

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213426Orig1s000**

**OTHER ACTION LETTERS**



NDA 213426

**COMPLETE RESPONSE**

Esteve Pharmaceuticals, S.A.  
c/o Esteve Pharmaceuticals, LLC  
909 Davis Street, Suite 500  
Evanston, IL 60201

Attention: Rebecca Nortz  
US Agent for Esteve Pharmaceuticals, S.A.

Dear Ms. Nortz:

Please refer to your new drug application (NDA) dated and received May 15, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for celecoxib and tramadol hydrochloride tablets.

We acknowledge receipt of your major amendment dated March 2, 2020, which extended the goal date by three months.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**FACILITY INSPECTIONS**

1. Our field investigator could not complete inspection of the (b) (4) (FEI: (b) (4)) manufacturing facility (b) (4) because the facility was not ready for inspection.

**Information needed to resolve deficiency:**

Satisfactory inspection is required before this application may be approved.  
Please notify us in writing when this facility is ready for inspection.

**PRESCRIBING INFORMATION**

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR

Requirements for Prescribing Information<sup>1</sup> and Pregnancy and Lactation Labeling Final Rule<sup>2</sup> websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

We refer to the draft labeling and medication guide received via email on June 12, 2020, and March 12, 2020, respectively, which incorporated our requested revisions, also enclosed with the letter. We reserve additional comments on the proposed labeling and medication guide until the application is otherwise adequate. Resubmit the revised draft labeling and medication guide with your complete response submission.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.<sup>3</sup>

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all additional changes you propose, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

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<sup>1</sup> <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

<sup>2</sup> <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

<sup>3</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

### **PROPRIETARY NAME**

Please refer to correspondence dated, April 7, 2020, which addresses the proposed proprietary name, Seglentis. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

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

We acknowledge receipt of your proposed REMS, included in your submission dated May 15, 2019, which contains a Medication Guide, elements to assure safe use, an implementation system and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for celecoxib and tramadol hydrochloride tablets, if it is approved, to ensure that the benefits of the drug outweigh the risks of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. The REMS, should it be approved, will create enforceable obligations.

We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

For administrative purposes, designate all submissions related to the proposed REMS **“PROPOSED REMS for NDA 213426-AMENDMENT.”**

To facilitate review of your submission, we request that you submit your proposed 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.

### **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
  - Present tabulations of the new safety data combined with the original application data.
  - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

### **ADDITIONAL COMMENTS**

We have the following comments that are not approvability issues, however, they should be addressed in your complete response to this action:

Although you have stated that you have conducted a literature search since the time of original approval of the referenced products to support PLLR labeling, described the search terms you employed, and concluded that there were no

articles that further informed labeling, you did not identify the articles or provide an integrated synopsis to support your conclusion. A search of common databases identified several articles that should be reviewed and considered, including:

- a. Aboulhoda BE, Hassan SS. Effect of prenatal tramadol on postnatal cerebellar development: Role of oxidative stress. J Chem Neuroanat 2018
- b. Abdellatief RB, Elgamal DA, Mohamed EEM. Effects of chronic tramadol administration on testicular tissue in rats: an experimental study. Andrologia 2015
- c. Attia AM, Bakry OA, Yassin H, Sarhan N, Samaka R, Gamal N. Morphometric and ultrastructural analysis of tramadol effects on epididymis: an experimental study. Ultrastruct Pathol 2018
- d. Ghoneim FM, Khalaf HA, Elsamanoudy AZ, Helaly AN. Effect of chronic usage of tramadol on motor cerebral cortex and testicular tissues of adult male albino rats and the effect of its withdrawal: histological, immunohistochemical and biochemical study. Int J Clin Exp Pathol 2014
- e. Winnall WR, Muir JA, Liew S, et al. Effects of chronic celecoxib on testicular function in normal and lipopolysaccharide-treated rats. International Journal of Andrology. 32(5):542-55, 2009 Oct.
- f. Selmanoglu G, Kockaya EA, Akay MT, et al. Subacute toxicity of celecoxib on thyroid and testis of rats: Hormonal and histopathological changes. Environmental Toxicology & Pharmacology. 22(1):85-9, 2006 Jul.
- g. Olliges A., Wimmer S., Nusing R.M. Defects in mouse nephrogenesis induced by selective and non-selective cyclooxygenase-2 inhibitors. British Journal of Pharmacology. 163 (5) (pp 927-936), 2011. Date of Publication: July 2011
- h. Nagano, A. Arioka, M. Takahashi-Yanaga, F. Matsuzaki, E. Sasaguri, T. Celecoxib Inhibits Osteoblast Maturation by Suppressing the Expression of Wnt Target Genes J Pharmacol Sci . 2017 Jan;133(1):18-24

With your resubmission, provide summaries of the published nonclinical literature, including those noted above, for tramadol or celecoxib that could potentially provide new information with regard to the impact on pregnancy, lactation, and female and male fertility, and discuss why such information should or should not be included in labeling.

## **OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

*{See appended electronic signature page}*

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

### ENCLOSURE(S):

- Labeling
- Medication Guide

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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RIGOBERTO A ROCA  
06/15/2020 08:51:49 AM