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APPLICATION NUMBER:

209310Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	**NDA 209,310**
Supporting document/s:	**Sequences 001, 005, and 007,** **SDNs 1, 5, and 8**
Applicant's letter date:	**03/07/17, 6/02/17, and 8/03/17**
CDER stamp date:	**03/07/17, 6/08/17, and 8/04/17**
Product:	**Intersect ENT S8 Sinus Implant**
Indication:	(b) (4) **in adults after ethmoid sinus surgery**
Applicant:	**Intersect ENT**
Review Division:	**Pulmonary, Allergy, and Rheumatology Products**
Reviewer:	**Luqi Pei, Ph.D.**
Team Leader (acting):	**Carol Galvis, Ph.D.**
Division Director:	**Badrul Chowdhury, M.D., Ph.D.**
Project Manager:	**Nina Phuong Ton Lee, Pharm. D.**

Template Version: September 1, 2010

Disclaimer

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LABELING REVIEW

This review evaluates the nonclinical information in the following sections of the proposed label for S8 Sinus Stent submitted on August 4, 2017 (NDA 209-310, SDN 008): 8.1, 8.2, 12.1, 13.1, and 13.2. The review finds necessary to rewrite or revise them, except for Section 13.2 which should be removed. These changes are recommended to ensure consistency across mometasone product labels and a concise presentation of the information. See Section IV CONCLUSION and RECOMMENDATION for the recommended text.

I. INTRODUCTION

The S8 sinus stent (NDA 209310) is a device-drug combination product. The device is to be implanted in the sinus cavity in adult patients after ethmoid sinus surgery. The device contains 1350-mcg mometasone furoate (MF). The drug is slowly released over a period of 90-days. The device is biodegradable so there is no need to remove the device after implantation.

The S8 Sinus Stent is a 505(b)(2) application. Intersect ENT (the Applicant) uses ASMANEX@ TWISTHALER@ (NDA 21-067, approval date of March 30, 2005) as the listed drug. The application also references the Propel Sinus Implants (P100044, approved on August 11, 2011) for the nonclinical support of the device. Propel mini sinus implants contains a lower amount of MF (i.e., 200 mcg/implant).

The Applicant has submitted 3 product labeling proposals for the S8 Sinus Stent. These submissions were dated March 7, June 5, and August 4, 2017 (Sequence Nos. 1, 5, and 8, respectively). This review evaluates the August 4, 2017 proposal because it reflects the Applicant's most current thinking.

Sections 8.1, 8.2, 12.1, 13.1, and 13.2 are reviewed because they contain nonclinical information. The review recommends adopting the ASMANEX@ HFA label which is a recently approved label and is PLLR-compliant (approval date of July 12, 2016). The review is divided into three major sections: the Applicant's labeling proposal, evaluation of the proposal, and recommendations.

II. PROPOSED LABELING

The Applicant proposed the following text for nonclinical sections of the S8 sinus stent label (August 4, 2017 submission). These sections included 8.1, 8.2, 12.1, 13.1, and 13.2. The proposed text for the nonclinical information is essentially excerpts of the ASMANEX TWISTHALER label.

8.1 Pregnancy

Risk Summary

(b) (4)

(b) (4)

Data

Animal Data

(b) (4)

(b) (4)

…

8.2 Lactation

Risk Summary

There are no available data on the presence of <*PROPRIETARY NAME*> Sinus Implant in human milk, the effects on the breastfed child or the effects on milk production. (b) (4)
(b) (4)
(b) (4) Systemic absorption of a single inhaled 400 mcg mometasone dose was less than 1%. It is not known if mometasone furoate is excreted in human milk. Other inhaled corticosteroids, similar to mometasone furoate, are present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for the <*PROPRIETARY NAME*> Sinus Implant and any potential adverse effects on the breastfed infant from the <PROPRIETARY NAME> Sinus Implant.

12.1 Mechanism of Action

Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on inflammation is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

In a 2-year carcinogenicity study in Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase of tumors at inhalation doses up to 67 mcg/kg. In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 mcg/kg.

Mometasone furoate increased chromosomal aberrations in an in vitro Chinese hamster ovary cell assay, but did not increase chromosomal aberrations in an in vitro Chinese hamster lung cell assay.

Mometasone furoate was not mutagenic in the Ames test or mouse lymphoma assay, and was not clastogenic in an in vivo mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis in vivo in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced in male or female rats by subcutaneous doses up to 15 mcg/kg.

(b) (4)

(b) (4)

III. EVALUATION OF APPLICANT'S PROPOSAL

The proposed text for nonclinical sections of the product label deviated significantly from the approved PLLR-compliant labels for MF products and should be revised. The S8 sinus stent is a MF product. Its label should be not only PLLR-compliant but also consistent with the other approved MF product labels because these labels are based on the same set of nonclinical data.

Approved and PLLR-compliant MF product labels are those for ASMANEX HFA and DULERA (NDAs 205-641 and 22-518, approved on July 16, 2016). This review uses the ASMANEX@ HFA label as a template to evaluate the proposed labeling for the S8 sinus stent, although the stent application uses the ASMANEX TWISTHALER as its reference product. The reason is that: 1) the ASMANEX TWISTHALER label has not been converted into PLLR-compliant format, and 2) nonclinical sections of all MF product labels are based on the same set of nonclinical data. The ASMANEX HFA label is applicable to the S8 Stent application as the History of Mometasone Labeling Review below indicates.

III.A History of Mometasone Labeling Review

Several versions of MF labels are available among the marketed drug products as alluded to earlier. Some of these labels are PLLR-compliant and some are

not. Table 1 presents key MF products relevant to the labeling review of the current product. These products include ELOCON@ ointment, NASONEX@ nasal spray, ASMANEX@ HFA, DULERA@, and ASMANEX@ TWISTHALER@.

Table1: Key Relevant Mometasone Furoate Products on the Market

Product	NDA No.	Indication	Date of Approval	Most Current Label	
				Format	Approval date
Elocon@ ointment	19-543	Dermatosis	04/30/1987	Conventional	03/28/13
Nasonex@ nasal spray	20-762	Nasal Allergy	10/01/1997	Conventional	01/19/11
ASMANEX@ TWISTHALER [a]	21-067	Asthma	03/30/2005	Conventional	09/17/10
Dulera@ MDI [b]	22-518	Asthma	06/22/2010	PLLR	07/12/16
ASMANEX@ HFA	205641	Asthma	04/25/2014	PLLR	07/12/16

a. The listed drug.
b. Dulera contains both MF and formoterol as the API.

Only the ASMANEX HFA and DULERA labels are PLLR-compliant, as alluded to earlier. In fact, these two products carry exactly the same label, although they differ in their APIs: MF for ASMANEX HFA and MF/formoterol in DULERA, respectively. The Division approved the labels in the Action Letter dated July 12, 2016 (DARRTS ID# 3957542). Dr. Timothy Robison completed reviews of the nonclinical sections of these labels on June 19, 2016 (Table 2).

Table 2: Most Recent Labeling Reviews of Mometasone Furoate

NDA #	Drug name	DARRTS ID#	Reviewer	Date of completion
022518	DULERA	3948028	Robison	06/19/16
205641	ASMANEX HFA	3948026	Robison	06/19/16

III.B Evaluation of the Proposed Label

The proposed text of the label for S8 sinus stent deviated significantly from the approved, although it is mostly excerpts of the ASMANEX TWISTHALER label. Table 3 provides the text of the first paragraph under Animal Data in Section 8.1 Pregnancy between the proposed for S8 stent and approved for ASMANEX HFA.

Table 3: Text of the 1st Paragraph of Animal Data under Section 8.1 between Approved and Proposed Labels of MF Product

Approved ASMANEX HFA (NDA 205-641) [a]	Proposed for S8 Stent (NDA 209-310)
In an embryofetal development study with pregnant mice dosed throughout the period of organogenesis, mometasone furoate produced cleft palate at an exposure approximately one-third of the MRHD (on a mcg/m^2 basis with maternal subcutaneous doses of 60 mcg/kg and above) and decreased fetal survival at an exposure approximately equivalent to the MRHD (on a mcg/m^2 basis with a maternal subcutaneous dose of 180 mcg/kg). No toxicity was observed with a dose that produced an exposure approximately one-tenth of the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 20 mcg/kg and above).	Animal reproduction studies in mice, rats, and rabbits revealed evidence of teratogenicity. When administered to pregnant mice, rats, and rabbits, mometasone furoate increased fetal malformations and decreased fetal growth (measured by lower fetal weights and/or delayed ossification). Dystocia and related complications were also observed when mometasone furoate was administered to rats late in gestation. However, experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans. [b]

a. Approved on April 25, 2014.
b. The statements in this section (and the remaining statement in the Animal Data section) were identical to that of ASMANEX TWISTHALER, except for the first sentence which was adopted from the first paragraph.

This review evaluates both the wording of the proposed label but also dose ratios between animals and humans. Dose ratios are evaluated because of the difference in the recommended clinical doses of MF between products.

III.B.1 Dose ratio

The proposed dose ratios between animals and humans for the nonclinical sections of the labeling for S8 sinus stent are acceptable. The applicant proposed to use the same dose ratios for S8 sinus stent and ASMANEX TWISTHALER. The approach is acceptable because these ratios were from the ASMANEX TWISTHALER label and represented the worst-case scenario for both products. The maximum recommended human dose (MRHD) of MF is 30 and 880 mcg per day for S8 sinus stent and ASMANEX TWISTHALER, respectively. Dose ratios of MF exposure between animals and humans from the S8 sinus stent is a fraction of that from the ASMANEX TWISTHALER (listed drug) because of the differences in clinical dose among MF applications. Also, the same dose ratios are used for other MF product labels although the MRHD of MF may be lower. For example, the MRHD of MF in ASMANEX HFA is 200 mcg, only ¼ of the ASMANEX TWISTHALER.

The MRHD of 30-mcg mometasone is estimated using the following calculations: Each S8 sinus stent contains 1350-mcg mometasone furoate (MF). The device will release MF slowly over a period of 90-days. The average release rate of MF per device is 15 mcg per day [1350 (mcg/stent)/90 (days) = 15 mcg/day]. Because each patient may get two stents (one ethmoid sinus each), the MF

exposure in patients with the stent is 30 mcg per day [15 (mcg/stent) x 2 (stents/patient) = 30 mcg/day].

III.B.2 Text evaluation

The proposed text for the S8 sinus stent should be rewritten. The Applicant proposed the text for the nonclinical sections based on the label for ASMANEX TWISTHALER (the listed drug, NDA 21-067 approved on September 10, 2010). However, the current ASMANEX TWISTHALER label is non-PLLR compliant, as alluded to earlier. The label for the S8 sinus stent will be PLLR-compliant. Because approved PLLR-compliant labels are available (e.g., ASMANEX HFA label), it is unnecessary to generate a detailed review on PLLR-conversion of the S8 sinus stent label. This review recommends adopting the ASMANEX HFA label for the S8 sinus stent label. The review also recommends deleting section 13.2 as recommended by Dr. Timothy Robison in a nonclinical labeling review completed on June 19, 2016 (DARRTS Reference ID# 3948026). See IV Conclusion and Recommendation for the recommended text.

The Applicant also proposed to delete the following statement from Section 12.1 Mechanism of Action of ASMANEX TWISTHALER label: “Inflammation is an important component in the pathogenesis of asthma.” This is acceptable because the statement is irrelevant to the current indication.

III.C Summary

This review has compared the nonclinical sections of the proposed label for S8 Sinus stent and the approved labels for ASMANEX HFA and ASMANEX TWISTHALER. The review recommends adopting the text of the ASMANEX HFA label. The review also recommends deleting 13.2 of the proposed label because the Division has determined that this section of corticosteroid labels can be omitted. See Section V CONCLUSIONS AND RECOMMENDATIONS for the recommended content. In the future, the nonclinical sections of all other MF labels should be harmonized appropriately.

IV. CONCLUSION AND RECOMMENDATION

Nonclinical evaluations of the proposed text for Sections 8.1, 8.2, 12.1, 13.1, and 13.2 of the proposed labeling for S8 sinus stent have been completed. The proposed text is excerpts of the ASMANEX TWISTHALER label. The review recommends adopting the nonclinical sections of the ASMANEX HFA label which is PLLR-compliant. Below is the recommended text for the nonclinical portions of Section 8.1, 8.2, 12.1, and 13.1. Section 13.2 is not shown because it will be deleted.

8.1 Pregnancy

Risk Summary: There are no randomized clinical studies of <PROPRIETARY NAME> Sinus Implant in pregnant women. There are clinical considerations with the use of < PROPRIETARY NAME> Sinus Implant in pregnant women *[see Clinical Considerations]*. In animal reproduction studies, subcutaneous administration of mometasone furoate to pregnant mice, rats, or rabbits caused increased fetal malformations and decreased fetal survival and growth following administration of doses that produced exposures approximately 1/3 to 8 times the maximum recommended human dose (MRHD) on a mcg/m^2 or AUC basis *[see Data]*. However, experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans.

…

Data

Animal Data

In an embryofetal development study with pregnant mice dosed throughout the period of organogenesis, mometasone furoate produced cleft palate at an exposure approximately one-third of the MRHD (on a mcg/m^2 basis with maternal subcutaneous doses of 60 mcg/kg and above) and decreased fetal survival at an exposure approximately equivalent to the MRHD (on a mcg/m^2 basis with a maternal subcutaneous dose of 180 mcg/kg). No toxicity was observed with a dose that produced an exposure approximately one-tenth of the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 20 mcg/kg and above).

In an embryofetal development study with pregnant rats dosed throughout the period of organogenesis, mometasone furoate produced fetal umbilical hernia at exposures approximately 6 times the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 600 mcg/kg and above) and delays in fetal ossification at exposures approximately 3 times the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 300 mcg/kg and above).

In another reproductive toxicity study, pregnant rats were dosed with mometasone furoate throughout pregnancy or late in gestation. Treated animals had prolonged and difficult labor, fewer live births, lower birth weight, and reduced early pup survival at an exposure that was approximately 8 times the MRHD (on an area under the curve (AUC) basis with a maternal subcutaneous dose of 15 mcg/kg). There were no findings with an exposure approximately 4 times the MRHD (on an AUC basis with a maternal subcutaneous dose of 7.5 mcg/kg).

Embryofetal development studies were conducted with pregnant rabbits dosed with mometasone furoate by either the topical dermal route or oral route throughout the period of organogenesis. In the study using the topical dermal route, mometasone furoate caused multiple malformations in fetuses (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at an exposure

approximately 3 times the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 150 mcg/kg and above). In the study using the oral route, mometasone furoate caused increased fetal resorptions and cleft palate and/or head malformations (hydrocephaly and domed head) at an exposure approximately 1/2 of the MRHD (on AUC basis with a maternal oral dose of 700 mcg/kg). At an exposure approximately 2 times the MRHD (on an AUC basis with a maternal oral dose of 2800 mcg/kg), most litters were aborted or resorbed. No effects were observed at an exposure approximately 1/10 of the MRHD (on an AUC basis with a maternal oral dose of 140 mcg/kg).

8.2 Lactation

There are no available data on the presence of <PROPRIETARY NAME> Sinus Implant in human milk, the effects on the breastfed child, or the effects on milk production. Other inhaled corticosteroids, similar to mometasone furoate, are present in human milk. Due to species specific differences in lactation physiology, animal lactation data may not reliably predict levels in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for < PROPRIETARY NAME> Sinus Implant and any potential adverse effects on the breastfed infant from < PROPRIETARY NAME> Sinus Implant (b) (4)

12.1 Mechanism of Action

Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on inflammation is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 mcg/kg (approximately 14 times the MRHD on an AUC basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 mcg/kg (approximately 9 times the MRHD on an AUC basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not have this effect in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse

micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 mcg/kg (approximately 8 times the MRHD on an AUC basis).

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/s/

LUQI PEI
10/23/2017

CAROL M GALVIS
10/23/2017
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 209-310 **Applicant: Intersect ENT** **Stamp Date: 03/07/2017**

Drug Name: Mometasone S8 Sinus Stent **NDA/BLA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not applicable. This is a 505(b)(2) application. No quality nonclinical data was submitted or required per October 4, 2012 Pre-IND meeting. See meeting minutes (DARRTS Reference ID# 3205947).
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable. See comments in Item 1.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable. See comments in Item 1.
4	Are all required and requested IND studies in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable. See comments in Item 1. The application contained a couple of reports of nonclinical studies (Reports #R10085 and R10086). These reports are of limited value due to their poor quality. Dr. C. Galvis completed a preliminary review of the studies previously (DARRTS ID# 3235544). No comprehensive review of the studies is necessary.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. See comments in Item 1.
6	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 applicant submitted a rationale to justify the alternative route?			Not applicable. See comments in Item 1.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable. See comments in Item 1.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable. See comments in Item 1.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	Yes		A labeling review will be completed to address PLLR.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)			Not applicable. See comments in Item 1.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable. This product is for hospital use only.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			Not applicable. See comments in Item 1. Reference products of the application are Asmanex Twisthaler (NDA 21067) and Propel Nasal Implant (P100044) approved on March 30, 2005 and August 11, 2011; respectively.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

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

NOTES

No comprehensive review of the nonclinical data submitted to the application is necessary. The application contained a couple of reports of nonclinical studies (Reports #R10085 and R10086). Dr. Carol Galvis completed a preliminary review of these studies previously on December 21, 2012 in IND 116,042 (DARRTS ID# 3235544). The review concluded that the studies were of limited value due to their poor quality. It is unnecessary to complete a comprehensive review of the studies because they have no added value during the review process. A labeling review will be completed at a late time to address PLLR.

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/s/

LUQI PEI
05/01/2017

CAROL M GALVIS
05/01/2017