CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205641Orig1s000

PHARMACOLOGY 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:	205,641
Supporting document/s:	#01
Applicant's letter date:	June 27, 2013
CDER stamp date:	June 27, 2013
Product:	ASMANEX HFA (Mometasone Furoate)
Indication:	Asthma
Applicant:	Merck
Review Division:	Pulmonary, Allergy, and Rheumatology Products
Reviewer/Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Jessica Lee

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205641 are owned by Merck or are data for which Merck has obtained a written right of reference. Any information or data necessary for approval of NDA 205641 that Merck does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205641.

Reference ID: 3467446

TABLE OF CONTENTS

Reference ID: 3467446

Table of Tables

Reference ID: 3467446

1 Executive Summary

1.1 Introduction

ASMANEX® HFA (Mometasone Furoate [MF]) is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. The MF MDI is essentially the same product as the approved DULERA® (MF + Formoterol Fumarate [FF]) without the formoterol fumarate component. Two dosing regimens of MF MDI (200 mcg BID and 400 mcg BID) are proposed to offer treatment options for a spectrum of patients to step-down from MF/FF to MF alone. This is to support the goal of an optimal step-down approach that decreases treatment to the least medication necessary to maintain control of asthma.

1.2 Brief Discussion of Nonclinical Findings

There is a complete nonclinical program for mometasone furoate. No new nonclinical pharmacology or toxicology studies were submitted with this application.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, the application is recommended for approval.

1.3.2 Additional Nonclinical Recommendations

There are no outstanding issues from a nonclinical perspective.

1.3.3 Labeling

No changes are recommended for product labeling with respect to Indications and Usage and Sections 8.1, 8.2, 8.3, 12.1, 13.1, and 13.2 at this time.

INDICATIONS AND USAGE

ASMANEX HFA is a corticosteroid indicated for:

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of ASMANEX HFA in pregnant women. Animal reproduction studies of mometasone furoate in mice, rats, and rabbits revealed evidence of teratogenicity. Because animal reproduction studies are not always predictive of human response, ASMANEX HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects

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.

In a mouse reproduction study, subcutaneous mometasone furoate produced cleft palate at approximately one-third of the maximum recommended daily human dose (MRHD) on a mcg/m^2 basis and decreased fetal survival at approximately 1 times the MRHD. No toxicity was observed at approximately one-tenth of the MRHD on a mcg/m^2 basis.

In a rat reproduction study, mometasone furoate produced umbilical hernia at topical dermal doses approximately 6 times the MRHD on a mcg/m^2 basis and delays in ossification at approximately 3 times the MRHD on a mcg/m^2 basis.

In another study, rats received subcutaneous doses of 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 a dose that was approximately 8 times the MRHD on an area under the curve (AUC) basis. Similar effects were not observed at approximately 4 times MRHD on an AUC basis.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses approximately 3 times the MRHD on a mcg/m^2 basis. In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at a dose less than the MRHD based on AUC. At a dose approximately 2 times the MRHD based on AUC, most litters were aborted or resorbed *[see Nonclinical Toxicology (13.2)]*.

Nonteratogenic Effects
Hypoadrenalism may occur in infants born to women receiving corticosteroids during pregnancy. Infants born to mothers taking substantial corticosteroid doses during pregnancy should be monitored for signs of hypoadrenalism.

8.2 Labor and Delivery

There are no adequate and well-controlled human studies that have studied the effects of ASMANEX HFA during labor and delivery.

8.3 Nursing Mothers

It is not known whether ASMANEX HFA is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when ASMANEX HFA is administered to a nursing woman.

Since there are no data from well-controlled human studies on the use of ASMANEX HFA on nursing mothers, a decision should be made whether to discontinue nursing or

to discontinue ASMANEX HFA, taking into account the importance of ASMANEX HFA to the mother.

12.1 Mechanism of Action

Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory 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 and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Mometasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor, which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone. The clinical significance of these findings is unknown.

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).

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above (approximately one-third of the maximum recommended human dose MRHD on a mcg/m^2 basis). Fetal survival was reduced at 180 mcg/kg (approximately equal to

the MRHD on a mcg/m^2 basis). No toxicity was observed at 20 mcg/kg (approximately one-tenth of the MRHD on a mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately 6 times the MRHD on a mcg/m^2 basis). A dose of 300 mcg/kg (approximately 3 times the MRHD on a mcg/m^2 basis) produced delays in ossification, but no malformations.

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (approximately 8 times the MRHD on an AUC basis) caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 mcg/kg (approximately 4 times the MRHD on an AUC basis).

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above (approximately 3 times the MRHD on a mcg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 mcg/kg (less than the MRHD on an AUC basis). At 2800 mcg/kg (approximately 2 times the MRHD on an AUC basis) most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg (less than the MRHD on an AUC basis).

2 Drug Information

2.1 Drug

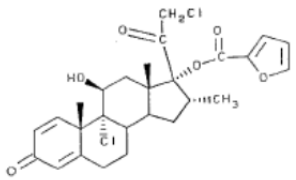
Tradename: Asmanex HFA

Generic Name: Mometasone Furoate

Chemical Name: 9α,21-dichloro-11β,17α-dihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione17-(2')-furoate

Molecular Formula/Molecular Weight: $C_{27}H_{30}O_6Cl_2$ / 521.4 g/mole

Structure:



Pharmacologic Class: Corticosteroid

2.2 Relevant IND/s, NDA/s, and DMF/s

NDA 22-518 (Merck, DULERA®) and IND 70,283 (Merck, Mometasone Furoate + Formoterol Fumarate)
Mometasone from Merck: IND 24,088, (b) (4), (b) (4), IND 46,216, IND 52,214, IND 55,108, NDA 19-543, NDA 19-625, NDA 19-796, NDA 20-762, (b) (4) (b) (4) NDA 21-067 (Merck, Asmanex® Twisthaler®), and (b) (4).

2.3 Drug Formulation

The Mometasone Furoate pressurized metered dose inhalers (pMDIs) are formulated with two strengths of mometasone furoate (100 and 200 µg per actuation ex-actuator. The drug products also contains (b) (4) ethanol (b) (4) (USP-NF), (b) (4) oleic acid (b) (4) (USP-NF), and (b) (4) HFA 227 (1,1,1,2,3,3,3-heptafluoropropane) (IPACT-II, (b) (4)). One therapeutic dose is obtained from two single actuations of the drug products.

Table 1 Mometasone Furoate: 100 µg per actuation

Table 2 Composition of the 100 mcg per Actuation Drug Product

Ingredient	Theoretical Quantity					Function	Reference to Standards
	mg/metered actuation[a]	mg/mL	mg/g	% w/w	mg/filled canister		
Mometasone Furoate	(b) (4)					Drug substance	USP, (b) (4) (b) (4)
Ethanol						(b) (4) (b) co-solvent	USP-NF
Oleic Acid						Surfactant	USP-NF
HFA 227						Propellant	IPACT-II[b] (b) (4)
Total	69.5901				13000.0000		

Calculated using a theoretical formulation density of (b) (4) g/mL
The target fill weight of a filled canister is 13.0 g
a (b) (4)
b International Pharmaceutical Aerosol Consortium for Toxicology Testing of HFA 227
c (b) (4)

BEST AVAILABLE COPY

Table 2 Mometasone Furoate: 200 µg per actuation

Table 3 Composition of the 200 mcg per Actuation Drug Product

Ingredient	Theoretical Quantity					Function	Reference to Standards
	mg/metered actuation[a]	mg/mL	mg/g	% w/w	mg/filled canister		
Mometasone Furoate	(b) (4)					Drug substance	USP, (b) (4) (b) (4)
Ethanol						(b) (4) (b) co-solvent	USP-NF
Oleic Acid						Surfactant	USP-NF
HFA 227						Propellant	IPACT-II[b] (b) (4)
Total	69.5903				13000.0000		

Calculated using a theoretical formulation density of (b) (4) g/mL
The target fill weight of a filled canister is 13.0 g
a (b) (4)
b International Pharmaceutical Aerosol Consortium for Toxicology Testing of HFA 227
c (b) (4)

BEST AVAILABLE COPY

The container closure system for the drug products consists of a 16 mL aluminum canister (b) (4) closed with a (b) (4) valve. A (b) (4) press and breathe actuator with the mouthpiece cap is provided with the pressurized canister to deliver a dose to the patient. The (b) (4) actuator incorporates an integrated displacement driven dose counter.

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

ASMANEX HFA is a corticosteroid indicated for maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. The dosing regimen is 2 inhalations twice daily of ASMANEX HFA 100 mcg or 200 µg. The starting dosage is based on prior asthma therapy.

2.7 Regulatory Background

DULERA®, a combination product containing the corticosteroid, mometasone furoate (MF), and the long-acting beta$_2$-adrenergic agonist (LABA), formoterol fumarate dihydrate (FF), was approved on June 22, 2010 for treatment of asthma in patients ≥12 years old. The approved dose of DULERA® is two inhalation twice daily of 100 µg/5 µg or 200 µg/5 µg.

In discussion during the review of DULERA®, the FDA noted that commercial availability of the MF monotherapy metered dose inhaler (MDI) comparator used in the DULERA® program would facilitate step-down to inhaled corticosteroids alone for patients no longer in need of continuous LABA treatment, and suggested that Schering Corporation, a subsidiary of Merck & Co, Inc., consider its development. Oral MF monotherapy is commercially available as a dry powder inhaler (ASMANEX®), but not as the Agency-suggested MDI. The proposed NDA is in response to that request.

The MF MDI is essentially the same product as the approved MF/F without the formoterol fumarate component. The clinical benefit of the MF MDI was demonstrated in the MF/FF adult asthma program, in which three dose regimens of MF MDI (100 mcg twice daily [BID], 200 mcg BID, and 400 mcg BID) were included in the trials as active comparators to better define the efficacy and safety of MF/FF.

Two dosing regimens of MF MDI (200 mcg BID and 400 mcg BID) are proposed to offer treatment options for a spectrum of patients to step-down from MF/FF to MF alone. This is to support the goal of an optimal step-down approach that decreases treatment to the least medication necessary to maintain control of asthma.

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical pharmacology or toxicology studies were submitted with this application.

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Reviews of NDA 22-518 dated January 19, 2010, May 12, 2010, June 7, 2010, and June 10, 2010

11 Integrated Summary and Safety Evaluation

ASMANEX® HFA (Mometasone Furoate [MF]) is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. The MF MDI is essentially the same product as the approved DULERA® (MF + Formoterol Fumarate [FF]) without the formoterol fumarate component. Two dosing regimens of MF MDI (200 mcg BID and 400 mcg BID) are proposed to offer treatment options for a spectrum of patients to step-down from MF/FF to MF alone. This is to support the goal of an optimal step-down approach that decreases treatment to the least medication necessary to maintain control of asthma.

Mometasone furoate, a synthetic 17-heterocyclin glucocorticosteroid, has been approved by the FDA as a multiple dose DPI formulation (NDA 21,067, ASMANEX®) for maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. Mometasone furoate (ASMANEX®) has been marketed in the US for the treatment of asthma since 2005.

Pharmacology:

Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory 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 and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

General Toxicology:

See NDAs 20-762 and 21-067 for reviews of general toxicology studies conducted with mometasone furoate.

Multiple target organs were observed in rats and dogs treated with mometasone by the inhalation route (see table below). These findings were attributed to the pharmacological action of mometasone (lymphoid depletion in BALT and GALT, thymus, spleen, and lymph nodes; atrophy of the adrenal cortex).

Table 3 Target organs of toxicity observed in rats and dogs treated with mometasone by the inhalation route

Organ/Tissue	Rat	Dog
Lungs	BALT (bronchial-associated lymphoid tissue) depletion, accumulation of alveolar macrophages, and pigmented macrophages.	Hyperplasia of bronchioloalveolar cells and bronchial inflammation
Thymus	Involution/atrophy	Lymphoid depletion
Nose/Turbinates	Lymphoid depletion	Lymphoid depletion
Spleen	Lymphoid depletion	Lymphoid depletion
Mesenteric LN	Lymphoid depletion and infiltration of mast cells	Lymphoid depletion and erythrophagocytosis
Bronchial LN	Lymphoid depletion	Lymphoid depletion
Mandibular LN	Lymphoid depletion	Lymphoid depletion
Mediastinal LN	Lymphoid depletion	Lymphoid depletion
Mammary gland	Abnormal lobule development	
Bone marrow	Increased marrow fat	
Ovaries	Decrease corpora lutea	Hypoplasia
Vagina	Abnormal mucification	
Adrenal gland		Vacuolization and/or atrophy of the adrenal cortex
Cecum		Lymphoid depletion
Colon		Lymphoid depletion
Duodenum		Lymphoid depletion
Ileum		Lymphoid depletion
Jejunum		Lymphoid depletion
Larynx		Lymphoid depletion
Axillary LN		Lymphoid depletion
Pharynx		Lymphoid depletion
Rectum		Lymphoid depletion
Stomach		Lymphoid depletion
Salivary gland		Infiltration of adipocytes
Uterus		Hypoplasia
Liver		Cytoplasmic vacuolation
Femur		Increased fat deposition
Rib		Increased fat deposition
Sternum		Increased fat deposition
Trachea		Decreased globule leukocytes

Genetic Toxicology:

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.

Reference ID: 3467446

Carcinogenicity:
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 µg/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 µg/kg.

Reproductive Toxicology:
In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 µg/kg.

In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 µg/kg and above. Fetal survival was reduced at 180 µg/kg. No toxicity was observed at 20 µg/kg.

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 µg/kg and above. A dose of 300 µg/kg produced delays in ossification, but no malformations. When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 µg/kg caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 µg/kg.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 µg/kg and above. In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 µg/kg. At 2800 µg/kg most litters were aborted or resorbed. No toxicity was observed at 140 µg/kg.

Excipients/Propellant:
The excipients, [redacted] ethanol [redacted] (USP-NF) and [redacted] oleic acid [redacted] (USP-NF) and the propellant, [redacted] HFA 227 (1,1,1,2,3,3,3-heptafluoropropane) (IPACT-II, [redacted], are the same as those found in the approved product, DULERA® (Merck, NDA 22-518).

Recommendations:
There is a complete nonclinical program for mometasone furoate. The application is recommended for approval from the nonclinical perspective.

Both the DULERA® and ASMANEX HFA® labels should be revised at the same time to comply with the Maternal and Lactation Labeling Rule that is expected in 2014.

Labeling Review:
The Sponsor submitted proposed labeling in general conformance with 21 CFR Parts 201, 314, and 601 Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products and Draft Guidances and Two Guidances for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Final Rule and Notices (January 24, 2006).

ASMANEX HFA is essentially the same product as the approved DULERA® (MF + Formoterol Fumarate [FF]) without the formoterol fumarate component. Doses of mometasone furoate in the ASMANEX HFA and DULERA® products are identical. Thus, there are no changes of exposure ratio calculations in the Sponsor's proposed labeling for ASMANEX HFA.

The Reviewer recommends no changes for Indications and Usage and Sections 8.1, 8.2, 8.3, 12.1, 13.1, and 13.2 at this time.

It is standard labeling practice at this time to delete Section 13.2 and incorporate the information into Section 8.1. However, Section 13.2 is still present in the current DULERA® label. Deletion of Section 13.2 and revision of Section 8.1 in the ASMANEX HFA label would cause the same information in the two product labels for mometasone to appear different. No changes are recommended at this time. Both the DULERA® and ASMANEX HFA® labels should be revised at the same time to comply with the Maternal and Lactation Labeling Rule that is expected in 2014.

INDICATIONS AND USAGE

Sponsor's Labeling:
ASMANEX HFA is a corticosteroid indicated for:

Evaluation: The established pharmacological classification is listed. No changes are recommended.

8.1 Pregnancy

Sponsor's Labeling:
Teratogenic Effects: Pregnancy Category C
There are no adequate and well-controlled studies of ASMANEX HFA in pregnant women. Animal reproduction studies of mometasone furoate in mice, rats, and rabbits revealed evidence of teratogenicity. Because animal reproduction studies are not always predictive of human response, ASMANEX HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects
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.

In a mouse reproduction study, subcutaneous mometasone furoate produced cleft palate at approximately one-third of the maximum recommended daily human dose (MRHD) on a mcg/m^2 basis and decreased fetal survival at approximately 1 times the MRHD. No toxicity was observed at approximately one-tenth of the MRHD on a mcg/m^2 basis.

In a rat reproduction study, mometasone furoate produced umbilical hernia at topical dermal doses approximately 6 times the MRHD on a mcg/m^2 basis and delays in ossification at approximately 3 times the MRHD on a mcg/m^2 basis.

In another study, rats received subcutaneous doses of 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 a dose that was approximately 8 times the MRHD on an area under the curve (AUC) basis. Similar effects were not observed at approximately 4 times MRHD on an AUC basis.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses approximately 3 times the MRHD on a mcg/m^2 basis. In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at a dose less than the MRHD based on AUC. At a dose approximately 2 times the MRHD based on AUC, most litters were aborted or resorbed *[see Nonclinical Toxicology (13.2)]*.

Nonteratogenic Effects
Hypoadrenalism may occur in infants born to women receiving corticosteroids during pregnancy. Infants born to mothers taking substantial corticosteroid doses during pregnancy should be monitored for signs of hypoadrenalism.

Evaluation: The labeling is identical to the mometasone section of the DULERA® labeling. No changes are recommended at this time. Both the DULERA® and ASMANEX HFA® labels should be revised at the same time to comply with the Maternal and Lactation Labeling Rule that is expected in 2014.

8.2 Labor and Delivery

Sponsor's Labeling:
There are no adequate and well-controlled human studies that have studied the effects of ASMANEX HFA during labor and delivery.

Evaluation: No changes are recommended.

8.3 Nursing Mothers

Sponsor's Labeling:
It is not known whether ASMANEX HFA is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when ASMANEX HFA is administered to a nursing woman.

Since there are no data from well-controlled human studies on the use of ASMANEX HFA on nursing mothers, a decision should be made whether to discontinue nursing or to discontinue ASMANEX HFA, taking into account the importance of ASMANEX HFA to the mother.

Evaluation: No changes are recommended at this time. Both the DULERA® and ASMANEX HFA® labels should be revised at the same time to comply with the Maternal and Lactation Labeling Rule that is expected in 2014.

12.1 Mechanism of Action

Sponsor's Labeling:
Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory 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 and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Mometasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor, which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone. The clinical significance of these findings is unknown.

Evaluation: The labeling is identical to the mechanism of action description for mometasone in the DULERA® labeling. No changes are recommended.

13 Nonclinical Toxicology

Sponsor's Labeling:

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).

Evaluation: The labeling is identical to the description of studies with mometasone in Section 13.1 of the DULERA® label. No changes are recommended.

13.2 Animal Toxicology and/or Pharmacology

Sponsor's Labeling:

Reproductive Toxicology Studies

In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above (approximately one-third of the maximum recommended human dose MRHD on a mcg/m^2 basis). Fetal survival was reduced at 180 mcg/kg (approximately equal to the MRHD on a mcg/m^2 basis). No toxicity was observed at 20 mcg/kg (approximately one-tenth of the MRHD on a mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately 6 times the MRHD on a mcg/m^2 basis). A dose of 300 mcg/kg (approximately 3 times the MRHD on a mcg/m^2 basis) produced delays in ossification, but no malformations.

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (approximately 8 times the MRHD on an AUC basis) caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 mcg/kg (approximately 4 times the MRHD on an AUC basis).

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150

mcg/kg and above (approximately 3 times the MRHD on a mcg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 mcg/kg (less than the MRHD on an AUC basis). At 2800 mcg/kg (approximately 2 times the MRHD on an AUC basis) most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg (less than the MRHD on an AUC basis).

Evaluation: The labeling is identical to the description of studies with mometasone in Section 13.2 of the DULERA® label. It is standard labeling practice at this time to delete Section 13.2 and incorporate the information into Section 8.1. However, Section 13.2 is still present in the current DULERA® label. Deletion of Section 13.2 and revision of Section 8.1 in the ASMANEX HFA label would cause the same information in the two product labels for mometasone to appear different. No changes are recommended at this time. Both the DULERA® and ASMANEX HFA® labels should be revised at the same time to comply with the Maternal and Lactation Labeling Rule that is expected in 2014.

Reference ID: 3467446

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

/s/

TIMOTHY W ROBISON
03/07/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205641 **Applicant: Merck** **Stamp Date: June 27, 2013**

Drug Name: ASMANEX HFA NDA Type: 505b1

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. No new nonclinical pharmacology and toxicology studies were provided in the NDA. The applicant did provide a summary of the nonclinical program.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable. No new nonclinical pharmacology and toxicology studies were provided in the NDA. The applicant did provide a summary of the nonclinical program.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable. No new nonclinical pharmacology and toxicology studies were provided in the NDA. The applicant did provide a summary of the nonclinical program.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 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)?	X		Nonclinical pharmacology and toxicology studies with mometasone were reviewed under NDAs 19-543, 19-625, 19-796, 20-762, (b) (4), 21-067, (b) (4), and 22-518
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. Inhalation bridging toxicology studies with the marketed formulation were provided and reviewed under NDA 22-518.
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?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
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?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			The Applicant indicated that impurities were identical to those found in the approved product, DULERA. Will consult with the Chemist regarding any impurity issues.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

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.

None

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

None

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Pharmacologist	Date
Team Leader/Supervisor	Date

Reference ID: 3355316

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

/s/

TIMOTHY W ROBISON
08/09/2013