CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213426Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

NDA #:	213426
Product:	SEGLENTIS (celecoxib and tramadol HCl) tablets
Applicant:	Esteve Pharmaceuticals, S.A.
From:	CDR Mark A. Liberatore, PharmD, RAC Deputy Director for Safety, DAAP
Date:	*see electronic signature*

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

Although the use of prescription opioid analgesics has begun to decline since 2012, there is still substantial use of this class of drugs. With that widespread use, a substantial problem persists with the abuse and misuse of prescription opioid products, resulting in serious adverse outcomes such as addiction, unintentional overdose, and death. The spectrum of behaviors contributing to these problems include inappropriate prescribing such as improper dosing, patient selection, and patient counseling as well as inappropriate patient behaviors such as improper use, storage, and disposal of prescription opioid products.

In July 2012, FDA determined that a REMS was required for the group of extended-release and long-acting (ER/LA) opioid analgesic formulations because

there was a concern that ER/LA opioid analgesic formulations pose unique risks to patients due to their pharmacokinetic properties, duration of use, and the amount of active ingredient contained in the drug product in comparison to their immediate-release opioid counterparts. This REMS included a Medication Guide to be dispensed with each ER/LA opioid analgesic prescription and elements to assure safe use that provides for training to be made available to healthcare providers who prescribe ER/LA opioid analgesics. The content of the training was based on the learning objectives established by the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting (ER/LA) Opioid Analgesics.

On September 18, 2018, the Division of Anesthesia, Analgesia, and Addiction Products (*former division name*) approved the Opioid Analgesics REMS which expanded the ER/LA Opioid Analgesics REMS to include immediate-release (IR) opioid analgesics used in the outpatient setting. The REMS program required, for the first time, that training be made available to health care providers who are involved in the management of patients with pain (e.g., nurses, pharmacists), and not only to prescribers. Through a revised "Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain", the new REMS also required that the education cover broader information about appropriate pain management, including alternatives to opioids for the treatment of pain.

After consultations with the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for SEGLENTIS (celecoxib and tramadol hydrochloride) tablets to ensure that the benefits of the drug outweigh the risks of adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse.

In reaching this determination, we considered the following:

A. The indications for the IR opioid analgesics products result in use of these products in millions of patients. SEGLENTIS (celecoxib and tramadol hydrochloride) is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

B. Pain that is severe enough to require an opioid analgesic such as tramadol in SEGLENTIS (celecoxib and tramadol hydrochloride) is a fairly serious condition, particularly for those patients who have pain due to etiologies that are unlikely to improve and/or for whom alternative treatments are inadequate.

C. The expected benefit of SEGLENTIS (celecoxib and tramadol hydrochloride) is the analgesic properties that enable the treatment of pain for which other treatments have been inadequate or not tolerated.

D. The expected duration of treatment with SEGLENTIS (celecoxib and tramadol hydrochloride) is generally from days to weeks. Depending on the specific indication, treatment may be longer.

E. The most serious of the known adverse events associated with opioids, including the tramadol in SEGLENTIS (celecoxib and tramadol hydrochloride) are death, overdose, respiratory depression, CNS depression, abuse, and addiction.

F. SEGLENTIS (celecoxib and tramadol hydrochloride) contains tramadol, which is not a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR Part 208, FDA has determined that a Medication Guide is required for SEGLENTIS (celecoxib and tramadol hydrochloride). FDA has determined that SEGLENTIS (celecoxib and tramadol hydrochloride) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of SEGLENTIS (celecoxib and tramadol hydrochloride). FDA has determined that SEGLENTIS (celecoxib and tramadol hydrochloride)is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use SEGLENTIS (celecoxib and tramadol hydrochloride).

The elements of the REMS will be a Medication Guide, elements to assure safe use including healthcare providers who prescribe the drug have particular training, and a timetable for submission of assessments of the REMS.

The shared system Opioid Analgesic REMS was approved on September 18, 2018. Upon approval, SEGLENTIS (celecoxib and tramadol hydrochloride) will be joining this shared system REMS.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	213426
PDUFA Goal Date	October 15, 2021
OSE RCM #	2019-1059
Reviewer Name	Victoria Sammarco, Pharm.D., M.B.A.
Team Leader	Carolyn Tieu, Pharm.D., M.P.H.
Division Director	LaCivita, Cynthia, Pharm.D.
Review Completion Date	September 7, 2021
Subject	Evaluation of Need for a REMS
Established Name	celecoxib and tramadol hydrochloride
Trade Name	Seglentis
Name of Applicant	Esteve Pharmaceuticals, S.A.
Therapeutic Class	NSAID and Opioid Analgesic
Formulation	tablets: celecoxib 56 mg and tramadol hydrochloride 44 mg
Dosing Regimen	two tablets every 12 hours as needed for pain relief

This is a memorandum to the risk evaluation and mitigation strategy (REMS) review which was completed by the Division of Risk Management (DRM) in the previous cycle and was submitted to DARRTS on June 1, 2020 (DARRTS reference ID: 4617425). The Agency had determined that a REMS was necessary for opioid analgesics intended to be used in the outpatient setting to ensure the benefits of the drugs outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. Seglentis contains tramadol, an opioid analgesic, with a proposed indication that includes use in the outpatient setting, and therefore a REMS was determined necessary for Seglentis.

During this review cycle, no additional or new clinical information was submitted and no new risks were identified. The clinical reviewer concluded that the benefit:risk evaluation favored approval of Seglentis. A REMS is required for Seglentis to be approved.

On May 13, 2019, the Applicant submitted a letter of authorization cross-referencing the approved Opioid Analgesic REMS. This REMS includes all opioid analgesics intended for use in the outpatient setting, which are not covered by another REMS, and mitigates the risks of serious adverse outcomes from addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. The Opioid Analgesic REMS has a Type V Drug Master File (DMF), #031551, that contains the REMS Document, appended materials, and supporting document approved by the Agency on September 18, 2018. This meets the Agency requirements for a REMS for Seglentis and is acceptable.

Upon approval, the list of approved products will be updated on FDA's Approved Risk Evaluation and Mitigation Strategies (REMS) website, available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=9.

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/s/

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Division of Risk Management (DRM)
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PDUFA Goal Date	June 15, 2020
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Division Director	LaCivita, Cynthia, Pharm.D.
Review Completion Date	June 1, 2020
Subject	Evaluation of Need for a REMS
Established Name	celecoxib and tramadol tablets
Trade Name	Seglentis
Name of Applicant	Esteve Pharmaceuticals, S.A.
Therapeutic Class	NSAID and Opioid Analgesic
Formulation(s)	tablets containing tramadol hydrochloride 44 mg and celecoxib 56 mg
Dosing Regimen	two tablets every 12 hours as needed

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the combination oral tablet Seglentis (celecoxib and tramadol) is necessary to ensure the benefits outweigh its risks. Esteve Pharmaceuticals, S.A. submitted New Drug Application (NDA) 213426 for Seglentis with the proposed indication of management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The risks associated with Seglentis include those previously labeled for the constituent drugs, celecoxib and tramadol, including abuse, misuse, and overdose. The Agency has determined that a class-wide REMS is necessary for all opioid analgesics used in the outpatient setting, to ensure that the benefits outweigh the risks of adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. On September 18, 2018, the Opioid Analgesics REMS was expanded to include immediate release (IR) opioid analgesics in addition to extended-release and long-acting (ER/LA) opioid analgesics used in the outpatient setting.

This application will receive a Complete Response (CR) due to Chemistry Manufacturing and Controls (CMC) issues and a lack of evaluation of the potential risks associated with the unintended use of Seglentis. At this time, the Applicant has indicated that they intend to join to Opioid Analgesic REMS; however, DRM defers our evaluation of the REMS for Seglentis until the Applicant submits a response to the CR.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the combination product Seglentis (celecoxib and tramadol) is necessary to ensure the benefits of the drug outweigh the risks. Esteve Pharmaceuticals, S.A. submitted New Drug Application (NDA) 213426 for Seglentis (celecoxib and tramadol) with the proposed indication of management of acute[a] pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.[1] The applicant submitted a 505(b)(2) application referencing the two reference listed drugs (RLDs) celecoxib and tramadol which have been marketed in the US for more than 20 years.[b,2,3] This application is under review in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAMPM). The Applicant submitted a letter of authorization to join the Opioid Analgesic REMS.

2 Background

2.1 PRODUCT INFORMATION

Seglentis oral tablets are a combination of the approved products Celebrex (celecoxib) and Ultram (tramadol) for the proposed indication of management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The Applicant's rationale for development is that the combination product will provide a unique multimodal pain

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

management approach while limiting opioid exposure. Celebrex was initially approved in December 1998 and is a cyclooxygenase-2 (COX-2) selective inhibitor in the class of nonsteroidal anti-inflammatory drugs (NSAIDs).[2] Ultram was initially approved in March 1995 and is a μ-opioid agonist and a norepinephrine and serotonin re-uptake inhibitor.[3] One 100-mg tablet of Seglentis contains 56 mg of celecoxib and 44 mg of tramadol hydrochloride, with a molecular ratio of 1:1 for celecoxib and tramadol. The proposed dosing regimen is two tablets every twelve hours as needed for pain relief.[1] At the time of this review, there are no approved products containing combinations of tramadol and celecoxib anywhere in the world.

Ultram and Celebrex both carry boxed warnings. Boxed warnings for tramadol products include: potential for addiction, misuse, and abuse; respiratory depression especially in children with accidental overdose and post tonsillectomy and/or adenoidectomy; neonatal abstinence syndrome if prolonged use in pregnancy; and potential for interactions with drugs affecting cytochrome P450 isoenzymes and concomitant use with benzodiazepines or other central nervous system depressants which may cause additive respiratory depression.[c,4] The Agency has determined that a class-wide REMS is necessary for all opioid analgesics used in the outpatient setting, to ensure that the benefits outweigh the risks of adverse outcomes including addiction, unintentional overdose, and death.[5] The Opioid Analgesic (OA) REMS was approved in September 2018 and tramadol products are included in this class-wide REMS. The goal of the OA REMS is to educate prescribers and other healthcare providers (including pharmacists and nurses) on the treatment and monitoring of patients with pain. The education will provide information about the risks of opioids and use of other therapies which is intended to assist healthcare providers in reducing adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. Because Seglentis contains tramadol, if it were approved, it would join the OA REMS.

Celecoxib carries boxed warnings of: serious cardiovascular thrombotic events, including myocardial infarction and stroke; a contraindication in coronary artery bypass graft surgery; and increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.[c,6]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 213426 relevant to this review:

[c] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- May 17, 2018 - Pre-NDA meeting- Sponsor informed that the product would be required to join the OA REMS.
- May 15, 2019 - NDA submission received. The Applicant submitted a letter of authorization to reference the drug master file (DMF) in support of the Opioid Analgesic REMS.
- January 15, 2020- A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held to advise the approvability of Seglentis. The committee voted 13/13 regarding approval. Seglentis' proposed inclusion in the OA REMS was noted by committee members.
- February 13, 2020- an information request (IR) was sent requesting a risk assessment of abuse of Seglentis by the IV route per concerns from January 2020 advisory committee (AC).
- March 6, 2020- Major amendment acknowledgment letter sent to the applicant; PDUFA goal date extended by 3 months.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Pain is defined as an unpleasant sensory and potentially emotional experience caused by actual or potential tissue damage.[7] Pain can be multifactorial and further classified into acute or chronic depending upon the duration. Acute pain is generally self-limiting and requires treatment for no more than a few weeks.[7] Untreated or poorly treated acute pain can result in patient dissatisfaction, increased cost of treatment, prolonged hospital stays, and progression of acute pain to chronic pain.[d,8] The ubiquity of pain diagnoses makes the population likely to use the product proposed potentially very large.[e] Further, as pain can have vast implications on patients' general well-being, the personal and ultimately societal impacts of appropriate pain management are far-reaching.

3.2 Description of Current Treatment Options

Acute pain is treated with opioid and non-opioid medications, and somatic and behavioral supportive care. The opioids approved for pain management and included in the Opioid Analgesic (OA) REMS are brand name and generic products formulated with the active ingredients: buprenorphine, butorphanol, codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, tapentadol and, tramadol.[5] Multimodal therapy that limits the use of opioids when possible is an attractive option in the current acute pain treatment landscape, particularly in light of the ongoing opioid crisis.

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

4 Benefit Assessment

To prove the safety and efficacy of Seglentis, the Applicant submitted a 505(b)(2) application that relies in part on FDA's findings of safety and efficacy for Celebrex and Ultram as individual analgesic components. Further safety and efficacy of the combination product was established through five Phase 1 studies, one Phase 2 study, and one Phase 3 study.

The pivotal Phase 3 factorial trial, ESTEVE-SUSA-301[f], supporting this application consisted of a double-blind, active and placebo-controlled, multicenter study which evaluated Seglentis with celecoxib, tramadol, and placebo in 637 patients (Seglentis group=183, tramadol group=183, celecoxib group=182, placebo group=89) requiring pain management post bunionectomy. The primary endpoint of ESTEVE-SUSA-301 (83245) was the sum of the pain intensity difference (SPID) score taken throughout the 48 hour post-operative period. At all timepoints through 48 hours, the means of observed pain intensity scores were lower in the Seglentis group compared with all other treatment groups. The clinical reviewer concluded that the Applicant provided substantial evidence of efficacy for Seglentis compared to placebo based on decreased pain intensity scores. [g,9]

5 Risk Assessment & Safe-Use Conditions

The Applicant submitted a 505(b)(2) application that references the previous findings of safety of Ultram and Celebrex. Additionally, the Sponsor submitted safety results from seven studies used in the clinical program. From these studies, no new serious adverse events (SAEs)[h] were discovered with the combination product that were not previously illustrated in the RLDs.[9] A total of 21 non-novel SAEs were reported in 17 subjects from a pool of more than 2,000 subjects in the Seglentis clinical program. The most common adverse events reported in trials supporting this submission were nausea, vomiting, and somnolence, and dizziness.[9]

As previously mentioned, the RLDs in Seglentis carry numerous boxed warnings and tramadol is a member of the OA REMS. If approved, Seglentis will carry the boxed warnings as well as the following warnings and precautions based on what is included in labeling for the reference listed drugs for tramadol and celecoxib:[1]

- Serotonin Syndrome: May be life-threatening. Can occur with use of tramadol alone, with concomitant use of serotonergic drugs, with drugs that impair metabolism of serotonin or tramadol.

[f] NCT03108482

[g] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[h] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

- Risk of Seizure: Can occur at the recommended dose of tramadol. Concomitant use with other drugs may increase seizure risk. Risk may increase in patients with epilepsy, a history of seizures, and in patients with a recognized risk for seizures.
- Risk of Suicide: Do not prescribe for suicidal or addiction-prone patients.
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off the opioid.
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration.
- Severe Hypotension with tramadol: Monitor during dosage initiation. Avoid use in patients with circulatory shock.
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use in patients with impaired consciousness or coma.
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs.
- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop.
- Hypertension with Celecoxib: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.
- Heart Failure and Edema: Avoid use in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure.
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function.
- Exacerbation of Asthma Related to Aspirin Sensitivity: Seglentis is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity).
- Serious Skin Reactions: Discontinue at first appearance of skin rash or other signs of hypersensitivity.
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia.

Numerous contraindications also exist based on the established evidence and use of each RLD. If approved, Seglentis should not be used in the following populations:[1]

- Children younger than 12 years of age.
- Postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.
- Significant respiratory depression.
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment.
- Known or suspected gastrointestinal obstruction, including paralytic ileus.
- Hypersensitivity to tramadol, celecoxib, any other component of this product or sulfonamides, or opioids.
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.

- In the setting of CABG surgery.

The most common adverse events associated with either therapy which occur in more than 5% of users include: nausea, vomiting, dizziness, headache, and somnolence.[1]

The proposed dosage of Seglentis is two tablets every 12 hours, which contains tramadol 88 mg per dose with a total of 176 mg of tramadol per day. This is below the recommended maximum dose range for the reference product, Ultram, which is 200-400 mg per day.[9]

5.1 ABUSE, MISUSE AND OVERDOSE

Seglentis contains tramadol and all opioids are subject to potential abuse, misuse, and overdose. This potential is rooted in the biologically reinforcing properties of the drug. In 2017, the CDC reported 70,237 drug overdose deaths occurred in the United States and represented a continued increase in the age-adjusted rate of overdose deaths.[10] Further, more than 127,000 ED visits in 2016-2017 year were attributed to non-medical use of opioids.[8] The severity and extent of the opioid crisis continues to cause large scale pain and suffering in families afflicted as well the commitment of extensive resources from federal, state, local and private entities.

The Agency has determined that a class-wide REMS is necessary for all opioid analgesics used in the outpatient setting, to ensure that the benefits outweigh the risks. The goal of the OA REMS is to educate prescribers and other healthcare providers (including pharmacists and nurses) on the treatment and monitoring of patients with pain. The education provides information about the risks of opioids and use of other therapies which is intended to assist healthcare providers in reducing adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse.

The Drug Enforcement Administration (DEA) scheduled all tramadol-containing products to a Schedule IV designation in July 2014 in light of abuse and dependence potential.[8] Tramadol's scheduling is reflective of the limited "drug high" at supratherapeutic doses. However, the abuse of tramadol may have increased in recent years among those with Opioid Use Disorder.[8] Tramadol-involved overdose deaths increased from 2011 to 2017 though it is uncertain whether the observed increase is due to changes in use and abuse, increased surveillance, improved documentation, or other factors. Recent surveillance data implicate tramadol less frequently in prescription opioid misuse, abuse, and related outcomes than hydrocodone and oxycodone, but results were mixed for tramadol's position relative to codeine and morphine.[i,8]

The Comprehensive Addiction and Recovery Act of 2016, Section 106, requires FDA to refer new drug applications for opioids to an advisory committee before approval. The product was taken to the Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk

[i] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

Management Advisory Committee held on January 15, 2020 where expert panel voting resulted in a split vote (13 voted "no" and 13 "yes" to approval). Supporters of approval argued that the drug delivers less tramadol than does standalone tramadol dosing, a positive attribute in light of the ongoing opioid crisis, and that the combination product may be a better option than what is currently marketed for acute pain management. Detractors worried about the lack of drug abuse studies, inability to titrate dosing, the potential expansion of the population using opioids, and the potential lack of efficacy when compared to products individually titrated to effect.

Although abuse deterrent mechanisms are also encouraged to ensure safe use of new opioids to the market, Seglentis has not been formulated with any excipients to impart abuse-deterrent characteristics.

6 Expected Postmarket Use

If approved, Seglentis will be used in outpatient and inpatient settings. The likely prescribers will range from general practitioners and specialists who care for patients requiring acute pain management and are DEA registered to prescribe controlled substances. Training on pain management must be made available through the OA REMS to healthcare providers who are involved the prescribing and monitoring of patient treated with Seglentis. Prescribers should adhere to the OA REMS requirements, including participation in pain management education and appropriate patient counseling. If used in the outpatient setting, Seglentis will be dispensed by retail and/or mail-order pharmacies.

7 Risk Management Activities Proposed by the Applicant

The applicant did not submit a REMS with this application but did include a letter of authorization for the Drug Master File for the OA REMS and is proposing to join the existing shared system OA REMS if approved.

8 Discussion of Need for a REMS

The clinical reviewer recommends a Complete Response (CR) to this application due to lack of evaluation of the potential risks associated with the unintended use of Seglentis.[9] However, on March 2, 2020, the Applicant submitted an evaluation that is currently under review by the nonclinical team. The application will also receive a CR due to the Chemistry Manufacturing and Controls (CMC) issue of the Agency not being able to inspect a manufacturing facility due to a catastrophic event. Due to the CR action, DRM ultimately defers the evaluation of the need for a REMS though it is noted that Applicant has indicated that Seglentis will join the OA REMS if approved.

Seglentis contains the opioid tramadol, often used in the outpatient setting for pain management. Tramadol single ingredient and combination products are included in the OA REMS to ensure that the benefits of the drug outweigh the risks of abuse, misuse, and overdose. The OA REMS is a shared system REMS that was initially approved as the Extended-Release and Long-Acting (ER/LA) Opioid Analgesic

REMS in July 2012 and was expanded in September 2018 to include all application holders of immediate-release (IR) opioid analgesics that are expected to be used in the outpatient setting and that are not already covered by another REMS program.[5] The goal of the OA REMS is to educate prescribers and other healthcare providers (including pharmacists and nurses) on the treatment and monitoring of patients with pain. The education provided through the REMS program is based on the *Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain* ("FDA Blueprint"). Through better education, the healthcare team will have an improved understanding of how to manage pain and the role of opioid analgesics along with nonpharmacologic and non-opioid analgesics in pain management. The education will also provide information about the risks of opioids and use of other therapies which is intended to assist healthcare providers in reducing adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. Under the OA REMS, application holders are required to make educational programs available to healthcare providers. The application holders meet this requirement by providing educational grants to accredited continuing education (CE) providers who offer training to healthcare providers at no or nominal cost. The training includes successful completion of a knowledge assessment and proof of successful program completion.[5] The components of the OA REMS includes the following:

- Medication Guide
- Elements to Assure Safe Use
    - Prescriber Training
        - Based on FDA Blueprint
        - Letters to DEA Registered Prescribers
        - Letters to Professional Organizations/Licensing Boards
        - REMS website
- Timetable for Submission of Assessments

The Applicant has taken steps to have Seglentis included in the Opioid Analgesic (OA) REMS.

9 Conclusion & Recommendations

Because Seglentis contains tramadol, an opioid often used for outpatient pain management, inclusion in the OA REMS is necessary to ensure the benefits outweigh the risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from inappropriate prescribing, misuse, and abuse.

The review division recommends a CR; therefore, DRM will defer final review until additional safety information and product quality information is provided and reviewed if/when the NDA is resubmitted.

10 Appendices

10.1 References

[1] Proposed prescribing information for Seglentis as currently edited by FDA, Accessed June 1, 2020.

[2] "Drug Approval Package." Celebrex (Celecoxib) NDA# 20-998, FDA, 5 July 2005, www.accessdata.fda.gov/drugsatfda_docs/nda/98/20998.cfm.

[3] "Drugs@FDA: FDA-Approved Drugs." Tramadol Hydrochloride, FDA, 7 Oct. 2019, www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=020281.

[4] Ultram (tramadol) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2019.

[5] Approved Risk Evaluation and Mitigation Strategies (REMS), Opioid Analgesic (OA) REMS. FDA. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=17

[6] Celebrex (celecoxib) [package insert]. NY, NY: Pfizer, Inc.; 2019.

[7] IASP Terminology. IASP. https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698. Published December 14, 2017. Accessed April 9, 2020.

[8] Lowy N, Advisory Committee Background Materials for AADPAC/DSaRM Meeting to Discuss NDA 213426, dated January 15, 2020.

[9]Haghpanah, Sepideh. Clinical Review for E-58425 [TRADENAME] (celecoxib and tramadol, tablet), NDA 213426, March 16, 2020.

[10] Drug Overdose Deaths. Centers for Disease Control and Prevention. https://www.cdc.gov/drugverdose/data/statedeaths.html. Published March 19, 2020. Accessed March 9, 2020

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/s/

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