CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205641Orig1s000

SUMMARY REVIEW

Summary Review of Regulatory Action

Date	April 25, 2014
From	Lydia I. Gilbert-McClain, MD
Subject	Summary Review of regulatory action
NDA	NDA 205-641
Applicant	Merck, Sharpe, and Dohme
Date of Submission	June 27, 2013
PDUFA Goal Date	April 25, 2014
Proprietary Name/Established (USAN) names	Asmanex HFA/mometasone furoate inhalation aerosol
Dosage forms/Strength	Inhalation aerosol(metered dose inhaler)/100 and 200 mcg mometasone furoate/actuation
Proposed Indication (s)	"maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older
Recommended Action	Approval
MATERIALS REVIEWED	**Reviewers**
Clinical Review	Kimberly Witzmann, MD
CDTL Memo	Anthony Durmowicz, MD
Biometrics Review	Robert Abugov, PhD
Division of Medical Policy Programs (DMPP) – OPDP review	Twanda Scales, RN, MSN/Ed

1. Introduction

Merck, Sharp, and Dohme (the Applicant) submitted a 505(b) (1) NDA on June 27th 2013, to support approval of Asmanex HFA (mometasone furoate) inhalation aerosol for the maintenance treatment of asthma in patients 12 years of age and older. This product is the corticosteroid component of the already approved fixed dose combination product Dulera comprised of a inhaled corticosteroid (ICS) mometasone furoate (MF) and a long-acting beta agonist (LABA) formoterol (FF). Dulera was approved on June 22, 2010, for the (b) (4) treatment of asthma in patients 12 years of age and older. The Division encouraged the Applicant to develop the corticosteroid component of the Dulera combination product as a monotherapy for asthma. Conceptually, patients on a fixed dose combination of LABA/ICS would have a smoother transition when stepping down from an ICS/LABA fixed dose combination product if they can step down to the ICS of the same formulation as in the combination product and vice versa. The Applicant moved forward with the Division's recommendation and completed development of the ICS (mometasone furoate) HFA for marketing. There is already a single ingredient mometasone furoate inhalation product approved and marketed for asthma, however, this product (Asmanex Twisthaler) is a different formulation (dry powder). The clinical data to support the single ingredient mometasone furoate HFA is principally derived from the studies

conducted to support the approval of the fixed dose combination LABA/ICS product. This summary review highlights the key elements of the application and basis for the regulatory decision.

2. Background

Asthma is a chronic inflammatory respiratory disease characterized by periods of acute symptoms of wheezing, and shortness of breath, and inhaled corticosteroids play a principal therapeutic role in the management of patients with persistent asthma. Patients with persistent asthma whose disease remains uncontrolled in spite of treatment with controller therapy such as inhaled corticosteroids are candidates for treatment with LABA/ICS fixed dose combination products. Patients can be stepped down from LABA/ICS treatment to a monotherapy steroid when stable as deemed appropriate by their healthcare provider and having a monotherapy ICS in the same formulation as the combination product, makes for a smoother transition. Therefore, during the review of the Dulera NDA the Applicant was encouraged to pursue marketing approval for the ICS component and this NDA was submitted to support the efficacy and safety of MF in the same HFA formulation as the Dulera fixed dose combination product.

3. CMC/Facilities/Inspections

The active ingredient (API) is mometasone furoate which is a well known corticosteroid approved in another single ingredient product for oral inhalation (Asmanex Twisthaler), and as the ICS in the Dulera fixed dose combination product. Asmanex HFA is an inhalation aerosol in a pressurized mini dose inhaler propelled by the hydrofluroalkane (HFA) 227. The product is formulated in 2 strengths of MF 100 and 200 mcg/actuation [ex-actuator]. The product also contains (b) (4) ethanol (b) (4) and (b) (4) oleic acid. The product has a dose counter attached to the pressurized canister. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology studies were required or performed for this application. Pharmacology/toxicology information was previously submitted and reviewed under NDA 22-518 [Dulera].

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology/biopharmaceutics were conducted to support this application. Supporting clinical pharmacology information is referenced from NDA 22-518 [Dulera].

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical Efficacy

The determination of efficacy for Asmanex HFA was based on the data generated from the clinical studies conducted with the Dulera program. Table 1(copied from Dr. Anthony Durmowicz's CDTL review) outlines the relevant studies used to support the efficacy of Asmanex HFA.

Table 1: Clinical Studies Used to Support the Efficacy of Mometasone HFA

Study/ Year Initiated	Study Design	Study Duration	Age	Baseline FEV_1	N	Treatments	Primary Endpoint
Primary Efficacy and Safety							
P04334 US, Canada, EU, Asia, South America *2008*	R, DB, PC Safety Efficacy	26 week	12-76	60-90% predicted	781	MF/F 200/10 BID MF 200 BID F10 BID Placebo	Post-dose FEV_1
P04431 US, Europe, South America *2008*	R, DB Safety Efficacy	12 week	12-84	50-85% predicted	728	MF/F 200/10 BID MF/F 400/10 BID MF 400 BID	Post-dose FEV_1
Dose Selection							
C97-208 US *1998*	PC, AC, Dose-range	12 week	12-81	60-90% predicted	435	MF-MDI 50 BID MF-MDI 200 BID MF-MDI 400 BID MF-MDI 600 BID BDP 168 BID Placebo	1-4 hr post-dose FEV_1
C97-225 US *1998*	PC Efficacy, Safety	12 week	12-72	60-90% predicted	232	MF-MDI 50 BID MF-MDI 200 BID BDP 168 BID Placebo	1-4 hr post-dose FEV_1
I97-200 EU, South America, South Africa *1998*	AC Efficacy, Safety	12 week	12-76	55-90% predicted	715	MF-MDI 100 BID MF-MDI 200 BID MF-MDI 400 BID FP MDI 250 BID-CFC	1-4 hr. post-dose FEV_1
Long Term Safety							
C97-222 US *1999*	R, AC, OL	52 week	12-70	60-90% predicted	308	MF MDI 200 BID MF MDI 600 BID BDP 168 BID	Safety
P04139	R, OL, AC HPA axis	52 weeks	12-75	60-90% predicted	404	MF/F 200/10 BID MF/F 400/10 BID F/SC 250/50 BID F/SC 500/50 BID	Safety

MF=mometasone furoate; F=formoterol fumarate; MF/F=mometasone + formoterol; BDP= beclomethasone diproprionate; F/SC= fluticasone + salmeterol; FP= fluticasone propionate; R=randomized; DB=double blind; OL=open label; AC=active control

Studies that provided support for the doses selected for the phase 3 trials (C97-208, C97-225, and 197-200) were conducted with a closely related but older MF MDI formulation and the studies showed that after 12 weeks of treatment there is not much of a dose response (based on FEV_1 assessment) from doses 200 mg and higher (up to 800 mg). The doses in this range are all on the flat part of the dose response curve. This range of doses is within the approved recommended dose ranges for Asmanex Twisthaler, and this range of doses was studied in the Dulera program. The data to support efficacy of the MF monotherapy are from the two factorial designed studies in the Dulera program. Both of these studies provide adequate support for MF as monotherapy for asthma. In one study (P04334 – supports 200 mcg twice daily dosing) the change in mean trough FEV_1 from baseline to week 12 compared to placebo showed significantly greater improvement in patients on MF monotherapy compared to placebo with a treatment difference from placebo of 120 mL, 95% CI (0.05, 0.20) and patients on MF monotherapy had less deteriorations in asthma compared to placebo patients. In the other study

(P04431 – supports the 400 mcg twice daily dosing) conducted to demonstrate the added benefit of the higher dose of mometasone (400 mcg twice daily) compared to 200 mcg twice daily in the fixed dose combination product, there was numerical separation between the two product products MF/FF 200 mcg/10 mcg, and 400 mcg/10 mcg for trough FEV_1. This finding indicates that the MF 400 mcg component had an additional efficacy benefit above the efficacy shown with MF/FF 200 mcg/10 mcg. As this study was conducted in a more severe asthma population a placebo arm was (appropriately) not included in the study. There is however, placebo-controlled data (from the dose ranging studies) comparing the 400 mcg MF to placebo. Given that efficacy of MF 200 mcg twice daily has been demonstrated, the efficacy of MF 400 mcg is not in question. More appropriately, the MF 400 mcg product should be recommended for patients with more severe asthma on higher doses of ICS or oral corticosteroids.

8. Safety

There are no new safety signals with this HFA formulation of mometasone furoate. Like all ICS, the product will be labeled with the standard class labeling safety warnings and precautions that are in other ICS labels. No new safety signals emerged from the program to suggest that the HFA formulation of MF has a different or worse safety profile than other ICS for the treatment of asthma.

9. Advisory Committee Meeting

An advisory committee meeting was not necessary for this application. The active ingredient in the product is a well know corticosteroid.

10. Pediatrics

This application triggered PREA because it is a new dosage form. The Applicant has asked for a waiver of pediatric studies in children less than 5 years of age and a deferral of pediatric studies in children 5 to 11 years of age. These are reasonable requests and the PeRC agrees with granting the partial waiver and deferral of pediatric studies.

11. Other Relevant Regulatory Issues

- **Data Quality, Integrity, and Financial Disclosure**

  There was no need for a DSI audit for this application. The financial disclosure information for this application is contained in the Dulera NDA22-518 (already approved) the three investigators who had disclosable financial interests did not affect the outcome of the studies.

12. Labeling

There are no outstanding labeling issues. The name Asmanex HFA is acceptable.

Patient Labeling and Medication Guide

A medication guide for this product is not warranted.

13. Action and Risk Benefit Assessment

Regulatory action

The regulatory action for the application is approval. The submitted data support approval of Asmanex HFA for the maintenance treatment of asthma in patients 12 years of age and older. The recommended dose for patients on medium (b) (4) inhaled corticosteroids is 200 mcg twice daily (from the Asmanex HFA 100 mcg product) and for patients with more severe asthma

on oral corticosteroids, the recommended dose is 400 mcg twice daily (from the Asmanex HFA 200 mcg product).

Risk Benefit Assessment

Inhaled corticosteroids for the maintenance treatment of asthma have a well established risk benefit profile. The safety profile of this product appears to be similar to other approved ICS and the benefit of ICS in the management of asthma is well established.

Postmarketing Risk Management Activities

None

Postmarketing Study Commitments/Requirements

No additional postmarketing studies are required for this application. The PREA requirements are being conducted under the Dulera pediatric development program

Comments to the Applicant

There are no deficiency comments to be conveyed to the Applicant.

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

/s/

LYDIA I GILBERT MCCLAIN
04/25/2014