

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-466

PHARMACOLOGY REVIEW(S)



FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

**SUPERVISOR'S SECONDARY REVIEW
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

NDA number: 22-466
Drug Substance: Articaïne hydrochloride (4%) with epinephrine bitartrate (1:100,000 and 1:200,000) Injection
PDUFA Goal Date: 25-Sept-2009
Sponsor: Pierrel S.p.A.

Reviewer name: R. Daniel Mellon, Ph.D., Pharmacology Toxicology Supervisor
Division name: Division of Anesthesia, Analgesia, and Rheumatology Products
HFD #: 170
Review completion date: 31-July-2009

Recommendation: Approval with PMCs.

Pierrel submitted a 505(b)(2) NDA for articaïne hydrochloride (4%) with epinephrine bitartrate (1:100,000 and 1:200,000) for use as a dental anesthetic. There were no new nonclinical pharmacology or toxicology studies submitted with this application. Rather Pierrel's application relies upon the Agency's previous findings of safety for Deproco's Septocaine NDAs (20-971 and 22-010).

Dr. Carlic Huynh completed the primary review of NDA 22-466. As noted in his review, Dr. Huynh concludes that the Sponsor has provided adequate characterization of potential leachables and extractables from the container closure system and there are no novel excipients in the drug product that suggest any safety concerns. Dr. Huynh has recommended approval with agreement to the proposed post-marketing commitment from the Sponsor to investigate the potential for optimizing the sensitivity of the drug substance analytical methodology with regard to two theoretical process-related drug substance impurities that were identified as containing structural alerts for mutagenicity. In addition, the Sponsor has proposed to test both of the impurities in an in vitro mutagenicity test. I concur that the NDA may be approved and with the proposed post marketing commitment (PMC).

The Sponsor's application identified possible drug substance process related impurities. During evaluation of the drug substance synthetic pathway, two potential process related

impurities were identified as containing structural alerts for mutagenicity, as summarized in the table below:

(b) (4)



Dr. Huynh submitted these structures, which were identified as structural alerts following discussion with the CMC review team, to CDER's Computational Toxicology Consultation Service for a quantitative structure-activity relationship (QSAR) analysis. The results of the report predict low genotoxic potential.

CDER's current policy on genotoxic impurities is outlined in the December 2008 Draft FDA "Guidance to Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches." As noted in this draft guidance, genotoxic impurities should be limited to NMT (b) (4). The (b) (4) level is referred to as the threshold for toxicological concern (TTC), which is threshold exposure level to compounds that does not pose a significant risk for carcinogenicity or other toxic effects. For most compounds, this threshold corresponds to an incremental 10^{-5} lifetime risk of cancer (1 in 100,000).

According to the Sponsor of the NDA and the DMF holder, neither of these impurities is detected in the drug substance batches. The limit of detection of the assays is reasonable given current analytical methodology; therefore, the theoretical presence of these impurities should not preclude approval of the drug. However, as noted by Dr. Huynh, given the limit of detection of the assay methodology to date, it is not possible to state that these impurities will be below the threshold for toxicological concern and there are no actual data to demonstrate that they are or are not genotoxic. Therefore, the sponsor has proposed to investigate the potential for optimizing the sensitivity of the drug substance analytical methodology with regard to (b) (4) to evaluate the manufacturing processes used by other articaine hydrochloride suppliers, particularly with regard to purification procedures used to remove or mitigate the subject impurities, and to obtain the impurities in question and individually

subject them to appropriate in vitro mutagenicity testing (e.g., bacterial reverse mutation assay). The proposed approach would provide greater understanding of the potential genotoxicity of these compounds and may lead to drug substance improvements as technology advances. Therefore, I concur with Dr. Huynh's recommendation to accept the Sponsor's proposed postmarketing commitments to investigate the potential for optimizing the sensitivity of the drug substance analytical methodology and to conduct the in vitro bacterial reverse mutation studies for isolated (b) (4)

I concur with Dr. Huynh's recommendations regarding labeling.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22466	----- ORIG 1	----- PIERREL S.P.A.	----- ARTICAINE 4% /EPINEPHRINE 1:20000 INJ

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD D MELLON
07/31/2009

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA/BLA Number: 22-466 Applicant: Pierrel S.p.A Stamp Date: Nov. 25, 2008

**Drug Name: Articaine HCl 4%
with Epinephrine (1:100,000 and 1:200,000) NDA/BLA Type: 505(b)(2) DAARP/OND/CDER/FDA**

On **initial** overview of the NDA application for Refuse to File (RTF):

	Parameters	Yes	No	Comment
1	On its face, is the pharmacology section of the NDA/BLA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section of the NDA/BLA indexed and paginated in a manner allowing substantive review to begin?	X		
3	On its face, is the pharmacology/toxicology section of the NDA/BLA legible so that substantive review can begin?	X		
4	Are all required (*) and requested BBIND studies (in accord with 505(b1) and (b2) including referenced literature) completed and submitted in this NDA/BLA (carcinogenicity*, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, acute and repeat dose adult animal studies*, maximum tolerated dose determination, dermal irritancy, ocular irritancy, photo co-carcinogenicity, animal pharmacokinetic studies, safety pharmacology, etc)?			Not applicable. The Sponsor did not conduct any nonclinical studies. The submitted 505(b)(2) New Drug Application (NDA) included referenced nonclinical studies. The Sponsor relies upon the literature for carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, maximum tolerated dose determination, dermal irritancy, ocular irritancy, photo co-carcinogenicity, animal pharmacokinetic studies, safety pharmacology, etc.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies been conducted with the appropriate formulation?			Not applicable. The formulation of this NDA is the same as the referenced product (Septocaine®).

6	Is (are) the excipient(s) appropriately qualified (including interaction between the excipients if applicable)?	X		This NDA contains a different salt concentration than the referenced product (Septocaine®). The Sponsor has previously provided documentation proving comparable osmolarity.
7	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route?	X		
8	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			No new toxicity studies were submitted with this NDA. This NDA is a 505(b)(2) New Drug Application (NDA).
9	Has the sponsor submitted all special studies/ data requested by the Division during pre-submission discussions with the sponsor?			Justification of drug substance and drug product specs that exceed ICHQ3A and B will be a review issue.
10	Are the proposed labeling sections relative to pharmacology, reproductive toxicology, and carcinogenicity appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		
11	Has the sponsor submitted any toxicity data to address impurities, new excipients, leachables, etc. issues.			Justification provided in module 3. This will be a review issue.
12	Has the sponsor addressed any abuse potential issues in the submission?			No new studies were submitted in this NDA. This is a 505(b)(2) New Drug Application (NDA).
13	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable. This is a 505(b)(2) New Drug Application (NDA) submitted to support a Rx.

14	From a pharmacology/ toxicology perspective, is the NDA/BLA fileable? If ``no`` please state below why it is not.	X		FILING ISSUES: None
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IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments to Sponsor:

Please provide English translations for the following references:



Reviewing Pharmacologist: _____ Date

Team Leader: _____ Date

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Carlic K Huynh
1/16/2009 10:24:52 AM
PHARMACOLOGIST

R. Daniel Mellon
1/16/2009 02:21:44 PM
PHARMACOLOGIST
I concur.