine the minimum effective dose of granisetron for the prevention of POV in children undergoing general anesthesia for surgery (inguinal hernia and phimosis) | 4 arms:<br>Placebo (saline)<br>Granisetron 20 mcg/kg IV<br>Granisetron 40 mcg/kg IV<br>Granisetron 100 mcg/kg IV<br>Immediately after inhalation induction of anesthesia | 120 patients (ages 4-10 yrs)<br>N=30 for each arm | Complete response – no emesis and no need for another rescue med during the first 24h after anesthesia | CR<br>Placebo- 57%<br>20 mcg/kg-67%<br>40 mcg/kg-90%<br>100 mcg/kg-100% |
| The dose-response relation and cost-effectiveness of granisetron for the prophylaxis of pediatric postoperative emesis<br><br>Cieslak et. al<br>1996 | Randomize, DB, placebo controlled | To determine the dose response relation of granisetron and the financial impact of using the drug in preventing PONV after pediatric outpatient surg | 3 arms:<br>Placebo<br>10 mcg/kg IV<br>40 mcg/kg IV | 97 patients (ages 2-16 yrs) | Episodes of postoperative retching, vomiting and times to D/C readiness were recorded. | No emesis 24h post anesthesia period<br><br>Placebo-58%<br>10 mcg/kg-67%<br>40mcg/kg-91% |

Reviewer's table

## References:

Aouad MT, Siddik SS. The effect of dexamethasone on postoperative vomiting after tonsillectomy. Anesth Analg 2001;92:636-40.

Carnahan D, Dato K, Hartsuff J. The safety and efficacy of granisetron in postoperative vomiting in pediatric patients undergoing tonsillectomy. J Am

Assoc Nurse Anesth 1997; 65:154-159.

Cieslak GD, Watcha MF, Phillips MB, Pennant JH. The dose-response relation and cost-effectiveness of granisetron for the prophylaxis of pediatric postoperative emesis. Anesthesiology 1996; 85:1076-85.

Fujii Y, Tanaka H. Granisetron reduces post-operative vomiting in children: a dose-ranging study. Eur J Anaesthesiol 1999; 16:62-65.

Fujii Y, Tanaka H, Toyooka H. Prevention of postoperative vomiting with granisetron in paediatric patients with and without a history of motion sickness. Paediatr Anaesth 1999;9527-530.

Fujii Y, Toyooka H. Effective dose of granisetron for preventing postoperative emesis in children. Can J Anaesth 1996;43:660-664.

Kovac AL. Benefits and risks of newer treatments for chemotherapy induced and postoperative nausea and vomiting. Drug Safety 2003; 26(4): 227-59.

Kovac AL. Management of postoperative nausea and vomiting in children. Pediatr Drugs 2007;9(1):47-69.

Kranke P, Apfel CC. The influence of a dominating centre on a quantitative systemic review of granisetron for the preventing postoperative nausea and vomiting. Acta Anaesthesiol Scand 2001;45:659-670.

Rose JB, Watcha MF. Postoperative nausea and vomiting in paediatric patients. Br J Anaesth 1999; 83:104-117.

Watcha MF, White PF. Postoperative Nausea and Vomiting, its etiology, treatment and prevention- Review article. Anesthesiology 1992; 77:162-184.

## 9.2 Labeling Recommendations

The Applicant did not propose adding a new indication for the prevention of PONV in pediatric patients aged 2 to 16 years. The Applicant proposed adding information throughout the label that described the clinical trial (to include trial design, dosing, results and adverse events, in sections 2.2, 6.2, 8.4 and 14.2). The following was the Applicant's proposed label change related to the clinical trial:

(b) (4),

(b) (4)

(b) (4)

(b) (4)

. This reviewer recommends that a description of the clinical trial, including factors that limit interpretation of efficacy and safety data, such as dose response, QT prolongation and AEs be included in the Pediatric Use Section (8.4) only.

This reviewer recommends the following language for the label to describe the pediatric PONV trial. This should be inserted in the Pediatric Use Section (8.4).

*Postoperative Nausea and Vomiting:*

*Granisetron has been evaluated in a pediatric patient clinical trial for use in the prevention of postoperative nausea and vomiting (PONV). Due to the lack of efficacy and the QT prolongation observed in this trial, use of granisetron for the prevention of PONV in children is not recommended. The trial was a prospective, multicenter, randomized, double-blind, parallel-group study that evaluated 157 children aged 2 to 16 years who were undergoing elective surgery for tonsillectomy or adenotonsillectomy. The purpose of the trial was to assess two dose levels (20 mcg/kg and 40 mcg/kg) of intravenous granisetron in the prevention of PONV. There was no active comparator or placebo. The primary endpoint was total control of nausea and vomiting (defined as no nausea, vomiting/retching, or use of rescue medication) in the 2 hours following surgery. Efficacy was not established due to lack of a dose response. The trial also included standard 12 lead ECGs performed pre-dose and after the induction of anesthesia. ECGs were repeated at the end of surgery after the administration of granisetron and just prior to reversal of anesthesia. QT prolongation was seen at both dose levels. Five patients in this trial experienced an increase of ≥ 60 msec in QTcF. In addition, there were two patients whose QTcF was ≥ 500 msec. Interpretation of the QTcF prolongation was confounded by multiple factors, including the use of concomitant medication and the lack of either a placebo or active control. A thorough QT study has not been performed.*

*Other adverse reactions that occurred in the study included: vomiting (5-8%), post-procedural hemorrhage (3-5%), and dehydration (0-5%).*

*Pediatric patients under 2 years of age have not been studied.*

Consults were requested from Pediatric and Maternal Health Staff (PMHS), the Division of Medication Error, Prevention and Analysis (DMEPA), the Division of Drug Marketing, Advertising, and Communications (DDMAC), and the Division of Risk Management (DRISK) to provide input on the label. I concur with recommendations from these Divisions on conversion of the Kytril I.V. label to the PLR format. Recommendations included changes to the container label and carton labeling, such as removing dangerous abbreviations to minimize the potential for medication errors.

Recommendations from PMHS included their agreement with addressing the trial description information in Pediatric Use Section (8.4).

Labeling negotiations are ongoing with the Applicant.

## 9.3 Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

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/s/

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KARYN L BERRY
04/06/2011

RUYI HE
04/06/2011