Tramadol IV: A Multidisciplinary Review

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Presentation Overview

DAAP Clinical

- Regulatory history
- Tramadol hydrochloride's metabolism and mechanism of analgesia
- Efficacy and safety data
- Published literature and real-world data

CSS

- Abuse liability considerations

OSE

- Public health considerations

DAAP Clinical

- Benefit-Risk profile

Regulatory History

First review cycle:

- New Drug Application submitted December 10, 2019
  - Referencing Ultram® (NDA 020281 – approved March 1995)
  - Proposed indication: Management of moderate to moderately severe pain in adults in a medically supervised health care setting
  - Proposed dosing regimen: Tramadol 50 mg IV at Hour 0, Hour 2, Hour 4, then every 4 hours thereafter

Regulatory History

First Complete Response Letter (CRL) issued October 9, 2020:

- Product quality deficiency
- Safety issue – Tramadol IV's delayed onset of analgesia combined with its inability to be titrated to effect leads to a serious safety concern of additive opioid-related adverse events from use of opioids in succession, also referred to as opioid stacking
- Identify a population for which tramadol IV is both safe and effective for the acute pain indication

Regulatory History

First Post-Action Meeting held November 19, 2020:

- Applicant agreed with the Division about tramadol IV's delayed onset of analgesia
- Applicant disagreed with the Division about the need for an immediate-release opioid as rescue analgesia and the safety concern of opioid stacking
- Applicant stated that communication in labeling should be an effective way to address the Division's concerns

Regulatory History

Second review cycle:

- Applicant submitted a response to the Division's CRL on February 12, 2021
  - No new clinical data
  - Product quality deficiency addressed
  - Added language to sections of the label
  - Revised indication: Management of moderate to moderately severe pain in adults in a medically supervised setting, alone or in combination with other analgesics

Regulatory History

Second Complete Response Letter issued June 11, 2021:

- Information provided in the resubmission does not adequately support the proposed indication for tramadol IV
  - Safety issue – Tramadol IV's delayed onset of analgesia leads to a theoretical, yet serious safety concern of additive opioid-related adverse events from opioid stacking
  - The studies in the NDA submission were not designed to evaluate the analgesic effect of tramadol IV combined with another analgesic

Regulatory History

Second Complete Response Letter (continued):

- Tramadol IV's delayed onset of analgesia does not support its benefit as a monotherapy to treat patients in acute pain
- Insufficient information in the NDA to support the conclusion that tramadol IV in combination with other analgesics is safe and effective for the intended patient population

Regulatory History

Second Post-Action Meeting held on July 23, 2021:

- Applicant stated that the totality of the data from the NDA, looking at endpoints other than time to meaningful pain relief, demonstrated that tramadol IV can be successfully used in a multimodal analgesic approach in the postoperative pain setting
- Applicant stated that opioid stacking not a safety concern in the NDA
- Applicant stated that opioid stacking not a safety concern in countries outside the U.S. where intravenous tramadol is utilized

Regulatory History

First Formal Dispute Resolution Request (FDRR):

- Applicant submitted FDRR to the Office of Neuroscience on July 27, 2021
- Dispute Appeal Denied Letter issued on August 26, 2021
  - Tramadol IV's delayed onset of effect raises a safety concern about the risk of opioid stacking that has not been adequately addressed in the NDA

Second Formal Dispute Resolution Request

- Applicant submitted FDRR to the Office of New Drugs on August 31, 2021
- Dispute Appeal Interim Response Letter issued October 21, 2021
  - Input from the Advisory Committee needed

Tramadol Hydrochloride

- Atypical opioid analgesic
- Weak norepinephrine and serotonin reuptake inhibitor
- Major metabolite, M1 (O-desmethyltramadol), more potent mu-opioid receptor agonist than parent drug, tramadol
- M1 formed by O-demethylation of tramadol in the liver primarily via the cytochrome P450 2D6 enzyme
- IV administration of tramadol bypasses first-pass metabolism resulting in delayed formation of M1

Studies in Support of Efficacy

- Study AVE-901-102 (Study 102)
  - Post-operative pain after bunionectomy
  - Tramadol IV 25 mg, Tramadol IV 50 mg, and placebo arms
  - Primary endpoint: time-weighted summed pain intensity difference from baseline over 48 hours (SPID48)
- Study AVE-901-103 (Study 103)
  - Post-operative pain after abdominoplasty
  - Tramadol IV 50 mg, Morphine IV 4 mg, and placebo arms
  - Primary endpoint: time-weighted summed pain intensity difference from baseline over 24 hours (SPID24)

Surgical Pain Models

- Study 102 (Bunionectomy)
  - General and regional anesthesia
  - Regional anesthesia stopped at approximately 4 to 5 am on morning following surgery
  - Moderate or severe rating on a 4-point categorical rating scale and NPRS score ≥ 5 within 8 hours of removal of popliteal block
- Study 103 (Abdominoplasty)
  - General anesthesia
  - No regional anesthesia
  - Moderate or severe rating on a 4-point categorical rating scale and NPRS score ≥ 5 within 3 hours following end of surgery
  - NPRS score ≥ 5 at baseline (Time 0)

Rescue Medication

- Oral Ibuprofen 400 mg every 4 hours as needed (maximum 2400 mg/day)
- Patients were encouraged to wait at least 60 minutes after the first dose of study drug before receiving rescue medication
- No opioids allowed

Efficacy

- Studies 102 and 103 provided substantial evidence of efficacy for the acute pain indication

Results – Primary and Secondary Endpoints

	Study 102 Bunionectomy		Study 103 Abdominoplasty	
	Endpoints	**p-value tramadol IV 50 mg vs. placebo**	**Endpoints**	**p-value tramadol IV 50 mg vs. placebo**
Primary Endpoints	SPID48	0.005	SPID24	<0.001
Key Secondary Endpoints	SPID24	<0.001	PGA24	<0.001
	Total rescue medication use	0.002	SPID48	<0.001
	PGA24	<0.001	Total rescue medication use	<0.001
	PGA48	<0.001		

Efficacy

- Studies 102 and 103 also suggested that tramadol IV has a delayed onset of analgesia, likely beyond two hours

Analgesia over the Dosing Interval – Study 102

Study 102 (Bunionectomy): Number (%) of Patients With First Rescue Within Two Hours of Initiating First Dose

Planned Treatment	N	Within 30 minutes	Within 1 hour	Within 2 hours
Placebo	136	3 (2%)	15 (11%)	61 (45%)
Tramadol 25 mg	134	5 (4%)	13 (10%)	56 (42%)
Tramadol 50 mg	139	4 (3%)	13 (9%)	46 (33%)

Source: Statistical Reviewer

Analgesia over the Dosing Interval – Study 103

Study 103 (Abdominoplasty): Number (%) of Patients With First Rescue Within Two Hours of Initiating First Dose

Planned Treatment	N	Within 30 minutes	Within 1 hour	Within 2 hours
Placebo	136	15 (11%)	35 (26%)	69 (51%)
Tramadol 50 mg	141	10 (7%)	25 (18%)	61 (43%)
Morphine 4mg	93	5 (5%)	16 (17%)	26 (28%)

Source: Statistical Reviewer

Time to Meaningful Pain Relief – Study 102

Study 102 (Bunionectomy): Number (%) of Patients who Recorded Meaningful Pain Relief Within Two Hours of Initiating First Dose

Planned Treatment	N	Within 30 minutes	Within 1 hour	Within 2 hours
Placebo	136	27 (20%)	35 (26%)	41 (30%)
Tramadol 25 mg	134	28 (21%)	42 (31%)	50 (37%)
Tramadol 50 mg	139	40 (29%)	54 (39%)	63 (45%)

Source: Statistical Reviewer

Time to Meaningful Pain Relief – Study 103

Study 103 (Abdominoplasty): Number (%) of Patients who Recorded Meaningful Pain Relief Within Two Hours of Initiating First Dose

Planned Treatment	N	Within 30 minutes	Within 1 hour	Within 2 hours
Placebo	136	37 (27%)	49 (36%)	65 (48%)
Tramadol 50 mg	141	44 (31%)	61 (43%)	72 (51%)
Morphine 4mg	93	43 (46%)	51 (55%)	57 (61%)

Source: Statistical Reviewer

Safety Implications of Tramadol IV's Efficacy Profile

- Delayed onset of analgesia
- If rescue analgesia needed, then likely choice would be IR opioid
- Opioid stacking may increase likelihood of additive opioid-related AEs, including sedation and respiratory depression
- Opioid stacking is a theoretical, yet serious safety concern

Studies in Support of Safety

The Applicant submitted results from three studies:

- Two controlled studies - Study 102 (Bunionectomy) and Study 103 (Abdominoplasty)
- One uncontrolled study – Study AVE-901-104 (Study 104)
  - Post-operative pain after a variety of elective surgeries
  - Most common surgery types: breast augmentation, total hip replacement, hernia surgeries, and total knee replacement

Safety

- Safety profile of tramadol IV 50 mg consistent with safety profile of Ultram® and typical safety profile of other opioids

Most Common Adverse Events

- Studies 102 and 103 –

  Nausea, vomiting, dizziness, headache, somnolence, constipation, hypoxia

- Study 104 –

  Nausea, vomiting, hypoxia, blood creatine phosphokinase increased, constipation, infusion site pain

Respiratory-related TEAEs

- Tramadol IV 50 mg associated with more respiratory impairment events than either morphine IV or placebo

TEAEs Related to Respiratory Impairment Study 102 (Bunionectomy)

Adverse Event by Preferred Term	Placebo N=136 n (%)	Tramadol 25 mg N=133 n (%)	Tramadol 50 mg N=140 n (%)
Hypoxia	1 (0.7)	0	5 (3.6%)
Dyspnea	1 (0.7)	1 (0.8)	0

Source: CSR/Study AVE-901-102, AE Analysis Dataset.
Abbreviations: N, number of subjects; n, number of subjects in subgroup; PT, preferred term; TEAE, treatment-emergent adverse event

Respiratory Impairment – Study 103

- Prespecified safety assessment
- Defined as a clinically relevant worsening in respiratory status based on the safety parameters of respiratory rate, oxygen saturation, and somnolence or sedation
- Respiratory impairment event = AE of respiratory disorder
- AE of hypoxia = AE of respiratory disorder

Respiratory Impairment Events
Study 103 (Abdominoplasty)

Respiratory Impairment Events	Placebo N=135 n (%)	Tramadol 50 mg N=142 n (%)	Morphine N=93 n (%)	Total N=370 n (%)
Number of patients with at least one respiratory impairment event	0	9 (6.3%)	4 (4.3%)	13 (3.5%)
Hypoxia	0	9 (6.3%)	4 (4.3%)	13 (3.5%)
Respiratory disorder	0	9 (6.3%)	4 (4.3%)	13 (3.5%)
Sedation	0	2 (1.4%)	1 (1.1%)	3 (0.8%)
Bradypnea	0	1 (0.7%)	0	1 (0.3%)
Number of patients who discontinued due to a respiratory impairment event	0	4 (2.8%)	3 (3.2%)	7 (1.9%)

Source: ISS/NDA 213231, Table 35
Abbreviations: N, number of subjects; n, number of subjects in subgroup

Adverse Events of Hypoxia – Study 104

MedDRA Preferred Term	Tramadol 50 mg (N=251) n (%)
Nausea	72 (28.7)
Vomiting	49 (19.5)
Hypoxia	17 (6.8)
Blood creatine phosphokinase increased	16 (6.4)
Constipation	14 (5.6)
Infusion site pain	13 (5.2)
Dizziness	10 (4.0)
Headache	6 (2.4)
Infusion site phlebitis	5 (2.0)

Source: CSR/Study AVE-901-104, Table 19, p. 58.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Authorities; N, number of subjects; n, number of subjects in subgroup; TEAE, treatment-emergent adverse event

TEAEs Related to Abuse Potential

- Applicant identified the following AEs related to abuse potential:
  - Dizziness/dizziness postural
  - Somnolence
  - Sedation
  - Euphoria/euphoric mood
  - Dysphoria
  - Disturbance in attention
- Dizziness, somnolence, and sedation signal CNS activity
- Euphoria and euphoric mood signal abuse potential due to subjective reinforcing effects

TEAEs Related to Abuse Potential Study 102 (Bunionectomy)

Adverse Event by Preferred Term	Placebo N=136 n (%)	Tramadol 25 mg N=133 n (%)	Tramadol 50 mg N=140 n (%)
Dizziness	4 (2.9)	7 (5.3)	21 (15.0)
Somnolence/Drowsiness	3 (2.2)	6 (4.5)	16 (11.4)
Euphoria	0	0	1 (0.7)
Anxiety	0	0	1 (0.7)
Agitation	1 (0.7)	0	0

Source: CSR/Study AVE-901-102, AE Analysis Dataset.
Abbreviations: N, number of subjects; n, number of subjects in subgroup; PT, preferred term; TEAE, treatment-emergent adverse event

TEAEs Related to Abuse Potential Study 103 (Abdominoplasty)

MedDRA System Organ Class Preferred Term	Placebo (N=135) n (%)	Tramadol 50 mg (N=142) n (%)	Morphine (N=93) n (%)	Total (N=370) n (%)
Number of patients with at least one TEAE related to substance abuse	11 (8.1)	23 (16.2)	21 (22.6)	55 (14.9)
Dizziness	9 (6.7)	18 (12.7)	17 (18.3)	44 (11.9)
Somnolence	2 (1.5)	3 (2.1)	2 (2.2)	7 (1.9)
Dizziness postural	1 (0.7)	2 (1.4)	3 (3.2)	6 (1.6)
Sedation	0	2 (1.4)	1 (1.1)	3 (0.8)
Disturbance in attention	1 (0.7)	0	0	1 (0.3)
Dysphoria	0	0	1 (1.1)	1 (0.3)

Source: CSR/Study AVE-901-103, Table 38, p. 104.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Authorities; N, number of subjects; n, number of subjects in subgroup; PT, preferred term; TEAE, treatment-emergent adverse event

Opioid Stacking

- Another opioid was NOT allowed as rescue medication in the Phase 3 studies
- Eight patients were administered tramadol IV followed in succession by another opioid:
  - One patient in Study 102 (Bunionectomy)
  - Six patients in Study 103 (Abdominoplasty)
  - One patient in Study 104

Opioids Used in the Phase 3 Program

Medication	Study 102 Bunionectomy	Study 103 Abdominoplasty		Study 104
Drug Class Drug Name	Tramadol 50 mg N=140 n (%)	Tramadol 50 mg N=142 n (%)	Morphine 4 mg N=93 n (%)	Tramadol 50 mg N=251 n (%)
Opioids	64 (45.7)	59 (41.5)	35 (37.6)	164 (65.3)
Tramadol	N/A	29 (20.4)	14 (15.1)	18 (7.2)
Ultracet	N/A	3 (2.1)	5 (5.4)	N/A
Panadeine co	29 (20.7)	7 (4.9)	5 (5.4)	1 (0.4)
Procet	10 (7.1)	1 (0.7)	0	13 (5.2)
Vicodin	23 (16.4)	13 (9.2)	8 (8.6)	106 (42.2)
Oxycocet	1 (0.7)	6 (4.2)	2 (2.2)	35 (13.9)

Sources: CSR/Study AVE-901-102, Table 14.1.6.2, p. 162, CSR/Study AVE-901-103, Table 14.1.6.2, p. 217, and CSR/Study AVE-901-104, Table 14.1.6.2, p. 160.

Published Literature Outside the U.S.

- Published Literature on Tramadol Hydrochloride for Injection
  - Limitations:
    - Tramadol HCl for injection administered at higher doses
    - Tramadol HCl for injection administered via patient-controlled analgesia
    - Subjects were not administered tramadol HCl for injection followed in succession by another opioid
  - Results:
    - No new or unexpected safety findings for tramadol identified
  - No conclusions can be made about the risk of opioid stacking

Real-World Experience Outside the U.S.

- VigiBase - International drug monitoring database
  - Limitations:
    - May be subject to underreporting and reporting biases
    - Incidence of AEs cannot be estimated as the database has no denominator
    - Safety signals identified may or may not represent AEs that are truly associated with oral or intravenous tramadol
    - Clinical review of the AE reports needed to better understand the data

Real-World Experience Outside the U.S.

- VigiBase
  - European Region results:
    - 12,600 AE reports for oral tramadol and 1,000 AE reports for intravenous tramadol
    - Percentage of AE reports of respiratory depression was low:
      - 0.5% with oral tramadol and 1.0% with intravenous tramadol
    - Percentage of AE reports in which “co-use of opioids” was documented:
      - 9% with oral tramadol and 20% with intravenous tramadol
      - No details on types of AEs reported when “co-use of opioids” was documented
  - No comparative statements can be made regarding data in spontaneous reports
  - Conclusions using the available data are limited

Benefit-Risk Profile of Tramadol IV

- Demonstrated efficacy in two adequate and well-controlled studies
- Delayed onset of analgesia – poses a safety concern of additive opioid-related AEs from opioid stacking
- Safety profile consistent with the safety profile of Ultram® and other available opioid products
  - More hypoxia than morphine IV in Study 103
  - Less dizziness than morphine IV in Study 103
  - Comparable rate of somnolence to morphine IV in Study 103
  - No AEs of euphoria in either treatment arm in Study 103
- Available published literature and real-world data do not address the safety concern of opioid stacking
- A Schedule IV opioid has less abuse liability than a Schedule II or III opioid
- No robust conclusions can be made with respect to whether intravenous use of tramadol in a medically supervised setting will confer a public health benefit


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Abuse Potential Considerations for Tramadol IV Injection Under NDA 213231

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February 15, 2022
FDA Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety & Risk Management Advisory Committee (DSaRM)

Abuse Potential Considerations

- Under NDA 213231 it is proposed that tramadol intravenous solution, as a Schedule IV drug, may offer an advantage over intravenous Schedule II opioids administered within a medically supervised setting for treatment of pain by decreasing the risk of subsequent and opioid use disorder.

- (From page 18 of the Sponsor's AC Briefing Document):

  "There is no direct data to determine that a limited exposure to intravenous Schedule II opioids increases risk for opioid use disorder that may be prevented by using intravenous Schedule IV opioid, however the availability of IV tramadol would allow further advancement of the concepts of multimodal analgesia to reduce exposure to highly addictive opioid."

Background for Abuse Potential Considerations

- The Controlled Substances Act (CSA) is intended to mitigate risks of abuse and diversion of legitimate and illicit drugs by regulating availability and supply of these drugs.
- Drugs are placed in one of five schedules (I thru V) depending on medical utility, as well as abuse and dependence potential. Schedule I drugs have no medical utility in the U.S.
- Schedules II through V are reserved for drugs having an accepted medical use and a progressively lower abuse and dependence potential (II → V).
  - **Most opioids are in Schedule II** indicating a "a high potential for abuse" and abuse "may lead to severe psychological or physical dependence"
  - **Tramadol is in Schedule IV indicating** "a low potential for abuse relative to the drugs or other substances in Schedule III" and abuse "may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III"

[21 U.S.C. 811(b)]

Relevant Information Contributing to Schedule IV Placement of Tramadol in 2014

- In August 2014 DEA, via final rule, placed tramadol in Schedule IV of the CSA.
- Support for Schedule IV was documented in a scientific and medical evaluation and scheduling recommendation, with NIDA concurrence, and sent to DEA by the Assistant Secretary of DHHS in September 2010. Supporting evidence included but was not limited to:
    - Opioid activity of tramadol is due to a metabolite as opposed to tramadol having intrinsic mu opioid activity.
    - Available nonclinical and clinical data, as well as epidemiological data supported abuse potential and physical dependence potential similar to Schedule IV opioids (propoxyphene or pentazocine) and less than Schedule II or III opioids.

Treatment of Acute Pain Within Medically Supervised Setting

- Tramadol IV is intended for slow intravenous infusion for pain control strictly within a medically supervised setting and not for take home use.
- Schedule II opioids (e.c., morphine, oxycodone, others) are also available for IV use. Recommendations are that they be given at the lowest dose possible and, importantly, that they be administered “slowly” to mitigate adverse events.
- Within the medically supervised setting, abuse by the patient is not likely.
- However, questions arise to whether within the medical setting a patient under treatment for acute pain may experience subjective rewarding effects or develop physical dependence.

Abuse Potential Perspective: Intravenous Injection of Tramadol

- Considering the dependency of tramadol on a metabolite for opioid activity, IV injection of tramadol with slower buildup of metabolite will likely result in less subjective reinforcing effects compared to rapid IV administration of Schedule II opioids having high mu opioid receptor activity.
  - Possibility of seizures also may limit dose and rate of injection of tramadol

- When factoring in the slow infusion rate as within a clinical setting, both tramadol and Schedule II opioids are less likely to produce subjective reinforcing effects. (Comer et al., 2009, J. Opioid Manag. Vol. 5: 203-212)

Clinical Development Program for Intravenous Tramadol

Adverse Events (AEs) Indicative of Subjective Reinforcing Effects

- Clinical Development Program: Three Phase 1 and Three Phase 3 Studies.
- AEs Documented: Euphoric Mood in two subjects.
- Studies in which "Euphoric Mood" was documented following slow infusion of IV tramadol included:
  - Phase 1 study RVG-12-001, one subject out of receiving single 200 mg Tramadol IV
  - Phase 3 study AVE-901-102, one subject out of 140 receiving multiple infusions 50 mg Tramadol IV
- No AEs indicative of subjective reinforcing effects were observed in Phase 3 study AVE-901-103. Subjects in this study received multiple 15 minutes intravenous administrations of either IV Tramadol IV 50 mg (142 subjects) or 4 mg morphine (93 subjects), or placebo (135 subjects).

Development of Physical Dependence to Opioids in the Medically Supervised Setting

- Studies, mainly involving oral administration indicate that prolonged use of tramadol at therapeutic and supratherapeutic doses can produce physical dependence.

- Currently approved tramadol products share opioid class labeling language about abuse risks, dependence, and withdrawal, and in general, there are increased risks of developing physical dependence to an opioid analgesic with longer duration of treatment.

- The extent to which a relatively short treatment duration with intravenous administration of tramadol or Schedule II opioids within a medically supervised setting for the treatment of pain induces individuals to use opioids nonmedically post-discharge due to physical dependence and withdrawal symptoms is not known.

Concluding Remarks

- Within a medically supervised setting in which slow intravenous infusion of tramadol or Schedule II opioids are administered for pain, there is low likelihood that patients will experience significant subjective reinforcing effects. Conversely, increasing infusion rates of Schedule II opioids would likely increase the differences in reinforcing effects, higher for Schedule II opioids relative to IV tramadol.

- It is not known the extent to which slow intravenous administration of tramadol or Schedule II opioids within a medically supervised setting for the treatment of pain results in subjective reinforcing effects or physical dependence sufficient to induce nonmedical opioid use post-discharge.

- We are not aware of direct data indicating a limited duration exposure to intravenous Schedule II opioids increases risk for opioid use disorder that may be prevented or reduced by using intravenous Schedule IV opioid such as tramadol. Impact of in-patient treatment with opioid analgesics for limited duration on the risks of opioid abuse, misuse, and addiction post-discharge is unknown but cannot be ruled out.


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Epidemiologic Data and Public Health Considerations in Evaluating Benefit-Risk of Intravenous (IV) Tramadol

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Benefit-Risk Assessment Framework for Opioid Analgesics: FDA Draft Guidance[1]

- FDA considers the public health risks of the drug related to misuse, abuse, opioid use disorder (OUD), accidental exposures, and overdose for patients and others, as well as any properties of the drug that may mitigate such risks.
- FDA considers the benefits and risks relative to other available therapies for the condition.

1. *Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework Guidance for Industry*, June 2019

Public Health Benefit-Risk Considerations for Intravenous (IV) Tramadol

- Applicant argues that this product would confer a public health benefit by reducing reliance on Schedule II opioids for management of post-operative pain in inpatient settings.
  - Improved safety relative to other currently available IV opioids through reducing risks of opioid abuse-related harms.
- **Public health consideration**: Would making IV tramadol available for use in these settings reduce the risk of subsequent opioid-related harms, such as misuse, abuse, opioid use disorder (OUD), and overdose in patients and others?

Epidemiologic Data

- We agree with the Applicant that there are no data that directly answer this question.
- To address these public health considerations, the Applicant provided the following:
  - Epidemiologic data on misuse and abuse of tramadol in community settings in the U.S. and select non-U.S. countries where IV tramadol is approved.
  - Published literature on short-term postoperative opioid exposure and development of prolonged opioid use in patients.

Epidemiologic Data on Misuse and Abuse of Tramadol in Community Settings

- Recent data on rates of misuse, abuse, and diversion of tramadol compared to selected Schedule II opioid analgesics.
  - Generally, tramadol's rates are lower than comparators, consistent with its Schedule IV status in the U.S.
    - Reflects primarily (and in the U.S., *only*) oral tramadol.
    - Manipulation of oral tramadol for abuse by injection route is uncommon relative to some oral formulations of Schedule II opioids, including morphine.
    - Documented abuse of tramadol liquid formulation for injection rare (in countries where approved[§])—not surprising given its use in inpatient settings.

[§] Includes France, Germany, Italy, Spain, and the U.K. where IV tramadol is available

Postoperative Exposure to Opioid Analgesics in Medical Setting

- Applicant cited five published articles on postoperative opioid use. [1-5]
  - One 2013 article reporting high prevalence of in-hospital postoperative use of opioid analgesics (98.6%)[1] -- no information on outpatient opioid use.
  - Narrative review[2] and editorial letter[3] cautioning against liberal use of opioid analgesics in postoperative setting.
  - Two retrospective U.S. cohort studies of outpatient opioid dispensing patterns in opioid-naïve patients who underwent surgery.[4-5]

[1]Kessler et. al, 2013 [2]Koepke et. al, 2018 [3]Mehra, 2018 [4]Brummett et. al, 2017 [5]Lee et. al, 2017

Postoperative Opioid Analgesic Use and Subsequent Outcomes in Outpatient Setting

- U.S. cohort studies found that 6-10% of opioid-naïve patients with an initial post-op opioid analgesic dispensing had “prolonged opioid use” (≥1 opioid fill 90-180 days after surgery).[1,2]
  - No data provided on association between IV/inpatient opioid use and opioids dispensed or used after discharge.
  - No clinical information on reason for subsequent opioid dispensings.
  - Use patterns were influenced by other factors (e.g., type of surgery, previous substance use, mental health conditions).[1]
  - No information on physiologic dependence, misuse, abuse, OUD, or overdose (although these are known risks of opioid analgesics).
    - Prolonged opioid use does not equal opioid dependence, abuse, or OUD.

[1]Brummett et. al, 2017 [2]Lee et. al, 2017

Summary of Epidemiologic Evidence

Known

- Postoperative opioid use is prevalent.
- Some opioid-naïve surgery patients will continue to receive opioid analgesics long-term.
- All outpatient opioid use carries a risk of misuse, abuse, OUD, and overdose.
- Tramadol abuse rates in the community are generally lower than for Schedule II opioids.
- Manipulation of oral tramadol for abuse by injection route is uncommon relative to some oral formulations of Schedule II opioids, including morphine.

Unknown

- Whether the type(s) of IV opioid analgesic administered postoperatively predict the type(s), amount, or duration of opioid analgesics used in the outpatient setting.
- Whether there is a difference in the risk of developing opioid misuse, abuse, dependence, or OUD following use of IV tramadol compared to other IV opioids administered in an inpatient setting.

Conclusions

- We agree that broader public health impacts such as misuse, abuse, OUD, and related risks are critical considerations in regulatory decisions related to opioid analgesic products.
- Based on available epidemiologic evidence, it is unknown whether availability of IV tramadol for use in inpatient settings would reduce these risks in patients or the broader community.


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