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You propose to use a shared system for the elements to assure safe use and the REMS assessments. This shared system, known as the Opioid Analgesic REMS program, includes the products listed on the FDA REMS website available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

Your proposed REMS, submitted to Drug Master File (DMF) 031551, amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Seglentis (celecoxib and tramadol hydrochloride) into interstate commerce. Because Seglentis (celecoxib and tramadol hydrochloride) will be a member of the Opioid Analgesic REMS, the assessment plan will be the same assessment plan required for the other products covered by this shared system REMS. The assessments are required to be submitted 6 months, and 12 months, and annually thereafter from the date of after the initial approval of the Opioid Analgesic REMS (September 18, 2018). Because the 6-month, 1-Year, and 2-Year assessment reports have already been submitted, and the 3-Year assessment report for the Opioid Analgesic REMS will not include this product, the first assessment report that includes Seglentis (celecoxib and tramadol hydrochloride) will be due September 18, 2022. This reporting date will align with the 4-Year report for the Opioid Analgesic REMS.

Submission of subsequent REMS assessment reports for Seglentis (celecoxib and tramadol hydrochloride) will align with the assessment reports of the Opioid Analgesic REMS.

Therefore, your REMS should include but is not limited to the following:

1. REMS Outreach and Communication
    a. For each healthcare provider (e.g., prescriber, pharmacist) to be sent information regarding REMS-compliant accredited continuing education (CE), provide the date when the letters were sent; the number of letters electronically sent, received, undeliverable, and opened; and the number of letters mailed and undeliverable.
    b. For each professional society, association, and licensing board to be sent information regarding REMS-compliant accredited CE, provide the number of letters electronically sent, received, undeliverable, and opened; and the number of letters mailed and undeliverable.
2. REMS Implementation and Operations
    a. Status of grants

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i. The status of the request for proposals for grants for REMS-compliant accredited CE including:

1. Request for Application (RFA) issued: date and number of applications submitted in response to each RFA
2. RFAs awarded: date, number, and name of grantee
3. Date/timeframe next RFA to be issued

ii. The status of the requests for proposals for any grants to CE Providers or other CE organizations with expertise in assessing CE outcomes who agree to conduct evaluations of health care providers who have taken REMS-compliant accredited CE funded under this REMS.

b. Grant review committee

i. Individuals from the REMS Program Companies (RPC) reviewing grants will include the following clinical licensures: pharmacists, nurses, physicians. Additionally, there will be involvement by individuals with regulatory and pharmacovigilance experience. The job title, licensure, and professional degree of individuals will be provided for each grant review cycle.

ii. Include any external members (non-RPC) involved in the grant review, including those from the broad-based CE community. Provide the job title, licensure and professional degree of the individual for each grant review cycle

c. For CE programs awarded during the assessment period:

i. Description of each grantee and projected number of completers

ii. For the first assessment, the date the first program based upon the FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain ("FDA Blueprint"), became available

iii. Description of CE program:

1. Level of outcome the activity[3] is designed to impact
2. CE format (live, webinar, etc.)
3. Duration of activity for live or webinar activities
4. Average duration to complete for internet/enduring activities

[3] Stevenson R, Moore DE. Ascent to the Summit of the CME Pyramid. JAMA 2018;319(6):543-544.

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5. Education methods and tools (case-based, multimedia, didactic, interactive, adaptive, etc.)[4,5]

iv. All reports submitted to the RPC by CE grantees during the assessment period.

d. Number of completers of OA REMS Continuing Education activities during the assessment period; provide description of learners by standard learner category data.[6]

i. Summary of reports from any CE Provider that tracks participants that begin an activity but do not complete it; only provide when insight on lack of completion is available (e.g., participant didn't complete because activity too long, too difficult, etc.)

e. Independent Audit: The results of independent audits of the CE. Audits must be conducted on a random sample of at least 10% of the REMS-compliant accredited CE funded under the Opioid Analgesic REMS and must include/evaluate:

i. a description of the organization(s) conducting the audit(s)

ii. whether the content of the REMS-compliant accredited CE covers all elements of the FDA Blueprint approved as part of the REMS;

iii. whether the integrated or post-course knowledge assessment measures knowledge of all sections of the FDA Blueprint; and

iv. whether the REMS-compliant accredited CE was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies

f. Concurrent Educational Interventions

i. For the year prior to the assessment period through the assessment period, provide an evaluation of the overall pain/opioid CE landscape including but not limited to:

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[4] Cervero R, Gaines J. The Impact of CME on Physician Performance and Patient Health Outcomes: An Updated Synthesis of Systematic Reviews J Contin Educ Health Prof 2015;35(2):131–138.
[5] Agency for Research Health and Quality. (2007). Effectiveness of Continuing Medical Education. Retrieved May 9, 2018, from https://archive.ahrq.gov/downloads/pub/evidence/pdf/cme/cme.pdf.
[6] Standard Continuing Education (CE) learner data to be captured by all CE Providers for Opioid Analgesic REMS includes geographic location (state of primary practice), DEA prescriber status (individual registration or institutional authorization), profession, practice area, and length of time in practice.

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1. States requiring prescribers, pharmacists or nurses to complete opioid or pain management continuing education for licensing/renewal of licensing:
    a. Enumeration of these states and their requirements for continuing education on either pain or safe opioid use,
    b. estimates of annual licensed prescribers in those states
    c. which, if any, opioid analgesic or Extended-Release/Long-Acting ("ER/LA") Opioid Analgesic REMS CE (i.e., current and former REMS program) were permissible in which states, for prescribers to meet requirements
2. Health systems, including government (DOD, VA, IHS, etc.), that require opioid or pain management continuing education; include number of completers if available
3. Any additional available data on continuing education programs available during this time with a focus on pharmacological pain management or safe opioid use

3. Health Outcomes and/or Surrogates of Health Outcomes
    a. Surveillance and monitoring of data relating to opioid analgesic use, misuse, abuse, overdose, addiction, and death. Surveillance data should include the following:
        i. Nationally representative data or data from large stable populations on opioid analgesic misuse, abuse, addiction, overdose, and death, to allow reliable assessment of national trends and demographic patterns (e.g., age group specific rates and trends)
        ii. Both overall and drug-specific outcome rates, as available, in each data source
        iii. Data on trends and patterns of illicit opioid (e.g., heroin) use and related morbidity and mortality
    b. Evaluation of drug utilization patterns: Nationally-projected data on drug utilization trends and patterns, including an evaluation of trends in:
        i. Dispensing of opioid analgesics subject to the Opioid Analgesic REMS, by drug, age group, prescriber specialty
        ii. An evaluation of opioid tolerance for products that require patients to be opioid tolerant prior to use

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iii. Patient-level evaluation of concomitant prescribing of gabapentinoids, benzodiazepines, and other CNS depressants with opioid analgesics

c. An evaluation of patients' experiences with acute and chronic pain management in various settings: this may include a survey, focus group, or other assessment of patient experience, including but not limited to access to coordinated pain management care, non-pharmacological options, and judicious and informed prescribing of opioids. The evaluation may also include an assessment of negative patient experiences, such as perceived overprescribing of opioids, providers' refusal to provide care, or forced rapid tapering or discontinuation.

d. Evaluation of prescriber behavior and patient outcomes: The results of an evaluation of the effect of REMS-compliant CE on prescriber behavior and patient outcomes. This evaluation should include the following:

i. Development and use of metrics that assess prescriber behaviors and patient outcomes relating to key messages in the FDA Blueprint. The assessment should also include an evaluation of potential unintended adverse patient outcomes resulting from changes in prescribing practices (e.g., withdrawal symptoms or increased pain due to inappropriate rapid opioid tapering, patient abandonment, seeking of illicit opioids, suicide attempts/completion)

ii. Use of an appropriate control group (i.e., providers who have not completed REMS-compliant accredited CE), and rigorous control for confounding, to allow an assessment of whether any observed changes in prescriber behaviors or patient outcomes can be attributed to the CE

e. Evaluation of healthcare providers' perceptions of the key influences (e.g., education, state legislation, system-level policies, fear of reprimand or litigation, insurance reimbursement, time constraints) on pain management practices for prescribers and other members of the healthcare team and what the impacts have been on patient outcomes. For the 24-month assessment,

f. Conduct a literature review and summarize previous work in this area.

g. Propose a study or studies to address the evaluation of the key influences on a sample of opioid prescribers. These studies may employ mixed-methods approaches and other emerging research methodologies most appropriate for answering the question.

4. Knowledge

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a. Evaluation of CE participants: The results of evaluations to determine the impact of REMS-compliant accredited CE on participants' knowledge, attitudes, and self-reported behavior around pain management and appropriate opioid prescribing. All evaluations should be representative and generalizable to the targeted health care professionals taking the REMS-compliant accredited CE and assess understanding of key elements from all sections of the FDA Blueprint. Multiple methodologies should be used, including but not limited to the following:

    i. These assessments could be integrated into live, online, or multimedia formats using interactive approaches to enhance the educational value of the activity. Different versions or subsets of questions from a standardized assessment tool could be employed to cover all key messages and sections of FDA Blueprint, in aggregate, while reducing the time burden for individual participants and allowing the assessment to be tailored for different types of healthcare professionals.

    ii. A long-term follow-up evaluation of participants to assess retention of knowledge and skills, application of learning to clinical practice, self-reported change in behavior, and barriers to change. Consider incentivizing participation in follow-up assessment, for example through additional CE credits.

b. Evaluation of Patient Understanding: The results of an evaluation of patients' and caregivers' understanding of the serious risks of opioid analgesics and their understanding of how to use these products safely. This evaluation may include, for example, surveys of patients from a representative sample of patients taking opioid analgesics with respect to education level, insurance status, and geographic location.

5. During transition from the ER/LA Opioid Analgesics REMS to Opioid Analgesic REMS, data to be included until the last enduring activity has been reported:

    a. For each CE activity released under the ER/LA Opioid Analgesics REMS that remains active, provide the name of the CE Provider, the title of the activity, and the date the activity will expire

    b. Aggregate data on participants and completers should be collected using original MEMS 2.0 definitions

6. Methodologies: A timeline for submission of the assessment protocols, including data sources and the methodologies used to conduct all the above described analyses. Each assessment report should update the dates of submission for each component of the assessment.

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7. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan

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necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 213426 REMS ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 213426 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 213426/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 213426/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

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or

NEW SUPPLEMENT FOR NDA 213426/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 213426/S-000/
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 213426

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[7]

[7] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[8] Information and Instructions for completing the form can be found at FDA.gov.[9]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jaimin Patel, Regulatory Project Manager, at (301) 796-0412.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Director
Division of Anesthesiology, Addiction Medicine and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling
- REMS

[8] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[9] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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

SEGLENTIS (celecoxib and tramadol hydrochloride) tablets, for oral use, C-IV
Initial U.S. Approval: 2021

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; CARDIOVASCULAR THROMBOTIC EVENTS; GASTROINTESTINAL BLEEDING, ULCERATION, AND PERFORATION; ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
See full prescribing information for complete boxed warning.

- **SEGLENTIS exposes users to the risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing SEGLENTIS and monitor regularly for these behaviors or conditions. (5.1)**
- **To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially during initiation or following a dose increase. (5.3)**
- **Accidental ingestion of SEGLENTIS, especially by children, can result in a fatal overdose of tramadol. (5.3)**
- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use. (5.4)**
- **SEGLENTIS is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.4)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.5)**
- **Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism (5.6)**
- **SEGLENTIS is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (4). Avoid the use of SEGLENTIS in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol. (5.6)**
- **Prolonged use of SEGLENTIS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.7)**
- **The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with SEGLENTIS requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1. (5.8, 7)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.9, 7)**

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

SEGLENTIS contains tramadol hydrochloride, an opioid agonist, and celecoxib, a nonsteroidal anti-inflammatory drug, and is indicated for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate (1).

Limitations of Use (1):

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses (5.1), reserve SEGLENTIS for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- Have not been tolerated, or are not expected to be tolerated
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

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

- Use SEGLENTIS for the shortest duration consistent with individual patient treatment goals (2.1).
- Initiate treatment of SEGLENTIS with two tablets every 12 hours as needed for pain relief (2.3).
- When initiating treatment with SEGLENTIS, take into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse (2.1).
- Discuss availability of naloxone with the patient and assess each patient's need for access to naloxone, both when initiating and renewing treatment with SEGLENTIS. Consider prescribing naloxone based on the patient's risk factors for overdose (2.2, 5.1, 5.3, 5.9).
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with SEGLENTIS (2.1).
- Do not abruptly discontinue SEGLENTIS in a physically dependent patient (2.4, 5.28).
- Do not use with other celecoxib- or tramadol-containing products (2.1).

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

Tablets: celecoxib 56 mg and tramadol hydrochloride 44 mg (3).

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

- Children younger than 12 years of age (4).
- Postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (4).
- Significant respiratory depression (4).
- In the setting of CABG surgery (4).
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4).
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4).
- Hypersensitivity to tramadol, celecoxib, any other component of this product, or sulfonamides, or opioids (4).
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days (4).
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4).

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

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 (5.10).

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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 (5.11).

Risk of Suicide: Do not prescribe for suicidal or addiction-prone patients (5.12).

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off the opioid (5.13).

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration (5.14).

Severe Hypotension with Tramadol: Monitor during dosage initiation. Avoid use of SEGLENTIS in patients with circulatory shock (5.15).

Risk of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of SEGLENTIS in patients with impaired consciousness or coma (5.16).

Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.18).

Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.19).

Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.20, 7).

Heart Failure and Edema: Avoid use of SEGLENTIS in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.21).

Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of SEGLENTIS in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.22).

Exacerbation of Asthma Related to Aspirin Sensitivity: SEGLENTIS is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.23).

Serious Skin Reactions: Discontinue SEGLENTIS at first appearance of skin rash or other signs of hypersensitivity (5.24).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.25).

Fetal Toxicity: Limit use of NSAIDs, including SEGLENTIS, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.26, 8.1).

Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.27, 7)

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

Most common adverse reactions (incidence > 5% and > placebo) are nausea, vomiting, dizziness, headache, somnolence (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Kowa Pharmaceuticals America, Inc., at toll-free phone 1-888-SEGLENTIS or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with SEGLENTIS because they may reduce analgesic effect of SEGLENTIS or precipitate withdrawal symptoms (7).

Drugs that Interfere with Hemostasis (e.g., warfarin, aspirin, selective serotonin reuptake inhibitors [SSRIs]/serotonin norepinephrine reuptake inhibitors [SNRIs]): Monitor patients for bleeding who are concomitantly taking SEGLENTIS with drugs that interfere with hemostasis. Concomitant use of SEGLENTIS and analgesic doses of aspirin is not generally recommended (7).

Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with SEGLENTIS may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7).

ACE Inhibitors and ARBs: Concomitant use with SEGLENTIS in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high-risk patients, monitor for signs of worsening renal function (7).

Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7).

Digoxin: Concomitant use with SEGLENTIS can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7).

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

Pregnancy: May cause fetal harm (8.1)

Lactation: Breastfeeding not recommended (8.2).

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of SEGLENTIS in women who have difficulties conceiving (8.3).

Severe Renal Impairment: Use not recommended (8.6).

Moderate and Severe Hepatic Impairment: Use not recommended (8.7).

Poor Metabolizers of CYP2C9: Due to the inability to start SEGLENTIS at a lower dose, use of SEGLENTIS is not recommended (8.8).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

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ADDICTION, ABUSE, AND MISUSE

SEGLENTIS exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing SEGLENTIS and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

OPIOID ANALGESIC RISK EVALUATION AND MITIGATION STRATEGY (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.2)]*. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

LIFE-THREATENING RESPIRATORY DEPRESSION

Serious, life-threatening, or fatal respiratory depression may occur with use of SEGLENTIS. Monitor for respiratory depression, especially during initiation of SEGLENTIS *[see Warnings and Precautions (5.3)].*

ACCIDENTAL INGESTION

Accidental ingestion of even one dose of SEGLENTIS, especially by children, can be fatal *[see Warnings and Precautions (5.3)]*.

CARDIOVASCULAR THROMBOTIC EVENTS

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction, and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use *[see Warnings and Precautions (5.4)].***
- **SEGLENTIS is contraindicated in the setting of coronary artery bypass graft (CABG) surgery *[see Contraindications (4) and Warnings and Precautions (5.4)].***

GASTROINTESTINAL BLEEDING, ULCERATION, AND PERFORATION

NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can

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be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious (GI) events *[see Warnings and Precautions (5.5)]*.

ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN

Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism *[see Warnings and Precautions (5.6)]*. SEGLENTIS is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*. Avoid the use of SEGLENTIS in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol *[see Warnings and Precautions (5.6)].*

NEONATAL OPIOID WITHDRAWAL SYNDROME

Prolonged use of SEGLENTIS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.7)]*.

INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with SEGLENTIS requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1 *[see Warnings and Precautions (5.8), Drug Interactions (7)]*.

RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.9) and Drug Interactions (7)]*.

- **Reserve concomitant prescribing of SEGLENTIS and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit treatment to the minimum duration.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

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1 INDICATIONS AND USAGE

SEGLENTIS is indicated for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.1)]*, reserve SEGLENTIS for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- Have not been tolerated, or are not expected to be tolerated.
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Do not exceed the recommended dose of SEGLENTIS.
- Do not co-administer SEGLENTIS with other tramadol or celecoxib containing products.
- Use SEGLENTIS for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5.1)]*.
- When initiating treatment with SEGLENTIS, take into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy *[see Warnings and Precautions (5.3)]*.

2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with SEGLENTIS *[see Warnings and Precautions (5.3)]*.

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient’s risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. However, the presence of risk factors for overdose should not prevent the proper management of pain in any given patient *[see Warnings and Precautions (5.1, 5.3, 5.9)]*.

Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental exposure or overdose.

2.3 Recommended Dosage

The dose of SEGLENTIS 56 mg/44 mg is 2 tablets every 12 hours as needed for pain.

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2.4 Safe Reduction or Discontinuation of SEGLENTIS

Do not abruptly discontinue SEGLENTIS in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking SEGLENTIS, there are a variety of factors that should be considered, including the total daily dose of opioid (including SEGLENTIS) the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with co-morbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on SEGLENTIS who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily opioid dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with a reduced dosing schedule of SEGLENTIS to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.28), Drug Abuse and Dependence (9.2 and 9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

SEGLENTIS coated tablets contain 56 mg celecoxib and 44 mg tramadol hydrochloride (equivalent to

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39 mg tramadol). The tablets are white to off-white elongated coated tablets debossed with "100" on one side and "CTC" on the other.

4 CONTRAINDICATIONS

SEGLENTIS is contraindicated in:

- All patients younger than 12 years of age *[see Warnings and Precautions (5.6)]*.
- Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Warnings and Precautions (5.6)]*.

SEGLENTIS is also contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)].*
- In the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (5.4)].*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.14)].*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.17)].*
- Previous hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to tramadol, opioids, celecoxib, sulfonamides, or any other component of the drug product *[see Warnings and Precautions (5.18)].*
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days *[see Drug Interactions (7)]*.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs, have been reported in such patients *[see Warnings and Precautions (5.18, 5.23)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse and Misuse

<u>Tramadol</u>

SEGLENTIS contains tramadol, a Schedule IV controlled substance. As an opioid, SEGLENTIS exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed SEGLENTIS. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing SEGLENTIS, and monitor all patients receiving SEGLENTIS for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as SEGLENTIS, but use in such patients necessitates intensive counseling about the risks and proper use of SEGLENTIS along with intensive

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monitoring for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing SEGLENTIS. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

Tramadol

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.3 Life-Threatening Respiratory Depression

Tramadol

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of SEGLENTIS, the risk is greatest during the initiation of therapy. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with SEGLENTIS.

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To reduce the risk of respiratory depression, proper dosing of SEGLENTIS is essential *[see Dosage and Administration (2)]*. Overestimating the SEGLENTIS dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of SEGLENTIS, especially by children, can result in respiratory depression and death due to an overdose of tramadol.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia.

Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.4)].*

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with SEGLENTIS. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered.

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. However, the presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental exposure or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone *[see Warnings and Precautions (5.1, 5.9)*.

5.4 Cardiovascular Thrombotic Events

Celecoxib

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

In the APC (Adenoma Prevention with Celecoxib) trial, there was about a threefold increased risk of the composite endpoint of cardiovascular death, MI, or stroke for the celecoxib 400 mg twice daily

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and celecoxib 200 mg twice daily treatment arms compared to placebo. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction.

A randomized controlled trial entitled the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (PRECISION) was conducted to assess the relative cardiovascular thrombotic risk of a COX-2 inhibitor, celecoxib, compared to the non-selective NSAIDs naproxen and ibuprofen. Celecoxib 100 mg twice daily was non-inferior to naproxen 375 to 500 mg twice daily and ibuprofen 600 to 800 mg three times daily for the composite endpoint of the Antiplatelet Trialists' Collaboration (APTC), which consists of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke.

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

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as celecoxib, increases the risk of serious gastrointestinal (GI) events *[see Warnings and Precautions (5.5)]*.

Status Post Coronary Artery Bypass Graft (CABG) Surgery

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

Post-MI Patients

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

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

5.5 Gastrointestinal Bleeding, Ulceration, and Perforation

Celecoxib

NSAIDs, including celecoxib, a component of SEGLENTIS, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-

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term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

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

Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the CLASS trial, and 2.19% for the subgroup on low-dose ASA. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA.

Strategies to Minimize the GI Risks in NSAID-treated patients

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

5.6 Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children

Tramadol

Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to increased exposure to an active metabolite. Based upon postmarketing reports with tramadol or with codeine, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol. Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- SEGLENTIS is contraindicated for all children younger than 12 years of age because SEGLENTIS contains tramadol *[see Contraindications (4)]*.
- SEGLENTIS is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.
- Avoid the use of SEGLENTIS in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the

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benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.

- As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of opioid overdose *[see Use in Special Populations (8.4), Overdosage (10)].*

Lactating Women

Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of *O*-desmethyltramadol (M1). At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. A baby nursing from an ultra-rapid metabolizer mother taking SEGLENTIS could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with SEGLENTIS *[see Use in Specific Populations (8.2)]*.

CYP2D6 Genetic Variability: Ultra-rapid metabolizer

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert tramadol into its active metabolite, *O*-desmethyltramadol (M1), more rapidly and completely than other people. This rapid conversion results in higher-than-expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) *[see Overdosage (10)]*. Therefore, individuals who are ultra-rapid metabolizers should not use SEGLENTIS.

5.7 Neonatal Opioid Withdrawal Syndrome

Tramadol

Prolonged use of SEGLENTIS during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1)]*.

5.8 Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

Tramadol

The effects of concomitant use or discontinuation of CYP3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors on levels of tramadol and M1 from SEGLENTIS are complex. Use of CYP3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with SEGLENTIS requires careful consideration of the effects on the parent drug, tramadol, which is a weak serotonin and norepinephrine reuptake inhibitor and μ-opioid

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agonist, and the active metabolite, M1, which is more potent than tramadol in μ-opioid receptor binding *[see Drug Interactions (7)]*.

Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors

Because SEGLENTIS contains tramadol, the concomitant use of SEGLENTIS with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in tramadol plasma levels and a decrease in the levels of the active metabolite, M1. A decrease in M1 exposure in patients who have developed physical dependence to tramadol, may result in signs and symptoms of opioid withdrawal and reduced efficacy. The effect of increased tramadol levels may be an increased risk for serious adverse events including seizures and serotonin syndrome.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in tramadol plasma levels and an increase in active metabolite M1 levels, which could increase or prolong adverse reactions related to opioid toxicity and may cause potentially fatal respiratory depression.

Follow patients receiving tramadol and any CYP2D6 inhibitor for the risk of serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity, and opioid withdrawal when SEGLENTIS is used in conjunction with inhibitors of CYP2D6 *[see Drug Interactions (7)]*.

Cytochrome P450 3A4 Interaction

Because SEGLENTIS contains tramadol, the concomitant use of SEGLENTIS with cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in tramadol plasma concentrations, which could increase or prolong adverse reactions, increase the risk for serious adverse events including seizures and serotonin syndrome, and may cause potentially fatal respiratory depression.

The concomitant use of SEGLENTIS with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower tramadol levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal.

Follow patients receiving SEGLENTIS and any CYP3A4 inhibitor or inducer for the risk for serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity and opioid withdrawal when SEGLENTIS is used in conjunction with inhibitors and inducers of CYP3A4 *[see Drug Interactions (7)]*.

5.9 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

<u>Tramadol</u>

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of SEGLENTIS with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

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If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when SEGLENTIS is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7)]*.

5.10 Serotonin Syndrome Risk

Tramadol

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported with the use of tramadol, a component of SEGLENTIS, particularly during concomitant use with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7)]*. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use but may occur later than that. Discontinue SEGLENTIS if serotonin syndrome is suspected.

5.11 Increased Risk of Seizures

Tramadol

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range.

Concomitant use of SEGLENTIS increases the seizure risk in patients taking: *[see Drug Interactions (7)]*:

- Selective serotonin re-uptake inhibitors (SSRIs) and Serotonin-norepinephrine re-uptake inhibitors (SNRIs) antidepressants or anorectics,

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- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.),
- Other opioids,
- MAO inhibitors *[see Warnings and Precautions (5.10), Drug Interactions (7)]*
- Neuroleptics, or
- Other drugs that reduce the seizure threshold.

Risk of seizures may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In SEGLENTIS overdose, naloxone administration may increase the risk of seizure.

5.12 Suicide Risk

Tramadol

- Do not prescribe SEGLENTIS for patients who are suicidal or addiction-prone. Consideration should be given to the use of non-narcotic analgesics in patients who are suicidal or depressed *[see Drug Abuse and Dependence (9)]*.
- Prescribe SEGLENTIS with caution for patients with a history of misuse and/or are currently taking CNS-active drugs including tranquilizers, or antidepressant drugs, alcohol in excess, and patients who suffer from emotional disturbance or depression *[see Drug Interactions (7)]*.
- Inform patients not to exceed the recommended dose and to limit their intake of alcohol *[see Dosage and Administration (2), Warnings and Precautions (5.9)]*.

5.13 Adrenal Insufficiency

Tramadol

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.14 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

Tramadol

The use of SEGLENTIS in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease

SEGLENTIS-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at

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the recommended dosage of SEGLENTIS *[see Warnings and Precautions (5.3)]*.

Elderly, Cachectic, or Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics, or altered clearance, compared to younger, healthier patients *[see Warnings and Precautions (5.3)]*.

Monitor such patients closely, particularly when initiating SEGLENTIS and when SEGLENTIS is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.9), Drug Interactions (7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.15 Severe Hypotension

Tramadol

Tramadol, a component of SEGLENTIS, may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating dosage of SEGLENTIS. In patients with circulatory shock, tramadol may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of SEGLENTIS in patients with circulatory shock.

5.16 Risk of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

Tramadol

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), SEGLENTIS may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with SEGLENTIS.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of SEGLENTIS in patients with impaired consciousness or coma.

5.17 Risk of Use in Patients with Gastrointestinal Conditions

Tramadol

SEGLENTIS is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus *[see Contraindications (4)]*.

The tramadol in SEGLENTIS may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.18 Anaphylaxis and Other Hypersensitivity Reactions

Tramadol

Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol, a component of SEGLENTIS. When these events do occur, it is often following the first

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dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Patients with a history of hypersensitivity reactions to tramadol and other opioids may be at increased risk and therefore should not receive SEGLENTIS *[see Contraindications (4)]*. If anaphylaxis or other hypersensitivity occurs, stop administration of SEGLENTIS immediately, discontinue SEGLENTIS permanently, and do not rechallenge with any formulation of tramadol. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction *[see Contraindications (4)]*.

Celecoxib

Celecoxib, a component of SEGLENTIS has been associated with anaphylactic reactions in patients with and without known hypersensitivity to celecoxib and in patients with aspirin sensitive asthma. Celecoxib is a sulfonamide and both NSAIDs and sulfonamides may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people *[see Contraindications (4) and Warnings and Precautions (5.23)]*.

Seek emergency help if any anaphylactic reaction occurs.

5.19 Hepatotoxicity

As tramadol and celecoxib are both extensively metabolized by the liver, the use of SEGLENTIS in patients with moderate and severe hepatic impairment is not recommended *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].*

Celecoxib

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

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

In controlled clinical trials of celecoxib, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for celecoxib and 5% for placebo, and approximately 0.2% of patients taking celecoxib and 0.3% of patients taking placebo had notable elevations of ALT and AST.

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

5.20 Hypertension

Celecoxib

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

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

5.21 Heart Failure and Edema

Celecoxib

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

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

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

In the CLASS study, the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on celecoxib 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively.

5.22 Renal Toxicity and Hyperkalemia

Celecoxib

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

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

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

Correct volume status in dehydrated or hypovolemic patients prior to initiating SEGLENTIS. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of SEGLENTIS *[see Drug Interactions (7)]*. Use of SEGLENTIS in patients with advanced renal disease is not recommended *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these

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effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.23 Exacerbation of Asthma Related to Aspirin Sensitivity

Celecoxib

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

5.24 Serious Skin Reactions

Celecoxib

Serious skin reactions have occurred following treatment with celecoxib, a component of SEGLENTIS, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). These serious events may occur without warning and can be fatal.

Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of SEGLENTIS at the first appearance of skin rash or any other sign of hypersensitivity. SEGLENTIS is contraindicated in patients with previous serious skin reactions to NSAIDs *[see Contraindications (4)]*.

5.25 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as SEGLENTIS. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue SEGLENTIS and evaluate the patient immediately.

5.26 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus
Avoid use of NSAIDs, including SEGLENTIS, in pregnant women at about 30 weeks gestation and later. NSAIDs, including SEGLENTIS, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment
Use of NSAIDs, including SEGLENTIS, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

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Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit SEGLENTIS use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if SEGLENTIS treatment extends beyond 48 hours. Discontinue SEGLENTIS if oligohydramnios occurs and follow up according to clinical practice [*see Use in Specific Populations (8.1)*].

5.27 Hematological Toxicity

Celecoxib

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

In controlled clinical trials the incidence of anemia was 0.6% with celecoxib and 0.4% with placebo. Patients on long-term treatment with SEGLENTIS should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

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

5.28 Withdrawal

Tramadol

Do not abruptly discontinue SEGLENTIS in a patient physically dependent on opioids. When discontinuing SEGLENTIS in a physically dependent patient, gradually taper the dosage. Rapid tapering of tramadol in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.4), Drug Abuse and Dependence (9.3)]*. Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including SEGLENTIS. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

5.29 Driving and Operating Machinery

Tramadol

SEGLENTIS may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of SEGLENTIS and know how they will react to the medication.

5.30 Masking of Inflammation and Fever

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Celecoxib

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

5.31 Hyponatremia

Hyponatremia (serum sodium < 135 mmol/L) has been reported with the use of tramadol, a component of SEGLENTIS, and many cases are severe (sodium level < 120 mmol/L). Most cases of hyponatremia occurred in females over the age of 65 and within the first week of therapy. In some reports, hyponatremia resulted from the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Monitor for signs and symptoms of hyponatremia (e.g., confusion, disorientation), during treatment with SEGLENTIS, especially during initiation of therapy. If signs and symptoms of hyponatremia are present, initiate appropriate treatment (e.g., fluid restriction) and discontinue SEGLENTIS [*see Dosage and Administration (2.4)*].

5.32 Hypoglycemia

Cases of tramadol-associated hypoglycemia have been reported, some resulting in hospitalization. In most cases, patients had predisposing risk factors (e.g., diabetes). If hypoglycemia is suspected, monitor blood glucose levels and consider drug discontinuation as appropriate [*see Dosage and Administration (2.4)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- Cardiovascular Thrombotic Events *[see Warnings and Precautions (5.4)]*
- GI Bleeding, Ulceration and Perforation *[see Warnings and Precautions (5.5)]*
- Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children *[see Warnings and Precautions (5.6)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.7)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.9)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Suicide *[see Warnings and Precautions (5.12)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.13)]*
- Severe Hypotension *[see Warnings and Precautions (5.15)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.17)]*
- Anaphylaxis and Other Hypersensitivity Reactions *[see Warnings and Precautions (5.18)]*
- Hepatotoxicity *[see Warnings and Precautions (5.19)]*
- Hypertension *[see Warnings and Precautions (5.20)]*

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- Heart Failure and Edema *[see Warnings and Precautions (5.21)]*
- Renal Toxicity and Hyperkalemia *[see Warnings and Precautions (5.22)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.24)]*
- Hematologic Toxicity *[see Warnings and Precautions (5.27)]*
- Withdrawal *[see Warnings and Precautions (5.28)]*

6.1 Clinical Trials Experience

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

A total of 550 subjects in 7 clinical studies, from Phase 1 to Phase 3, were exposed to SEGLENTIS during the clinical development program, including 385 subjects exposed to 200 mg of SEGLENTIS, either single or multiple administration.

In a placebo-controlled post-bunionectomy acute pain trial, 637 patients received 200 mg of SEGLENTIS every 12 hours or 50 mg tramadol every 6 hours or 100 mg celecoxib every 12 hours or placebo, orally for 48 hours (blinded period) *[see Clinical Studies (14)]* and followed up to 7 days post-dose. Table 1 lists the adverse reactions reported by > 5% of patients in any treatment group and greater in SEGLENTIS than placebo. Discontinuation due to adverse events occurred in 1.6% of SEGLENTIS-treated patients (3 out of 183), 1.6% of tramadol-treated patients (3 out of 183), no celecoxib-treated patients, and no placebo-treated patients. The adverse reactions that led to discontinuation of study drug were nausea (1.1%) and pruritus/rash (0.5%) in the SEGLENTIS group, and vomiting (1.1%) and supraventricular tachycardia (0.5%) in the tramadol group.

Table 1: Reported Adverse Reactions in >5% of Patients in Any Treatment Group and greater in SEGLENTIS than Placebo

System Organ Class **Preferred Term**	**SEGLENTIS** **(N = 183)** **n (%)**	**Tramadol** **(N = 183)** **n (%)**	**Celecoxib** **(N = 182)** **n (%)**	**Placebo** **(N = 89)** **n (%)**
Gastrointestinal disorders				
Nausea	55 (30.1)	69 (37.7)	30 (16.5)	17 (19.1)
Vomiting	29 (15.8)	30 (16.4)	4 (2.2)	2 (2.2)
Nervous system disorders				
Dizziness	31 (16.9)	34 (18.6)	9 (4.9)	13 (14.6)
Headache	21 (11.5)	33 (18.0)	20 (11.0)	6 (6.7)
Somnolence	15 (8.2)	10 (5.5)	4 (2.2)	3 (3.4)
Metabolism and nutritional disorders				
Decreased appetite	6 (3.3)	11 (6.0)	1 (0.5)	0

Total daily dose: 400 mg of SEGLENTIS (200 mg twice a day); 200 mg of tramadol (50 mg four times a day); 200 mg of celecoxib (100 mg twice a day); or placebo.
Note: Acetaminophen 1 g IV and oxycodone hydrochloride 5 mg Immediate Release (IR) tablets were permitted as rescue medication.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of either tramadol or

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celecoxib-containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin Syndrome

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Androgen Deficiency

Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

QT Prolongation/Torsade De Pointes

Cases of QT prolongation and/or *torsade de pointes* have been reported with tramadol use. Many of these cases were reported in patients taking another drug labeled for QT prolongation, in patients with a risk factor for QT prolongation (e.g., hypokalemia), or in the overdose setting.

Eye Disorders

Miosis, mydriasis.

Metabolism and Nutrition Disorders
Cases of hypoglycemia have been reported very rarely in patients taking tramadol. Most reports were in patients with predisposing risk factors, including diabetes or renal insufficiency, or in elderly patients.

Hyponatremia
Cases of severe hyponatremia and/or SIADH have been reported in patients taking tramadol, most often in females over the age of 65, and within the first week of therapy [*see Warnings and Precautions (5.31)]*.

Hypoglycemia
Cases of hypoglycemia have been reported in patients taking tramadol. Most reports were in patients with predisposing risk factors, including diabetes or renal insufficiency, or in elderly patients *[see Warnings and Precautions (5.32)]*.

Nervous System Disorders
Movement disorder, speech disorder.

Psychiatric Disorders

Delirium.

Cardiovascular

Vasculitis, deep venous thrombosis.

General

Anaphylactoid reaction, angioedema.

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Liver and Biliary

Liver necrosis, hepatitis, jaundice, hepatic failure.

Hemic and Lymphatic

Agranulocytosis, aplastic anemia, pancytopenia, leucopenia.

Metabolic

Hypoglycemia, hyponatremia.

Nervous

Aseptic meningitis, ageusia, anosmia, fatal intracranial hemorrhage.

Renal

Interstitial nephritis.

7 DRUG INTERACTIONS

Table 2: Clinically Significant Drug Interactions with SEGLENTIS

Inhibitors of CYP2D6	
Clinical Impact:	The concomitant use of SEGLENTIS and CYP2D6 inhibitors may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1. Since M1 is a more potent μ-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase which could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity and may cause potentially fatal respiratory depression *[see Clinical Pharmacology (12.3)]*.
Intervention:	If concomitant use of a CYP2D6 inhibitor is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures, and serotonin syndrome. If a CYP2D6 inhibitor is discontinued follow patients closely for adverse events including respiratory depression and sedation.
Examples:	Quinidine, fluoxetine, paroxetine, and bupropion.
CYP2D6 Substrates	
Clinical Impact:	*In vitro* studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by CYP2D6 (e.g., atomoxetine), and celecoxib, which may enhance the exposure and toxicity of CYP2D6 substrate drugs.
Intervention:	If concomitant use of a CYP2D6 substrate drug is necessary, follow patients closely for adverse events of that CYP2D6 substrate drug. Evaluate each patient's medical history when consideration is given to prescribing SEGLENTIS *[see Clinical Pharmacology (12.3)]*.
Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of SEGLENTIS and CYP3A4 inhibitors can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1. Follow patients closely for

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	increased risk of serious adverse events including seizures and serotonin syndrome, and adverse reactions related to opioid toxicity including potentially fatal respiratory depression. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.
Intervention:	If concomitant use is necessary, follow patients closely for seizures and serotonin syndrome, and signs of respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, follow patients for efficacy maintenance and for signs and symptoms of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir).
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of SEGLENTIS and CYP3A4 inducers can decrease the plasma concentration of tramadol *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the tramadol plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause seizures and serotonin syndrome, and potentially fatal respiratory depression.
Intervention:	If concomitant use is necessary, follow patients for efficacy maintenance and for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression. Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of SEGLENTIS and carbamazepine is not recommended.
Examples:	Rifampin, carbamazepine, phenytoin.
CYP2C9 Inhibitors or inducers	
Clinical Impact:	Celecoxib metabolism is predominantly mediated via CYP2C9 in the liver. Coadministration of celecoxib with drugs that are known to inhibit CYP2C9 (e.g., fluconazole) may enhance the exposure and toxicity of celecoxib whereas co-administration with CYP2C9 inducers (e.g., rifampin) may lead to compromised efficacy of celecoxib.
Intervention:	If concomitant use with CYP2C9 inhibitor drugs is necessary, follow patients for adverse events of celecoxib from SEGLENTIS. If concomitant use with CYP2C9 inducer drugs is necessary, follow patients for efficacy maintenance of SEGLENTIS. Evaluate each patient's medical history when consideration is given to prescribing SEGLENTIS.
Drugs That Interfere with Hemostasis	
Clinical Impact:	Celecoxib and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of celecoxib and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding

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	more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of SEGLENTIS with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding *[see Warnings and Precautions (5.27)].*
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone *[see Warnings and Precautions (5.5)]*. In two studies in healthy volunteers, and in patients with osteoarthritis and established heart disease respectively, celecoxib (200-400 mg daily) has demonstrated a lack of interference with the cardioprotective antiplatelet effect of aspirin (100-325 mg).
Intervention:	Concomitant use of SEGLENTIS and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding *[see Warnings and Precautions (5.27)]*. SEGLENTIS is not a substitute for low dose aspirin for cardiovascular protection.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of celecoxib with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy *[see Warnings and Precautions (5.5)].*
Intervention:	The concomitant use of SEGLENTIS with other NSAIDs or salicylates is not recommended.
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.9)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation. Discontinue SEGLENTIS if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome *[see Warnings and Precautions (5.10)]* or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)].*

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Intervention:	Do not use SEGLENTIS in patients taking MAOIs or within 14 days of stopping such treatment.
Examples	Phenelzine, tranylcypromine, linezolid.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	During concomitant use of SEGLENTIS and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. During concomitant use of SEGLENTIS and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function *[see Warnings and Precautions (5.22)].* When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of SEGLENTIS and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine.
Muscle Relaxants	
Clinical Impact:	Tramadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed. During concomitant use of SEGLENTIS with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects *[see Warnings and Precautions (5.22)]*.
Digoxin	
Clinical Impact:	Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity. The concomitant use of celecoxib with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of SEGLENTIS and digoxin, monitor serum digoxin levels. Follow patients for signs of digoxin toxicity and adjust the dosage of digoxin as

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	needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when SEGLENTIS is used concomitantly with anticholinergic drugs.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of SEGLENTIS and lithium, monitor patients for signs of lithium toxicity.
Warfarin	
Clinical Impact:	Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times.
Intervention:	Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction). Celecoxib has no effect on methotrexate pharmacokinetics.
Intervention:	During concomitant use of SEGLENTIS and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of celecoxib and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of SEGLENTIS and cyclosporine, monitor patients for signs of worsening renal function.
Pemetrexed	
Clinical Impact:	Concomitant use of celecoxib and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of SEGLENTIS and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Corticosteroids	
Clinical Impact:	Concomitant use of corticosteroids with celecoxib may increase the risk of GI ulceration or bleeding.
Intervention:	Monitor patients with concomitant use of SEGLENTIS with corticosteroids for signs of bleeding *[see Warnings and Precautions (5.5)]*.

8 USE IN SPECIFIC POPULATIONS

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8.1 Pregnancy

Risk Summary

Based on animal data, advise pregnant women of the potential risk to fetus.
Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *(see Clinical Considerations).*

Use of NSAIDs, including SEGLENTIS, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of SEGLENTIS use between about 20 and 30 weeks of gestation and avoid SEGLENTIS use at about 30 weeks of gestation and later in pregnancy *(see Clinical Considerations, Data)*.

There are no available data on use of SEGLENTIS in pregnant women. In an animal reproduction study, oral administration of celecoxib and tramadol co-crystal to pregnant rabbits during the period of organogenesis, resulted in embryo-fetal deaths and an increase of incidence of vertebral defects at approximately 4.7 and 0.11 times the dose of celecoxib and tramadol, respectively, at the maximum recommended human dose (MRHD) of SEGLENTIS at 400 mg/day (224 mg celecoxib/176 mg tramadol) *(see Data)*.

Tramadol

Available data with tramadol use in pregnant women are insufficient to inform a drug-associated risk for major birth defects, miscarriage, or adverse maternal outcomes. There are adverse outcomes reported with fetal exposure to opioid analgesics *(see Clinical Considerations)*. In animal reproduction studies, tramadol administration during organogenesis decreased fetal weights and reduced ossification in mice, rats, and rabbits at 3.2, 1.4, and 8.2 times the tramadol dose of 176 mg at the MRHD of SEGLENTIS. In a pre- and post-natal development study, tramadol decreased pup body weight and increased pup mortality at 2.7 and 4.3 times the MRHD, respectively.

In a published study, tramadol caused structural abnormalities in the brains of fetuses when administered to female Sprague Dawley rats from Gestation Days 10 to 21 at 2.7 times the MRHD *(see Data).*

Celecoxib

Premature Closure of Fetal Ductus Arteriosus:
Use of NSAIDs, including SEGLENTIS, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:
Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, embryo-fetal deaths and an increase in diaphragmatic hernias were observed in rats administered celecoxib daily during the period of organogenesis at oral doses approximately 13 times the celecoxib dose of 224 mg at the MRHD of SEGLENTIS. In addition, structural abnormalities (e.g., septal defects, ribs fused, sternebrae fused and sternebrae misshapen) were observed in rabbits given daily oral doses

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of celecoxib during the period of organogenesis at approximately 4 times the MRHD *(see Data)*. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as celecoxib, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Tramadol:

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in respiratory depression and physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing, and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms and signs of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.7)].*

Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol hydrochloride during postmarketing.

Celecoxib:

Premature Closure of Fetal Ductus Arteriosus:
Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including SEGLENTIS, can cause premature closure of the fetal ductus arteriosus (*see Data*).

Oligohydramnios/Neonatal Renal Impairment:
If an NSAID is necessary, including SEGLENTIS, at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If SEGLENTIS treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue SEGLENTIS and follow up according to clinical practice (*see Data*).

Labor or Delivery

Tramadol:

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid induced respiratory depression in the neonate. SEGLENTIS is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques

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are more appropriate.

Opioid analgesics, including SEGLENTIS, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of SEGLENTIS, if any, on the later growth, development, and functional maturation of the child is unknown.

Celecoxib:

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

Data

Human Data

Celecoxib:

The available data do not establish the presence or absence of developmental toxicity related to the use of celecoxib.

Premature Closure of Fetal Ductus Arteriosus
Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment
Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

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Animal Data

Treatment of pregnant rabbits during organogenesis with celecoxib and tramadol co-crystal resulted in an increase in the incidence of scoliosis and other vertebral defects (including absent thoracic hemicentrum/a and neural arch(es) and fused thoracic vertebral centra and/or neural arch(es)) at an oral dose of 100 mg/kg/day (56 mg celecoxib/44 mg tramadol/kg/day; approximately 4.7 and 0.11 times the MRHD on the basis of celecoxib and tramadol, respectively, on an AUC basis), which is a dose that also caused maternal toxicity (decreased body weight gain). In addition, there was a slight increase of post-implantation loss in rabbits at 100 mg/kg/day. The No Observed Adverse Effect Level (NOAEL) for embryofetal toxicity was 55 mg/kg/day (approximately 3.3 and 0.02 times the MRHD of celecoxib and tramadol, respectively, on an AUC basis).

Tramadol:

Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages, but was not teratogenic at these dose levels. These doses on a mg/m^2 basis are 3.2, 1.4, and 8.2 times the MRHD of tramadol (176 mg) for mouse, rat, and rabbit, respectively. No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg), rats (up to 80 mg/kg) or rabbits (up to 300 mg/kg) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, decreased skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 3.9, 4.3, and 33 times the MRHD of tramadol (176 mg), respectively, on a mg/m^2 basis.

Tramadol was evaluated in pre-and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (2.7 times the MRHD of tramadol on a mg/m^2 basis) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (4.3 times the MRHD of tramadol on a mg/m^2 basis).

In a published study, oral administration of tramadol at 50 mg/kg (2.7 times the MRHD of tramadol on a mg/m^2 basis) to pregnant female rats from Gestation Days 10 to 21 caused structural abnormalities in the brains of the offspring.

Celecoxib:

Celecoxib at oral doses ≥150 mg/kg/day (approximately 4 times the level of celecoxib of 224 mg at the MRHD of SEGLENTIS based on AUC), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥30 mg/kg/day (approximately 13 times the MRHD based on AUC) throughout organogenesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses at oral doses ≥50 mg/kg/day (approximately 13 times the MRHD based on AUC).

Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 15 times the MRHD based on AUC). The effects of SEGLENTIS on labor and delivery in pregnant women are unknown.

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8.2 Lactation

Risk Summary

SEGLENTIS is not recommended for obstetrical preoperative medication or for post-delivery analgesia in lactating women because the safety of tramadol in infants and newborns has not been studied.

Tramadol

Tramadol and its metabolite, *O*-desmethyltramadol (M1), are present in human milk. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The M1 metabolite is more potent than tramadol in mu opioid receptor binding *[see Clinical Pharmacology (12.1)]*. Published studies have reported tramadol and M1 in colostrum with administration of tramadol to breastfeeding mothers in the early post-partum period. Women who are ultra-rapid metabolizers of tramadol may have higher than expected serum levels of M1, potentially leading to higher levels of M1 in breast milk that can be dangerous in their breastfed infants. In women with normal tramadol metabolism, the amount of tramadol secreted into human milk is low and dose dependent. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with SEGLENTIS *(see Data) [see Warnings and Precautions (5.6)]*.

Celecoxib

Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of celecoxib in breast milk. The calculated average daily infant dose was 10 to 40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year old-child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events.

Clinical Considerations

If infants are exposed to SEGLENTIS through breast milk, they should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped.

Data

Tramadol

Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post dose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1.

8.3 Females and Males of Reproductive Potential

Infertility

Tramadol

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2)].*

Published studies in adult male rodents report that tramadol, at clinically relevant doses, can produce adverse effects on male reproductive hormones and tissues [*see Nonclinical Toxicology (13.1)*].

Celecoxib

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Females:

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

8.4 Pediatric Use

The safety and effectiveness of SEGLENTIS in pediatric patients have not been established.

Tramadol

Life-threatening respiratory depression and death have occurred in children who received tramadol *[see Warnings and Precautions (5.6)]*. In some of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and one of the children had evidence of being an ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol. Because of the risk of life-threatening respiratory depression and death:

- SEGLENTIS is contraindicated for all children younger than age 12 years of age *[see Contraindications (4)]*.
- SEGLENTIS is contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.

Avoid the use of SEGLENTIS in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.

8.5 Geriatric Use

In the randomized, double-blind, active- and placebo-controlled, parallel group study comparing SEGLENTIS to tramadol, celecoxib, and placebo in patients with acute post-operative pain following unilateral first metatarsal osteotomy with internal fixation, 9.1% of patients were ≥65 years of age. Age subgroup examination was planned by protocol and it revealed a similar trend in efficacy compared to younger patients and no untoward or unexpected adverse reactions were seen in the elderly patients who received SEGLENTIS.

No dose adjustments are required for elderly patients.

Tramadol

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.14)]*.

Tramadol is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely

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to have decreased renal function, it may be useful to monitor renal function.

Celecoxib

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, monitor patients for adverse effects *[see Warnings and Precautions (5.4, 5.5, 5.19, 5.22, 5.30)]*. Because SEGLENTIS is approved at a unique dosage of celecoxib, SEGLENTIS is not recommended in patients that require dosages other than 2 tablets every 12 hours, containing a total daily dose of celecoxib of 224 mg.

Of the total number of patients who received celecoxib in pre-approval clinical trials, more than 3,300 were 65-74 years of age, while approximately 1,300 additional patients were 75 years and over. No substantial differences in effectiveness were observed between these subjects and younger subjects. In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers.

However, as with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients *[see Warnings and Precautions (5.5, 5.22)]*.

8.6 Renal Impairment

Because SEGLENTIS contains celecoxib, the use of SEGLENTIS in patients with severe renal impairment is not recommended *[see Warnings and Precautions (5.22) and Clinical Pharmacology (12.3)]*.

The pharmacokinetics and tolerability of SEGLENTIS in patients with renal impairment has not been studied.

Tramadol

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. With the prolonged half-life in these conditions, achievement of steady state is delayed, so that it may take several days for elevated plasma concentrations to develop.

8.7 Hepatic Impairment

As tramadol and celecoxib are both extensively metabolized by the liver, the use of SEGLENTIS in patients with moderate and severe hepatic impairment is not recommended *[see Warnings and Precautions (5.19), Clinical Pharmacology (12.3)]*.

The pharmacokinetics and tolerability of SEGLENTIS in patients with impaired hepatic function have not been studied.

Tramadol

Metabolism of tramadol and M1 is reduced in patients with severe hepatic impairment based on a study in patients with advanced cirrhosis of the liver.

Celecoxib

The daily recommended dose of celecoxib capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by 50%. Because the dose of celecoxib and tramadol cannot be adjusted individually for SEGLENTIS, the use in moderate hepatic impairment is not

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recommended. The use of celecoxib in patients with severe hepatic impairment is not recommended *[see Clinical Pharmacology (12.3)].*

8.8 Poor Metabolizers of CYP2C9 Substrates

Celecoxib

In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9*3/*3), based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) celecoxib is administered starting with half the lowest recommended dose *[see Clinical Pharmacology (12.5)]*. Because SEGLENTIS is not available in lower strengths of celecoxib, SEGLENTIS is not recommended in patients who are known or suspected to be poor CYP2C9 metabolizers *[see Clinical Pharmacology (12.5)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

SEGLENTIS contains tramadol, a Schedule IV controlled substance.

9.2 Abuse

SEGLENTIS contains tramadol, a substance with a high potential for abuse similar to other opioids and can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful, or potentially harmful, consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug seeking” behavior is very common in persons with substance use disorders. Drug seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

SEGLENTIS, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of SEGLENTIS

SEGLENTIS is for oral use only. Abuse of SEGLENTIS poses a risk of overdose and death. The risk is increased with concurrent abuse of SEGLENTIS with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Do not abruptly discontinue SEGLENTIS in a patient physically dependent on opioids. Rapid tapering of SEGLENTIS in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing SEGLENTIS, gradually taper the dosage using a patient-specific plan that considers the following: the dose of SEGLENTIS the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.4), Warnings and Precautions (5.28)]*. If SEGLENTIS is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

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SEGLENTIS is a combination drug composed of tramadol and celecoxib. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, celecoxib toxicity or both.

Tramadol

Acute overdosage with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, QT prolongation, hypotension, partial or complete airway obstruction, atypical snoring, seizures, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Deaths due to overdose have been reported with abuse and misuse of tramadol *[see Warnings and Precautions (5.1); Drug Abuse and Dependence (9.2)].* Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

Celecoxib

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare *[see Warnings and Precautions (5.4, 5.5, 5.20, 5.22)]*.

No overdoses of celecoxib were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity. No information is available regarding the removal of celecoxib by hemodialysis but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose.

Treatment of Overdose

Tramadol

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-supporting measures.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose.

For clinically significant respiratory or circulatory depression secondary to tramadol overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to tramadol overdose.

While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone.

Naloxone administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

Because the duration of opioid reversal is expected to be less than the duration of action of tramadol in SEGLENTIS, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional

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antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

Celecoxib

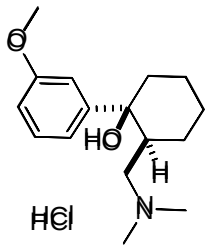
Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within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

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

11 DESCRIPTION

SEGLENTIS (celecoxib and tramadol hydrochloride) tablets contains a co-crystal with molecular weight of 681.2, composed of tramadol hydrochloride, an analgesic and opioid agonist, and celecoxib, a nonsteroidal anti-inflammatory drug, in a 1:1 molecular ratio.

The chemical name for tramadol hydrochloride is (1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride ($C_{16}H_{26}ClNO_2$). The structural formula is:



The molecular weight of tramadol hydrochloride is 299.84 (the molecular weight of tramadol is 263.38).

The chemical name for celecoxib is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole ($C_{17}H_{14}F_3N_3O_2S$). The molecular weight is 381.38 and it has the following chemical structure:

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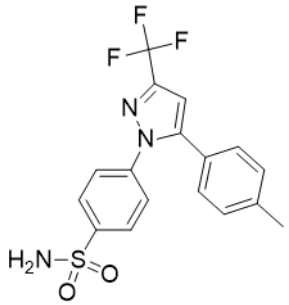

SEGLENTIS coated tablets contain 56 mg celecoxib and 44 mg of tramadol hydrochloride (equivalent to 39 mg tramadol) in a co-crystal structure. Tablets are white to off-white in color. Inactive ingredients in the tablet are sodium lauryl sulfate, crospovidone, mannitol, sodium stearyl fumarate, talc, cellulose microcrystalline, copovidone and color mixture (polyvinyl alcohol partially hydrolyzed, titanium dioxide, polyethylene glycol and talc).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SEGLENTIS is a co-crystal that contains tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake, and celecoxib, a nonsteroidal anti-inflammatory drug, in a 1:1 molecular ratio.

Tramadol

Although the mode of action of tramadol is not completely understood, the analgesic effect of tramadol is believed to be due to both binding to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity of tramadol is due to both low affinity binding of the parent compound and higher affinity binding of the *O*-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound *[see Clinical Pharmacology (12.2)]*.

Celecoxib

Celecoxib is an analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2).

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

12.2 Pharmacodynamics

Effects on the Central Nervous System

Tramadol produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory

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centers to both increases in carbon dioxide tension and electrical stimulation.

Tramadol administration may produce a constellation of symptoms including nausea and vomiting, dizziness, and somnolence.

Tramadol causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Tramadol causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Tramadol produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

The effect of oral tramadol on the QTcF interval was evaluated in a double-blind, randomized, four-way crossover, placebo-and positive-(moxifloxacin) controlled study in 68 adult male and female healthy subjects. At a 600 mg/day dose (1.5-fold the maximum immediate-release daily dose), the study demonstrated no significant effect on the QTcF interval.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Warnings and Precautions (5.13), Adverse Reactions (6)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent opioid agonists. The minimum effective analgesic concentration of tramadol for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance *[see Dosage and Administration (2)]*.

Concentration–Adverse Reaction Relationships

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There is a relationship between increasing tramadol plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2)]*.

Platelets

In clinical trials using normal volunteers, celecoxib at single doses up to 800 mg and multiple doses of 600 mg twice daily for up to 7 days duration (higher than recommended therapeutic doses) had no effect on reduction of platelet aggregation or increase in bleeding time. Because of its lack of platelet effects, celecoxib is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of celecoxib on platelets that may contribute to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of celecoxib.

Fluid Retention

Inhibition of PGE2 synthesis may lead to sodium and water retention through increased reabsorption in the renal medullary thick ascending loop of Henle and perhaps other segments of the distal nephron. In the collecting ducts, PGE2 appears to inhibit water reabsorption by counteracting the action of antidiuretic hormone.

12.3 Pharmacokinetics

Absorption

Tramadol is presented in SEGLENTIS as a racemate. After Tramadol immediate-release (IR) administration both the [-] and [+] forms of both tramadol and M1 are detected in the circulation.

The rate and extent of absorption of tramadol and celecoxib in SEGLENTIS show differences in absorption compared to Tramadol IR Tablets or Celecoxib capsule when those drugs are administered individually and concomitantly in a single four way cross-over study.

The PK parameters of tramadol, tramadol-M1 metabolite and celecoxib after single dose oral administration of SEGLENTIS Tablets, Tramadol IR Tablets, Celecoxib Capsule or Tramadol IR Tablets and Celecoxib Capsule administered concomitantly is shown in Table 3.

Table 3: The PK parameters of tramadol, tramadol-M1 metabolite and celecoxib after single dose oral administration of SEGLENTIS Tablets, Tramadol IR Tablets, Celecoxib Capsule, or Tramadol IR Tablets and Celecoxib Capsule administered concomitantly in four way cross-over study (male and female participants receiving all treatments in random order).

Analyte	***PK Parameter ****	***2 x SEGLENTIS Tablets (112 mg celecoxib + 88 mg tramadol)***	***2 x 50 mg Tramadol IR Tablets***	***1x 100 mg Celecoxib Capsule***	***2 x 50 mg Tramadol IR Tablets + 100 mg Celecoxib Capsule***
		n=33	***n=32***	***n=33***	***n=32***
Tramadol	C_{max} (ng/mL)	214 (29)	305 (23)	-	312 (22)
	T_{max} (h) [$]	3.0 (1.25, 8.0)	2.0 (0.75, 3.0)	-	1.9 (1.0, 6.0)
	AUC_{0-t} (ng·h/mL)	2507 (36)	2709 (35)	-	2888 (34)
	$AUC_{0-\infty}$ (ng·h/mL)	2590 (35) [a]	2802(32) [b]	-	2990 (32) [b]
	T½ (h)	6.5 (15)	6.1 (17)	-	6.2 (16)
Tramadol-M1 metabolite	C_{max} (ng/mL)	55 (29)	78 (29)	-	78 (29)
	T_{max} (h) [$]	4.0 (2.5, 8.0)	2.5 (1.25, 6.0)	-	2.5 (1.25, 8.0)
	AUC_{0-t} (ng·h/mL)	846 (27)	965 (25)	-	1010 (25)

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	$AUC_{0-\infty}$ (ng·h/mL)	880 (24) [a]	1002 (21) [b]	-	1049 (21) [b]
	$T_{½}$ (h)	7.2 (14)	6.7 (14)	-	7.0 (15)
Celecoxib	C_{max} (ng/mL)	259 (34)	-	318 (47)	165 (46)
	T_{max} (h) [$]	1.5 (0.75, 6.0)	-	3.0 (1.25, 8.0)	2.5 (1.0, 12.0)
	AUC_{0-t} (ng·h/mL)	1930 (41)	-	2348 (40)	1929 (38)
	$AUC_{0-\infty}$ (ng·h/mL)	2128 (42) [c]	-	2553 (43) [d]	2224 (39) [e]
	$T_{½}$ (h)	13 (27)	-	11 (46)	14 (29)

* *Arithmetic Mean (% CV);* [$] Median (minimum, maximum); [a] n=32, [b] n=31, [c] n=28, [d] n=27, [e] n=21

Multiple dose

After multiple dose administration of SEGLENTIS tablets twice daily for a total of 15 consecutive doses, the steady-state accumulation ratio of tramadol C_{max} and AUC_{τ} (15th dose/ 1st dose) were 2.20-fold and 2.37-fold, respectively. The steady-state accumulation ratio of celecoxib C_{max} and AUC_{τ} (15th dose/ 1st dose) were 1.76-fold and 2.15-fold, respectively. Based on pre-dose concentrations, the steady state appears to be achieved for all three analytes, tramadol, M1 metabolite and celecoxib, of SEGLENTIS tablets.

The absolute oral bioavailability of tramadol and celecoxib from SEGLENTIS have not been determined. Tramadol has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tramadol tablets. Absolute bioavailability studies have not been conducted for celecoxib.

Tramadol:

In general, both enantiomers of tramadol and M1 follow a parallel time course in the body following single and multiple doses although small differences (~ 10%) exist in the absolute amount of enantiomer present. Steady-state plasma concentrations of both tramadol and M1 are achieved within two days with four times per day dosing. There is no evidence of self-induction.

Celecoxib:

The coadministration of celecoxib with an aluminum- and magnesium-containing antacids resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC.

Food Effect

When SEGLENTIS tablets were administered with a high-fat, high-calorie meal, the C_{max} and the AUC of tramadol and tramadol-M1 metabolite were not significantly affected. For celecoxib, component of SEGLENTIS tablets, the T_{max} was delayed by approximately 2.5 hour and resulted in around a 30% increase in C_{max} and AUC, which was approximately similar to the food effect of Celecoxib capsule. SEGLENTIS can be administered without regard to timing of meals.

Distribution

Tramadol

The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 mcg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

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Celecoxib

In healthy subjects, celecoxib is highly protein bound (~ 97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primary to albumin and, to a lesser extent, α1-acid glycoprotein. The apparent volume of distribution at steady state (Vss/F) is approximately 400 L suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys.

The mean terminal plasma elimination half-life of tramadol were 6.5 hours and 9.0 hours after single-dose and multiple-dose administration of SEGLENTIS tablets, respectively. There was no change in the elimination half-life of celecoxib (13 hours) after single or multiple dose administration of SEGLENTIS tablets.

Metabolism

Tramadol:

Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites.

Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites.

The major metabolic pathways appear to be *N*- and *O*-demethylation and glucuronidation or sulfation in the liver. One metabolite (*O*-desmethyltramadol, denotated M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response *[see Warnings and Precautions (5.6); Drug Interactions (7)]*.

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine and quinidine could result in significant drug interactions.

In vitro drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of serotonin re-uptake inhibitors and MAO inhibitors may enhance the risk of adverse events, including seizure and serotonin syndrome *[*see *Warnings 5.10* and *Drug Interactions (7)].*

Celecoxib:

Celecoxib metabolism is primarily mediated via CYP2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid, and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors.

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Excretion

Tramadol:

Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites.

Celecoxib:

Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($T_{1/2}$) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Specific Populations

Geriatric Patients

Tramadol:

Healthy elderly subjects aged 65 to 75 years have plasma tramadol concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years, maximum serum concentrations are elevated (208 vs. 162 ng/mL) and the elimination half-life is prolonged (7 vs. 6 hours) compared to subjects 65 to 75 years of age *[see Use in Specific Populations (8.5)].*

Celecoxib:

At steady state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib C_{max} and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females.

Pediatric Patients

Pharmacokinetics of SEGLENTIS has not been established in pediatric patients.

Sex

Sex effects on the Pharmacokinetics of SEGLENTIS have not been assessed.

The absolute bioavailability of tramadol was 73% in males and 79% in females. The plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females following a 100 mg IV dose of tramadol. Following a single oral dose, and after adjusting for body weight, females had a 12% higher peak tramadol concentration and a 35% higher area under the concentration-time curve compared to males. The clinical significance of this difference is unknown.

Race

Race effects on the Pharmacokinetics of SEGLENTIS have not been assessed.

Celecoxib:

Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding

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is unknown.

Renal Impairment

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1.

In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied *[see Use in Specific Populations (8.6), Warnings and Precautions (5.22)]*.

Hepatic Impairment

Metabolism of tramadol and M1 is reduced in patients with severe hepatic impairment based on a study in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve for tramadol and longer tramadol and M1 elimination half-lives (13 hrs. for tramadol and 19 hrs. for M1).

A pharmacokinetic study in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment has shown that steady state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

In vitro studies indicate that celecoxib is not an inhibitor of CYP2C9, 2C19 or 3A4.

In vivo studies have shown the following:

Aspirin

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

Lithium

In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg twice daily with celecoxib 200 mg twice daily as compared to subjects receiving lithium alone *[see Drug Interactions (7)]*.

Fluconazole

Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole *[see Drug Interactions (7)]*.

Other Drugs

The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, *[see Drug Interactions (7)]*, phenytoin, and tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

Tramadol and Celecoxib

Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4. The formation of tramadol M1 metabolite is dependent on CYP2D6. *In vitro* studies indicate that celecoxib

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is an inhibitor of CYP2D6.

An *in vivo* multiple dose PK study of 100 mg tramadol (2x50 mg) and 100 mg celecoxib (1x100 mg) administered concomitantly twice daily for 15 doses demonstrates that steady-state C_{max} and AUC of tramadol and its active metabolite M1 are comparable along with comparable PK profiles to the 100 mg tramadol (2x50 mg) administered alone twice daily for 15 doses. The study results indicate that co-administration of celecoxib does not appear to affect the PK of tramadol or M1.

12.5 Pharmacogenomics

Poor Metabolizers of CYP2C9

CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *I/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups *[see Use in Specific Populations (8.8)]*.

Poor / Extensive Metabolizers of CYP2D6

The formation of the active metabolite, M1, is mediated by CYP2D6. Approximately 7% of the population has reduced activity of the CYP2D6. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan, and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies with immediate-release tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers,” while M1 concentrations were 40% lower.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or laboratory studies with SEGLENTIS (product composed of tramadol and celecoxib) to evaluate carcinogenesis, mutagenesis, or impairment of fertility. Data on the individual components are described below.

Carcinogenesis

Tramadol

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in an NMRI mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg in the drinking water (0.8 times the maximum recommended human dose (MRHD) of tramadol at 176 mg on a mg/m^2 basis) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No evidence of carcinogenicity was noted in a rat 2-year carcinogenicity study testing oral doses of up to 30 mg/kg in the drinking water (1.7 times the MRHD of tramadol on a mg/m^2 basis).

Celecoxib

Celecoxib was not carcinogenic in Sprague-Dawley rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 4 to 9 times the MRHD based on AUC) or in mice given oral

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doses up to 25 mg/kg for males and 50 mg/kg for females (approximately 2.2 times the MRHD based on AUC) for two years.

Mutagenesis

Tramadol

Tramadol was mutagenic in the presence of metabolic activation in the mouse lymphoma assay. Tramadol was not mutagenic in the *in vitro* bacterial reverse mutation assay using *Salmonella* and *E. coli* (Ames), the mouse lymphoma assay in the absence of metabolic activation, the *in vitro* chromosomal aberration assay, or the *in vivo* micronucleus assay in bone marrow.

Celecoxib

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

Impairment of Fertility

Tramadol

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats. These dosages are 2.7 and 4.1 times the maximum recommended human dose (MRHD) of tramadol (176 mg) on a mg/m^2 basis, respectively *[see Use in Specific Populations (8.3)]*.

However, published studies report that treatment of adult male rats with tramadol (40 mg/kg, IP and SC for 30 and 60 days, respectively, 2.2 times the MRHD of tramadol on a mg/m^2 basis; or 4.5 to 135 mg/kg, SC for 18 weeks, 0.2 to 7.4 times the MRHD of tramadol on a mg/m^2 basis) produced adverse effects on male reproductive hormones and male reproductive tissues.

Celecoxib

Celecoxib had no effect on male or female fertility or male reproductive function in rats at oral doses up to 600 mg/kg/day (approximately 24 times the MRHD of celecoxib (224 mg) based on AUC). At ≥50 mg/kg/day (approximately 13 times the MRHD of celecoxib (224 mg) based on AUC) there was increased preimplantation loss.

13.2 Animal Toxicology and/or Pharmacology

Celecoxib

An increase in the incidence of background findings of spermatocele with or without secondary changes such as epididymal hypospermia as well as minimal to slight dilation of the seminiferous tubules was seen in the juvenile rat. These reproductive findings while apparently treatment related did not increase in incidence or severity with dose and may indicate an exacerbation of a spontaneous condition. Similar reproductive findings were not observed in studies of juvenile or adult dogs or in adult rats treated with celecoxib. The clinical significance of this observation is unknown.

14 CLINICAL STUDIES

SEGLENTIS study on acute pain after bunionectomy with osteotomy

The efficacy and safety of SEGLENTIS was evaluated in one randomized, double-blind, parallel group study comparing SEGLENTIS to tramadol, celecoxib, and placebo (NCT03108482). The study

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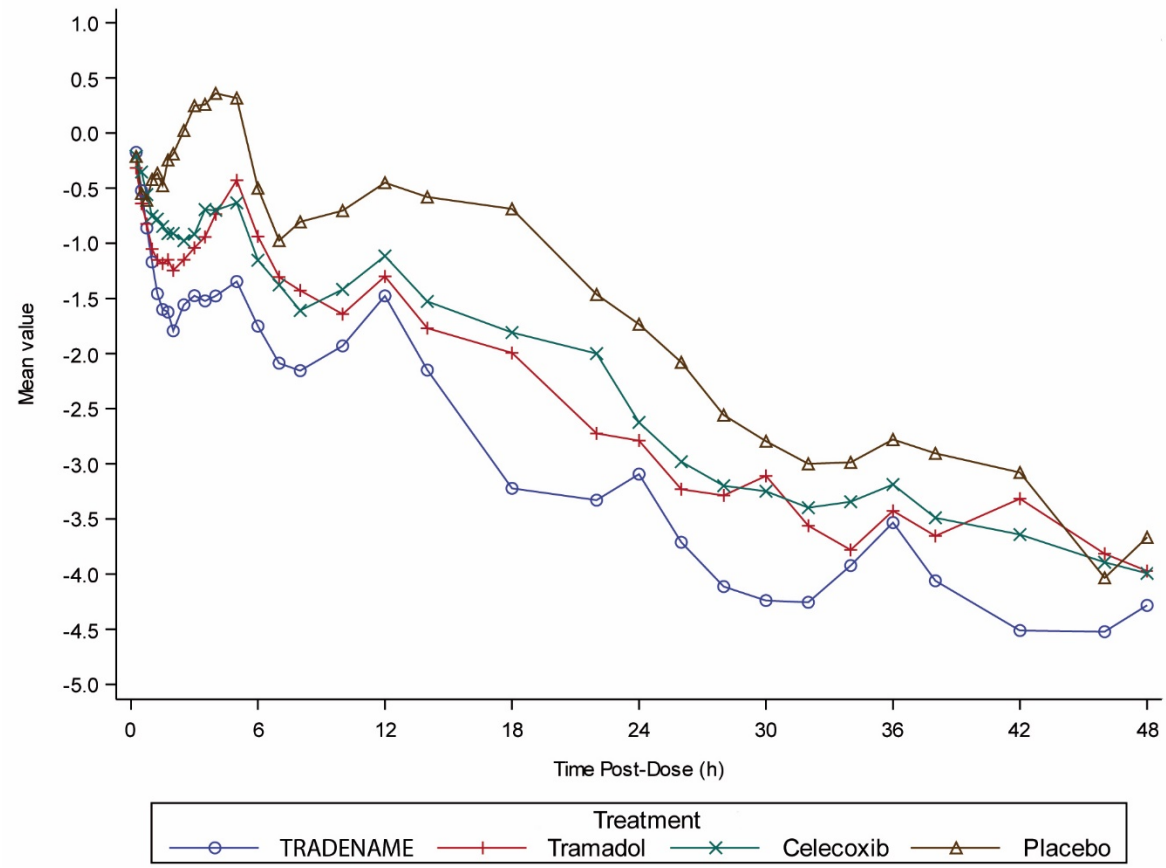
enrolled 637 patients 18 years of age or older (age ranged between 18 and 77) with acute post-operative pain (≥5 and ≤9 on a 0-10 Numeric Pain Rating Scale [NPRS]) following unilateral first metatarsal osteotomy with internal fixation. Patients were randomized at a ratio of 2:2:2:1 to SEGLENTIS 200 mg every 12 hours, tramadol 50 mg every 6 hours, celecoxib 100 mg every 12 hours, or placebo in a double-blind, double-dummy study. Use of rescue medication (acetaminophen and oxycodone HCl) was permitted during the study. Patients had a mean baseline pain intensity of 6.7 on the NPRS.

The primary efficacy endpoint was time-weighted summed pain intensity difference over 48 hours (SPID48). Patients in the SEGLENTIS group had statistically significantly better mean SPID48 scores than any of the other groups after bunionectomy. Pain intensity difference from baseline over 48 hours mean values by treatment group are shown in Figure 1.

Figure 1: Pain Intensity Difference by Evaluation Time Point from Baseline to 48 hours – Post Operative Bunionectomy with Osteotomy (Full Analysis Set Population)



16 HOW SUPPLIED/STORAGE AND HANDLING

SEGLENTIS (celecoxib and tramadol hydrochloride) tablets are coated tablets containing celecoxib 56 mg and tramadol hydrochloride 44 mg. The tablets are white to off-white elongated coated tablets debossed with "100 on one side and "CTC" on the other side and are available as follows:

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Bottles of 30 tablets: NDC 66869-564-30

Bottles of 90 tablets: NDC 66869-564-90

Dispense in a tight container. Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

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

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store SEGLENTIS securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home *[see Warnings and Precautions (5.1, 5.3), Drug Abuse and Dependence (9.2)]*. Inform patients that leaving SEGLENTIS unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Inform patients that medicine take-back options are the preferred way to safely dispose of most types of unneeded medicines. If no take back programs or Drug Enforcement Administration (DEA)-registered collectors are available, instruct patients to dispose of SEGLENTIS by following these four steps:

Mix SEGLENTIS (do not crush) with an unpalatable substance such as dirt, cat litter, or used coffee grounds;

- Place the mixture in a container such as a sealed plastic bag;
- Throw the container in the household trash;
- Delete all personal information on the prescription label of the empty bottle.
- Inform patients that they can visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse

Inform patients that the use of SEGLENTIS, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share SEGLENTIS with others and to take steps to protect SEGLENTIS from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting SEGLENTIS or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.3)]*.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.3)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with SEGLENTIS. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone

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dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered *[see Overdosage (10)]*.

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver know what to do.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.3)]*. Instruct patients to take steps to store SEGLENTIS securely and to dispose of unused SEGLENTIS in accordance with the local state guidelines and/or regulations.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately *[see Warnings and Precautions (5.4)]*.

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding *[see Warnings and Precautions (5.5)]*.

Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children

Advise caregivers that SEGLENTIS is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children ages 12 to 18 years of age receiving SEGLENTIS to monitor for signs of respiratory depression *[see Warnings and Precautions (5.6)]*.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if SEGLENTIS is used with benzodiazepines, CNS depressants, including alcohol, or some illicit drugs and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.9); Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from

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concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome, and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare provider if they are taking, or plan to take serotonergic medications *[see Warnings and Precautions (5.10)]*.

Seizures

Inform patients that SEGLENTIS may cause seizures with concomitant use of serotonergic agents (including SSRIs, SNRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol *[see Warnings and Precautions (5.11)]*.

MAOI Interaction

Inform patients not to take SEGLENTIS while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking SEGLENTIS *[see Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.13)]*.

Important Administration Instructions

- Instruct patients how to properly take SEGLENTIS [see *Dosage and Administration (2)*].
- Advise patients not to modify the dose of SEGLENTIS without consulting with a physician or other healthcare professional.
- If patients have been receiving treatment with SEGLENTIS for more than a few weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose as abrupt discontinuation of the medication could precipitate withdrawal symptoms. Provide a dose schedule to accomplish a gradual discontinuation of the medication *[see Dosage and Administration (2.4)]*.

Hypotension

Inform patients that SEGLENTIS may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.15)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in SEGLENTIS. Advise patients how to recognize such a reaction and when to seek medical attention.

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur *[see Contraindications (4) and Warnings and Precautions (5.18); Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of SEGLENTIS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated and that the patient should inform their healthcare provider if they have used opioids at

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any time during their pregnancy, especially near the time of birth *[see Warnings and Precautions (5.7); Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Advise female patients of reproductive potential that SEGLENTIS may cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Inform pregnant women to avoid use of SEGLENTIS and other NSAIDS starting at 30 weeks of gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with SEGLENTIS is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours *[see Warnings and Precautions (5.26) and Use in Specific Populations (8.1)].*

Lactation

Advise women that breastfeeding is not recommended during treatment with SEGLENTIS *[see Warnings and Precautions (5.6)*; *Use in Specific Populations (8.2)]*.

Infertility

Advise patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)].*

Advise females of reproductive potential who desire pregnancy that NSAIDs, including the celecoxib contained in SEGLENTIS, may be associated with a reversible delay in ovulation *[see Use in Specific Populations (8.3)].*

Driving or Operating Heavy Machinery

Advise patients that SEGLENTIS may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.29)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Maximum single-dose and 24-hour dose

Advise patients not to exceed the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures, and death *[see Dosage and Administration (2); Warnings and Precautions (5.3)]*.

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, instruct patients to stop SEGLENTIS and seek immediate medical therapy *[see Warnings and Precautions (5.19), Use in Specific Populations (8.6)]*.

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur *[see Warnings and Precautions (5.21)]*.

Serious Skin Reactions, including DRESS

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Advise patients to stop taking SEGLENTIS immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible *[see Warnings and Precautions (5.24, 5.25)]*.

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of SEGLENTIS with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in *efficacy [see Warnings and Precautions (5.5) and Drug Interactions (7)]*. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with SEGLENTIS until they talk to their healthcare provider *[see Drug Interactions (7)]*.

Manufactured and Packaged by:
Towa Pharmaceutical Europe, S.L.
Martorelles, 08107 Barcelona
Spain

Distributed by:
Kowa Pharmaceuticals America, Inc.
Montgomery, AL 36117 USA

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Medication Guide

SEGLENTIS [“Seg-LEN-tis”]
(celecoxib and tramadol hydrochloride) tablets, CIV

SEGLENTIS is:

- A strong prescription pain medicine that contains the opioid (narcotic) tramadol and the Nonsteroidal Anti-inflammatory Drug (NSAID) celecoxib.
- SEGLENTIS is used for the management of acute pain in adults, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about SEGLENTIS:

- **Get emergency help or call 911 right away if you take too much SEGLENTIS (overdose).** When you first start taking SEGLENTIS, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking SEGLENTIS with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your SEGLENTIS. They could die from taking it. Selling or giving away SEGLENTIS is against the law.
- Store SEGLENTIS securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.
- Celecoxib can cause serious side effects, including:
  - **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
    - with increasing doses of NSAIDs
    - with longer use of NSAIDs

  Do not take NSAIDs right before or after a heart surgery called a “coronary artery bypass graft” (CABG).
  Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.
  - **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
    - anytime during use
    - without warning symptoms
    - that may cause death

    The risk of getting an ulcer or bleeding increases with:
    - past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
    - taking medicines called “corticosteroids”, “antiplatelet drugs” “anticoagulants”, “SSRIs” or “SNRIs”
    - increasing doses of NSAIDs
    - longer use of NSAIDs
    - smoking
    - drinking alcohol
    - older age
    - poor health
    - advanced liver disease
    - bleeding problems

Important Information Guiding Use in Pediatric Patients:

- Do not give SEGLENTIS to a child younger than 12 years of age.
- Do not give SEGLENTIS to a child younger than 18 years of age after surgery to remove the tonsils and/or adenoids.
- Avoid giving SEGLENTIS to children between 12 to 18 years of age who have risk factors for breathing problems such as obstructive sleep apnea, obesity, or underlying lung problems.

Do not take SEGLENTIS if you have:

- Severe asthma, trouble breathing, or other lung problems.
- A bowel blockage or narrowing of the stomach or intestines.
- An allergy to tramadol, opioids, celecoxib, sulfonamides, or any of the inactive ingredients in SEGLENTIS.
- Had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- Taken a Monoamine Oxidase Inhibitor, MAOI (medicine used for depression) within the last 14 days or are currently taking one.

Do not take SEGLENTIS right before or after heart bypass surgery.

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Before taking SEGLENTIS, tell your healthcare provider about all of your medical conditions, including if you have a history of:

- Head injury, seizures
- Liver, kidney, thyroid problems
- Problems urinating
- Pancreas or gallbladder problems
- Abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems
- High blood pressure
- Asthma

Tell your healthcare provider if you are:

- **pregnant or plan to become pregnant**: Prolonged use of SEGLENTIS during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. Taking SEGLENTIS at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take SEGLENTIS for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take SEGLENTIS and other NSAIDs after about 30 weeks of pregnancy.** Tell your healthcare provider if you become pregnant or think that you may be pregnant.
- **breastfeeding**: Not recommended; may harm your baby.
- living in a household where there are small children or someone who has abused street or prescription drugs.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. **Taking SEGLENTIS with certain other medicines can cause serious side effects that could lead to death. Do not start taking any new medicine without talking to your healthcare provider first.**

When taking SEGLENTIS:

- Do not change your dose. Take SEGLENTIS exactly as prescribed by your healthcare provider. Use SEGLENTIS at the lowest dosage possible for the shortest time needed.
- The maximum dosage is 2 tablets every 12 hours. Do not take more than your prescribed dose and do not take more than 4 tablets per day. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking SEGLENTIS regularly, do not stop taking SEGLENTIS without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused SEGLENTIS immediately by taking your drug to an authorized Drug Enforcement Administration (DEA)-registered collector or drug take-back program. If one is not available, you can dispose of SEGLENTIS by mixing the product with dirt, cat litter, or used coffee grounds, placing the mixture in a sealed plastic bag, and throwing the bag in your trash.

While taking SEGLENTIS DO NOT:

- Drive or operate heavy machinery, until you know how SEGLENTIS affects you. SEGLENTIS can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with SEGLENTIS may cause you to overdose and die.

The possible side effects of SEGLENTIS:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.
- NSAIDs can cause serious side effects, including: new or worse high blood pressure, heart failure, liver problems including liver failure, kidney problems including kidney failure, low red blood cells (anemia), life-threatening skin reactions, life-threatening allergic reactions. Other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency medical help or call 911 right away if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

Stop taking SEGLENTIS and call your healthcare provider right away if you get any of the following symptoms:

- nausea, more tired or weaker than usual, diarrhea, itching, your skin or eyes look yellow, indigestion or stomach pain, flu-like symptoms, vomit blood, there is blood in your bowel movement or it is black and sticky like tar, unusual weight gain, skin rash or blisters with fever, swelling of the arms, legs, hands and feet.

SEGLENTIS may cause fertility problems in males and females, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of SEGLENTIS. Call your doctor for medical advice about side effects.
You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**.

Other information about NSAIDs:

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach,

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and intestines. Aspirin can also cause ulcers in the stomach and intestines.

- Some NSAIDs are sold in lower doses without a prescription (over the counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of SEGLENTIS.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SEGLENTIS for a condition for which it was not prescribed. Do not give SEGLENTIS to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about SEGLENTIS, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SEGLENTIS that is written for health professionals.

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