MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 20-829, 20-830, (b) (4)	**TRADE NAME:**	Singulair™
APPLICANT/SPONSOR:	Merck	**USAN NAME:**	montelukast sodium
MEDICAL OFFICER:	Jennifer Rodriguez Pippins, MD, MPH		
TEAM LEADER:	Susan Limb, MD	**CATEGORY:**	leukotriene receptor antagonist
DATE:	February 21, 2011	**ROUTE:**	oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
9/3/2010	9/3/2010	NDA 20-829, SD# 339, eCTD #128	PMC Study Report
9/3/2010	9/3/2010	NDA 20-830, SD# 336, eCTD #128	PMC Study Report
9/3/2010	9/3/2010	NDA 21-409, SD# 218, eCTD #128	PMC Study Report
5/26/2011	5/26/2011	NDA 20-829, SD# 350, eCTD# 137	Efficacy Supplement
5/26/2011	5/26/2011	NDA 20-830, SD# 347, eCTD # 138	Efficacy Supplement
5/26/2011	5/26/2011	NDA 21-409, SD# 228, eCTD# 135	Efficacy Supplement
9/30/2011	9/30/2011	NDA 20-829, SD# 1729, eCTD# 139	Efficacy Supplement
9/30/2011	9/30/2011	NDA 20-830, SD# 645, eCTD# 140	Efficacy Supplement
9/30/2011	9/30/2011	NDA 21-409, SD# 305, eCTD#139	Efficacy Supplement
2/14/2012	2/14/2012	NDA 20-829, SD# 1796, eCTD# 145	Efficacy Supplement
2/14/2012	2/14/2012	NDA 20-830, SD# 701, eCTD 146	Efficacy Supplement
2/14/2012	2/14/2012	NDA 21-409, SD# 364, eCTD# 146	Efficacy Supplement

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

EXECUTIVE SUMMARY:

Merck is submitting a final study report for Trial 377, in fulfillment of a PREA commitment, along with an Efficacy Supplement proposing the expansion of the exercise-induced bronchoconstriction (EIB) indication to include patients 6 to 14 years of age, as well as associated labeling changes to the product labels for Singulair™ Tablets (NDA 20-829), Singulair™ Chewable Tablets (20-830), and Singulair™ Oral Granules (NDA 21-409).

Singulair™ received approval for the prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older on April 13, 2007. The approval letter outlined a postmarketing commitment under the Pediatric Research Equity Act (PREA):

> *Deferred pediatric study under PREA for the prevention of exercise-induced bronchoconstriction in pediatric patients ages 4 to 14 years of age.*

Merck subsequently requested a partial waiver for the 4-5 year old patients from the PREA commitment, which was granted on August 27, 2010, on the basis that, "Necessary studies are highly impractical due to low recruitment for patients of ages 4 and 5 years of age who can reliably perform spirometry."

Trial 377 evaluated Singulair for the prevention of EIB in patients 6 to 14 years of age. The results for the primary endpoint, maximum percent fall in FEV_1 after exercise challenge performed at 2 hours postdose, demonstrated a statistically significant reduction for patients treated with montelukast, as compared to placebo, with a LS mean treatment difference of -4.65 percentage points (95% CI: -8.55, -0.75, p=0.02). Results for the secondary endpoints of maximum percent fall in FEV_1 after exercise challenge at 24 hours postdose, categorized maximum percent fall in FEV_1 after exercise challenge at 2 hours postdose, and $AUC_{0\text{-}60min}$ after exercise challenge at 2 and 24 hours postdose, were supportive of the findings for the primary endpoint.

The safety results for the trial do not raise any new safety concerns for Singulair™.

It is recommended that Trial 377 be considered as adequate to fulfill the described PREA commitment. In addition, the results of Trial 377, in conjunction with an extrapolation of the adult EIB data, are adequate to support the expansion of the EIB indication to include patients 6 to 14 years of age. The Applicant's proposed labeling changes incorporating the results of Trial 377 and the expansion of the EIB indication were also reviewed and found to be acceptable.

OUTSTANDING ISSUES: NONE

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	____	**SAFE TO PROCEED** ____ **CLINICAL HOLD**
OTHER ACTION:	X	**ACKNOWLEDGMENT OF PREA COMMITMENT FULFILLMENT**
	X	**APPROVAL OF EFFICACY SUPPLEMENT PROVIDING FOR AN EXPANSION OF THE EIB INDICATION TO INCLUDE PATIENTS 6-14 YEARS OF AGE, WHICH INCLUDES ASSOCIATED CHANGES TO THE PRODUCT LABELING**
	____	

1. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

The following regulatory actions are recommended:

(1) That the PREA commitment to conduct a "pediatric study for the prevention of exercise-inducted bronchoconstriction in pediatric patients ages 4 to 14 years of age" (April 13, 2007, Singulair™ Approval Letter), be considered fulfilled.

(2) That the efficacy supplement (including related labeling changes) proposing the expansion of the EIB indication to include patients 6 to 14 years of age be approved.

1.2 Risk Benefit Assessment

The Applicant has submitting a final study report for Trial 377, in fulfillment of a PREA commitment, along with an Efficacy Supplement proposing the expansion of the exercise-induced bronchoconstriction (EIB) indication to include patients 6 to 14 years of age, as well as associated labeling changes to the product labels for Singulair™ Tablets (NDA 20-829), Singulair™ Chewable Tablets (20-830), and Singulair™ Oral Granules (NDA 21-409).

The evidence supporting the use of Singulair™ in the prevention of exercise-induced bronchoconstriction (EIB) in patients 6 to 14 years of age is drawn from the results of Trial 377, as well as the results of trials conducted in support of the adult EIB indication, as summarized in the product label.

Trial 377 was a randomized, double-blind, placebo-controlled, cross-over trial evaluating a single 5 mg dose of Singulair™ chewable tablet for the prevention of EIB in patients 6 to 14 years of age. Sixty-six pediatric patients with a history of EIB or wheeze and/or SOB with exercise, with or without asthma, were randomized to one of two treatment sequences, and underwent exercise challenge testing and subsequent spirometric assessments.

The results for the primary endpoint, maximum percent fall in FEV_1 after exercise challenge performed at 2 hours postdose, demonstrated a statistically significant reduction for patients treated with montelukast, as compared to placebo, with a LS mean treatment difference of -4.65 percentage points (95% CI: -8.55, -0.75, p=0.02).

Results for the secondary endpoints of maximum percent fall in FEV_1 after exercise challenge at 24 hours postdose, categorized maximum percent fall in FEV_1 after exercise challenge at 2 hours postdose, and $AUC_{0\text{-}60min}$ after exercise challenge at 2 and 24 hours postdose, were supportive of the findings for the primary endpoint.

In addition to the results of Trial 377, evidence supporting the efficacy of a single dose of Singulair™ for the prevention of EIB in patients 6 to 14 years of age may be extrapolated from the results of clinical trials conducted in support of the adult EIB indication. These included three randomized, double-blind, placebo-controlled crossover trials that included a total of 160 adult and adolescent patients 15 years of age and older with EIB. Exercise challenge testing was conducted at 2 hours, 8.5 or 12 hours, and 24 hours following administration of a single dose of either Singulair™ 10 mg or placebo. The primary endpoint was the mean maximum percent fall in FEV_1 following the 2 hours postdose exercise challenge. Results demonstrated that treatment with Singulair was associated with a statistically significant protective benefit against EIB when taken 2 hours prior to exercise;

some patients were protected at the later time points as well. Given that pathophysiology of EIB is understood to be similar between adults and children, it is reasonable to extrapolate evidence of efficacy from the adult data to the pediatric population 6 to 14 years of age.

The modest magnitude of the treatment effect (-4.65 percentage points) for the primary endpoint is noted. The totality of the data, however, including the results for the secondary endpoints and for the evaluation of Singulair™ for EIB in adults, together support the efficacy of this product for the prevention of EIB in patients 6 to 14 years of age.

The review of safety took into account both the safety data from Trial 377, as well as the safety data available from prior clinical trials and the extensive postmarketing experience for Singulair™, as summarized in the product label.

There were no deaths, serious adverse events, or discontinuations due to a clinical adverse event reported for Trial 377. Overall, the occurrence of any adverse event when treated with montelukast was lower (n=4, 6.2%) than that when treated with placebo (n=5, 7.6%). The proposed dose and dosing frequency falls within current dosing recommendations for other indications approved for Singulair, and the safety profile observed in Trial 377 is consistent with the profile described in the current package insert for Singulair™. These results do not raise any new safety concerns for Singulair™.

Given the evidence of efficacy drawn from Trial 377 and from the adult EIB program, in conjunction with the satisfactory safety profile observed in Trial 377 which is consistent with the profile described in the current package insert for this product, this clinical review assesses the risk-benefit profile Singulair™ for the prevention of EIB in patients 6 to 14 years to be acceptable.

2. INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Montelukast sodium (Singulair™) is a member of the leukotriene receptor antagonist class. It is available in three oral dosage forms: a 10-mg film-coated tablet (NDA 20-829), 5-mg and 4-mg chewable tablets (NDA 20-830), and 4-mg oral granules (NDA 21-409).

Singulair™ received initial United States approval in 1998. It is currently indicated for:

- Prophylaxis and chronic treatment of asthma in patients 12 months of age and older,
- Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older, and
- Relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older, and perennial allergic rhinitis in patients 6 months of age and older.

2.2 Summary of Presubmission Regulatory Activity Related to Submission

The following timeline summarizes the presubmission regulatory activity related to the current submission:

- April 13, 2007

  Singulair™ receives approval for the prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older on April 13, 2007. The approval letter outlines a postmarketing commitment under the Pediatric Research Equity Act (PREA):

  > *Deferred pediatric study under PREA for the prevention of exercise-induced bronchoconstriction in pediatric patients ages 4 to 14 years of age.*

- May 7, 2007

  The Applicant submits a Protocol 377, which it intends to conduct in order to fulfill the PREA commitment described above. On August 9, 2007, the Division provides the following feedback to the Applicant regarding the protocol:

  - The study design is adequate to meet PREA requirements
  - The inclusion of an additional exercise challenge at an intermediate timepoint is recommended
  - The clinical relevance of the (b) (4) treatment difference proposed as the basis of the power calculation is raised as a review issue

- September 18, 2009

  The Applicant requests a partial waiver for the 4-5 year old patients from the PREA commitment, which was granted on August 27, 2010, on the basis that, "Necessary studies are highly impractical due to low recruitment for patients of ages 4 and 5 years of age who can reliably perform spirometry."

- September 3, 2010

  The Applicant submits the final study report for Trial 377, which is proposed as a fulfillment the PREA commitment described above.

- May 26, 2011

  In response to a request by the Division, the Applicant submits a Prior Approval Supplement (PAS) incorporating the results of Trial 377 into the product label. After internal discussions within the Division and with the Pediatric Review Committee (PeRC) on August 31, 2011, the decision is made to engage the Applicant in a discussion regarding the possibility of using the data from Trial 377 to support filing for an indication for pediatric EIB in the 6 to 14 year old age group.

- September 30, 2011

  The Applicant amends their submission to an Efficacy Supplement seeking the expansion of the current EIB claim to include patients 6 to 14 years of age. The submission includes updated proposed labeling reflecting this change.

- February 14, 2011

  In response to feedback provided by the Division, the Applicant resubmits their proposed labeling.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

The submission included a complete study report for Trial 377, appropriate case report forms, and proposed labeling. The clinical section was appropriate indexed and organized to allow review. The submission included raw datasets for Trial 377.

Review of the Application did not raise any data concerns, and the Applicant reports that all of the Investigators for Trial 377 were certified regarding the absence of financial interests and arrangements (see Section 3.3). For these reasons, no DSI review was recommended.

3.2 Compliance with Good Clinical Practices

The Application includes a statement of Good Clinical Practice (GCP), indicating that Trial 377 was conducted in conformance with applicable country and/or local statues and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. In addition to informed consent, assent was obtained for patients 7 years of age and older.

3.3 Financial Disclosures

In a submission dated November 18, 2011, the Applicant states all of the Investigators for Trial 377 were certified regarding the absence of financial interests and arrangements.

4. CLINICAL DATA SOURCES, REVIEW STRATEGY, AND TRIAL DESIGN

4.1 Table of Clinical Trials

Table 1. Table of Clinical Trials

Trial	Population	N*	Design	Treatments	Relevance
377	Children, 4 to 14 years of age, with EIB or wheeze and/or SOB with exercise, with or without asthma	66	R, DB, PC, CO	Montelukast chewable tablet, 5 mg (single dose) Placebo (single dose)	Efficacy, Safety

*** Number randomized.**

4.2 Review Strategy

The current submission includes data from a single trial (Trial 377), which were reviewed.

With regards to the organization of this review, Section 4.3 includes a discussion of the design of Trial 377. The efficacy results are discussed in Section 5, which is followed in Section 6 by a review of the safety findings.

The review of efficacy conducted for this particular submission took into account both the results of the single trial conducted (Trial 377), as well as the efficacy results of trials conducted in support of the adult EIB indication, as summarized in the product label. The review of safety took into account both the safety data from Trial 377, as well as the safety data available from prior clinical trials and the extensive postmarketing experience for Singulair™, as summarized in the product label.

Of note, the primary clinical review of the data had been substantially completed on an alternate review template prior to the September 30, 2011, amendment proposing an expanded indication. Typically, clinical reviewers use the 21st Century NDA clinical review template for all efficacy supplements. However, given that the review was substantially complete and that the supplement in question involved limited data for an otherwise well-characterized drug product, the review team and signatory authority agreed that rewriting the existing review to conform to the 21st Century NDA template was not indicated in this case.

4.3 Clinical Trial Design

A synopsis of the protocol for Trial 377 is provided here.

4.3.1. Title

Protocol 377: “A double-blind, placebo-controlled, multicenter, crossover study to evaluate the effects of a single oral dose of montelukast, compared with placebo, on exercise-induced bronchoconstriction (EIB) in pediatric patients aged 4 to 14 years.”

4.3.2. Investigative sites

Multicenter, 22 sites in the United States, Colombia, Costa Rica, and Estonia.

4.3.3. Objectives

4.3.3.1. Primary

- To determine the effect of a single oral dose of montelukast, compared with placebo, on EIB as measured by the maximal percent fall in FEV_1 (post-exercise change from pre-exercise baseline) after exercise challenge performed 2 hours postdose.

4.3.3.2. Secondary

- To determine the effect of a single oral dose of montelukast, compared with placebo, on:

- The maximal percent fall in FEV_1 (post-exercise change from pre-exercise baseline) following exercise challenge performed 24 hours postdose,
- The categorized maximum percent fall in FEV_1 (<10%, 10-20%, >20%) following exercise challenges performed 2 and 24 hours postdose,
- The area under the curve for the percent fall from pre-exercise FEV_1 over time ($AUC_{0\text{-}60\ mins}$) following exercise challenges performed 2 and 24 hours postdose,
- Time to recovery of FEV_1 to within 5% baseline following exercise challenges performed 2 and 24 hours postdose, and
- Need for rescue medication following exercise challenges performed 2 and 24 hours postdose.

- To determine the safety and tolerability of a single oral dose of montelukast in pediatric patients with EIB.

4.3.4. Endpoints

4.3.4.1. Primary

- Maximum percent fall in FEV_1 after exercise challenge at 2 hours postdose

4.3.4.2. Secondary

- Maximum percent fall in FEV_1 after exercise challenge at 24 hours postdose
- Categorized maximum percent fall in FEV_1 after exercise challenge at 2 and 24 hours postdose
- $AUC_{0\text{-}60min}$ after exercise challenge at 2 and 24 hours postdose
- Time to recovery after exercise challenge at 2 and 24 hours postdose
- Rescue medication within 90 minutes after exercise challenge at 2 and 24 hours postdose

4.3.5. General study design

Randomized, double-blind, placebo-controlled, crossover study.

4.3.6. Patient population

Pediatric patients, 4 to 14 years of age, with a history of EIB or wheeze and/or shortness of breath with exercise, with or without a diagnosis of asthma.

Reviewer's Comment:

While the trial original proposed the inclusion of children 4-14 years of age, the actual age range of children randomized was 6-15 years. Children aged 4-5 years were screened but none were randomized; one child turned 15 years old after Visit 1 but prior to randomization.

4.3.7. Selected Inclusion criteria

Visit 1

- 4-14 years of age

- History of EIB or wheeze and/or shortness of breath with exercise, with or without a diagnosis of asthma.
- Females of reproductive potential: agrees to abstinence or continues to use an acceptable method of birth control, as per the protocol
- Non-smoker
- Good health
- Able to perform acceptable spirometry

Visit 2

- Baseline pre-exercise FEV_1 of ≥ 70% of predicted at Visit 2
- Demonstrated evidence of EIB (i.e. decrease in FEV_1 of at least 20% within 60 minutes after the standardized exercise challenge at Visit 2, compared to the pre-exercise baseline FEV_1)
- Able to perform acceptable reproducible spirometry testing

Visit 3

- Baseline FEV_1 of ≥ 70% of predicted at Visit 3
- Demonstrated evidence of EIB (i.e. decrease in FEV_1 of at least 20% within 60 minutes after the standardized exercise challenge at Visit 3, compared to the pre-exercise baseline FEV_1)
- Able to perform acceptable reproducible spirometry testing

4.3.8. Selected Exclusion criteria

- Participation in a clinical trial within 4 weeks of Visit 1
- Pregnancy, recent pregnancy (≤ 8 weeks postpartum), or lactation
- Excessive intake of caffeine
- Asthma exacerbation within 4 weeks of Visit 1
- Any active, acute, or chronic pulmonary disorder other than asthma
- Unresolved upper respiratory tract infection within 2 weeks of Visit 1
- History of intubation for asthma
- Treated for asthma in an emergency room/urgent care facility/office setting within one month of Visit 1
- Hospitalized for asthma within 3 months of Visit 1
- Current hospitalization for any reason
- Major surgical procedure, trauma, or significant illness requiring medical attention within 4 weeks of Visit 1
- History of anaphylaxis to a drug product (any) or other hypersensitivity to inhaled β-agonist or montelukast
- History of clinically significant illness
- Significant abnormalities on physical examination or laboratory evaluation at Visit 1

- Use of disallowed medications and timeframe with respect to Visit 1:
    - Corticosteroids (oral, intravenous, rectal, intramuscular, or intra-articular) within 4 weeks
        - Nasal steroids for allergic rhinitis are allowable
        - Low-dose ICS are permitted in up to 50% of the patient population if they have been on a stable dose for at least 4 weeks
        - Topical corticosteroids (≤ 2.5% hydrocortisone) permitted if dose unchanged and therapy initiated at least 2 weeks prior to Visit 1

Reviewer's Comment

The 2002 "Guidance for Industry, Exercise-Induced Bronchospasm (EIB) – Development of Drugs to Prevent EIB" draft guidance specifies that patients be excluded if they have received parenteral or oral corticosteroids during the 12 weeks before study entry; this protocol utilizes a cut-off of 4 weeks, which is acceptable.

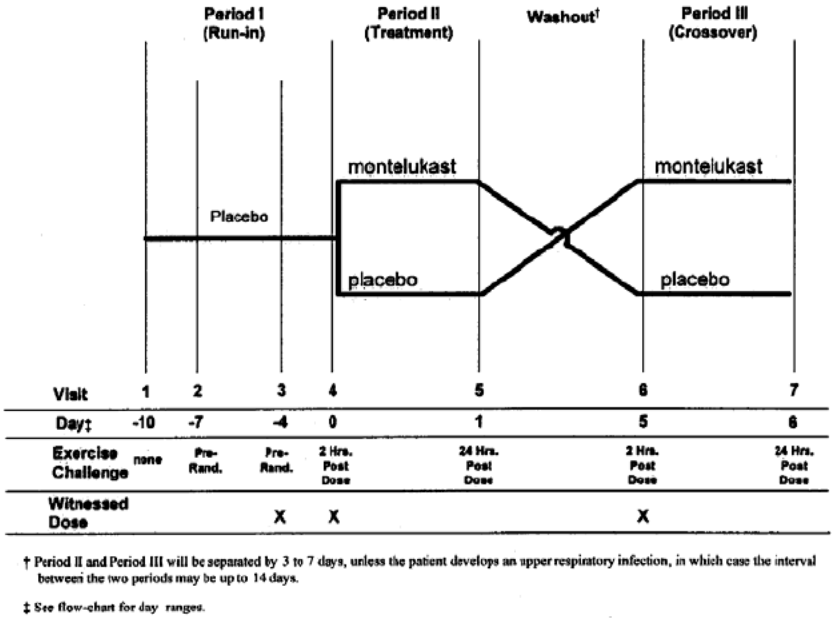
    - Cromolyn within 8 hours or nedodromil within 2 days
    - Leukotriene receptor antagonists, or 5-lipooxygenase synthase inhibitors within 1 week
    - Theophylline within 1 week
    - Oral or long-acting β-agonists or inhaled anticholinergic agents within 1 week
    - Astemizole within 12 weeks
    - Antibiotics for upper respiratory infection for >7 days in the 4 weeks prior to Visit 1 or during the Run-in period
    - Immunotherapy started within 6 months
    - Immunotherapy started more than 6 months before Visit 1, if the dose is expected to change during the course of the study
    - Short-acting inhaled bronchodilators other than albuterol or salbutamol (e.g. isoproterenol, isoetharine, metaproterenol, terbutaline, or OTC bronchodilators) within 8 hours
    - Antihistamines or decongestants, including OTC cold and/or sinus medications, within 2 days or cetirizine, levocetirizine, or hydroxyzine within 4 days
    - Ketotifen within 1 week
    - Any drug for an off-label indication within 4 weeks
    - Omalizumab at any time
- ECG abnormalities consistent with hypertrophic cardiomyopathy, conduction system disease, or other abnormality that the Investigator feels would put the patient at risk during exercise testing
- Clinically significant heart murmur
- Evidence of valvular, hypertrophic, familial or other forms of heart disease that would put the patient at risk or interfere with exercise testing
- Precipitous fall in FEV_1 following exercise at Visit 2

- Requires rescue treatment with short-acting β-agonist after exercise challenge and does not return to within 20% of pre-exercise baseline FEV_1 within 30 minutes of treatment at Visit 2
- Asthma exacerbation between Visit 1 and Visit 2
- Precipitous fall in FEV_1 following exercise at Visit 3
- Requires rescue treatment with short-acting β-agonist after exercise challenge and does not return to within 20% of pre-exercise baseline FEV_1 within 30 minutes of treatment at Visit 2
- Asthma exacerbation between Visit 2 and Visit 3
- Asthma exacerbation between Visit 3 and Visit 4

4.3.9. Study procedures

The study consisted of a Run-in Period (Period 1), a Treatment Period (Period 2), a Washout Period, and a Crossover Period (Period 3). A study schematic is presented in Figure 1.

Figure 1. Study Schematic



† Period II and Period III will be separated by 3 to 7 days, unless the patient develops an upper respiratory infection, in which case the interval between the two periods may be up to 14 days.

‡ See flow-chart for day ranges.

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 25 (Figure 9-1)

Run-in Period (Period 1)

During the run-in, or screening, period, subjects underwent two treadmill exercise challenges (one at Visit 2 and one at Visit 3). Subjects received a single dose of placebo in a single-blind manner 2 hours prior to the Visit 3 exercise challenge. Spirometry was performed 5 minutes prior to each exercise challenge and immediately, 5, 10, 15, 30, 45, and 60 minutes after each exercise challenge. If the patient had not yet returned to within 5% of pre-exercise FEV_1 by 60 minutes, then additional spirometry measurements were obtained at 75 minutes and 90 minutes (as necessary).

Treatment Period (Period 2)

Patients were assigned to 1 of 2 treatments, a single dose of montelukast 5-mg chewable tablet or placebo, in a double-blind manner. An exercise challenge was performed at 2 and 24 hours postdose. Spirometry was performed 5 minutes prior to each exercise challenge and immediately, 5, 10, 15, 30, 45, and 60 minutes after each exercise challenge. If the patient had not yet returned to within 5% of pre-exercise FEV_1 by 60 minutes, then additional spirometry measurements were obtained at 75 minutes and 90 minutes (as necessary).

Washout Period

The washout period was 3-7 days in length.

Crossover Period (Period 3)

During the crossover period, patients received the alternative study treatment. An exercise challenge was performed at 2 and 24 hours postdose. Spirometry was performed 5 minutes prior to each exercise challenge and immediately, 5, 10, 15, 30, 45, and 60 minutes after each exercise challenge. If the patient had not yet returned to within 5% of pre-exercise FEV_1 by 60 minutes, then additional spirometry measurements were obtained at 75 minutes and 90 minutes (as necessary).

4.3.10. Proposed dose and justification

Montelukast chewable tablet (CT), 5 mg single dose; this is the approved dose for children ages 6-14. No children 4-5 years of age were randomized into the study.

4.3.11. Safety assessment

Safety assessments included: adverse experiences (AEs), serious adverse experiences (SAEs), physical exam, vital signs, ECGs, and laboratory safety tests.

4.3.12. Statistical design and analysis

The analysis of efficacy data was conducted on the completers analysis population (i.e. all randomized patients who received study drug in both active treatment periods and had at least one post-exercise FEV_1 measurement in both active treatment periods). The analysis of safety data was conducted on the "all patients as treated" (APaT) population (i.e. all randomized patients who received at least 1 dose of study drug; each patient was counted in the treatment group of the study drug they actually received). Adverse experiences that occurred during the washout period were assigned to the previous treatment.

For the primary endpoint, a sample size of 60 completed patients was needed to detect a treatment difference of (b) (4) percentage points between montelukast and placebo with 90% power, assuming an α=0.05 and a standard deviation of difference of 14 percentage points. The planned total number of patients to be randomized was 66, in order to allow for a discontinuation rate of 10%.

For the primary efficacy endpoint (maximum percent fall in FEV_1 at 2 hours postdose), an ANOVA model was employed.

Reviewer's Comment

Protocol 377 is generally consistent with the 2002 "Guidance for Industry, Exercise-Induced Bronchospasm (EIB) – Development of Drugs to Prevent EIB" draft guidance and the trial design used to support the EIB indication in patients 15 years and older. The primary difference between the pediatric trial and the adult trial were the number of timepoints assessed (three in the adult trials vs. two in Trial 377) and the use of an active comparator in the adult trials.

5 REVIEW OF EFFICACY

Efficacy Summary

The evidence supporting the use of Singulair™ in the prevention of exercise-induced bronchoconstriction (EIB) in patients 6 to 14 years of age is drawn from the results of Trial 377, as well as the results of trials conducted in support of the adult EIB indication, as summarized in the product label.

Trial 377 was a randomized, double-blind, placebo-controlled, cross-over trial evaluating a single 5 mg dose of Singulair™ chewable tablet for the prevention of EIB in patients 6 to 14 years of age. Sixty-six pediatric patients with a history of EIB or wheeze and/or SOB with exercise, with or without asthma, were randomized to one of two treatment sequences, and underwent exercise challenge testing and subsequent spirometric assessments.

The results for the primary endpoint, maximum percent fall in FEV_1 after exercise challenge performed at 2 hours postdose, demonstrated a statistically significant reduction for patients treated with montelukast, as compared to placebo, with a LS mean treatment difference of -4.65 percentage points (95% CI: -8.55, -0.75, p=0.02).

Results for the secondary endpoints of maximum percent fall in FEV_1 after exercise challenge at 24 hours postdose, categorized maximum percent fall in FEV_1 after exercise challenge at 2 hours postdose, and $AUC_{0\text{-}60min}$ after exercise challenge at 2 and 24 hours postdose, were supportive of the findings for the primary endpoint.

In addition to the results of Trial 377, evidence supporting the efficacy of a single dose of Singulair™ for the prevention of EIB in patients 6 to 14 years of age may be extrapolated from the results of clinical trials conducted in support of the adult EIB indication. These included three randomized, double-blind, placebo-controlled crossover trials that included a total of 160 adult and adolescent patients 15 years of age and older with EIB. Exercise challenge testing was conducted at 2 hours, 8.5 or 12 hours, and 24 hours following administration of a single dose of either Singulair™ 10 mg or placebo. The primary endpoint was the mean maximum percent fall in FEV_1 following the 2 hours postdose exercise challenge. Results demonstrated that treatment with Singulair was associated with a statistically significant protective benefit against EIB when taken 2 hours prior to exercise; some patients were protected at the later time points as well. Given that pathophysiology of EIB is understood to be similar between adults and children, it is reasonable to extrapolate evidence of efficacy from the adult data to the pediatric population 6 to 14 years of age.

The modest magnitude of the treatment effect (-4.65 percentage points) for the primary endpoint is noted. The totality of the data, however, including the results for the secondary endpoints and for the

evaluation of Singulair™ for EIB in adults, together support the efficacy of this product for the prevention of EIB in patients 6 to 14 years of age.

5.1 Indication

The submission proposed the expansion of the current EIB indication, which applies to patients 15 years of age and older, to include children 6 to 14 years of age. The revised product label proposes the following language: "SINGULAIR is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 6 years of age and older."

5.1.1 Methods

Refer to Section 4.3 for a discussion of the protocol for Trial 377.

In addition to the results of Trial 377, which are described in Sections 5.1.2 – 5.1.5, this review of efficacy also took into account the efficacy results of trials conducted in support of the adult EIB indication. The product label for Singulair™ describes three randomized, double-blind, placebo-controlled crossover trials that included a total of 160 adult and adolescent patients 15 years of age and older with EIB. Exercise challenge testing was conducted at 2 hours, 8.5 or 12 hours, and 24 hours following administration of a single dose of either Singulair™ 10 mg or placebo. The primary endpoint was the mean maximum percent fall in FEV_1 following the 2 hours postdose exercise challenge. Results demonstrated that treatment with Singulair was associated with a statistically significant protective benefit against EIB when taken 2 hours prior to exercise; some patients were protected at the later time points as well.

The product label also notes that daily administration of Singulair has not been shown to prevent acute episodes of EIB. A 12-week, randomized, double-blind, parallel group study of 110 adult and adolescent asthmatics 15 years of age and older, with a documented history or exercise-induced exacerbation of asthma, demonstrated that treatment with a single 10 mg dose of Singulair was associated with a statistically significant reduction in mean maximal percent fall in FEV_1 and mean time to recovery within 5% of the pre-exercise FEV_1, with exercise challenge being conducted at 20-24 hours postdose. The effect was maintained throughout the treatment period. It is noted, however, that Singulair did not prevent clinically significant deterioration in maximal percent fall in FEV_1 after exercise (i.e., ≥ 20% decrease from pre-exercise baseline) in more than half of patients studied. The product label notes that an additional crossover study in adults, which evaluated two once-daily 10 mg doses of Singulair, had similar findings, as did a 2-day crossover study in pediatric patients 6-14 years of age using the 5 mg chewable tablet.

5.1.2 Demographics

Characteristics of the patient population are provided in Table 2.

Table 2. Patient Characteristics (all randomized patients)

	Montelukast/Placebo (n=33)		Placebo/Montelukast (n=33)		Total (n=66)	
	n	%	n	%	n	%
Male	19	57.6	18	54.5	37	56.1
Female	14	42.4	15	45.5	29	43.9
< 11.5* years	16	48.5	17	51.5	33	50.0
≥ 11.5 years	17	51.5	16	48.5	33	50.0
Black	7	21.2	4	12.1	11	16.7
White	24	72.7	25	75.8	49	74.2
Other	2	6.1	4	12.1	6	9.1
Hispanic	6	18.2	6	18.2	12	18.2
Non-Hispanic	27	81.8	27	81.8	54	81.8
Not on ICS	27	81.8	22	66.7	49	74.2
On ICS	6	18.2	11	33.3	17	25.8

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 54 (Table 10-4)

***11.5 years is the median age for the entire randomized population.**

Reviewer's Comment:

Although patients aged 4 and 5 years were screened, none were randomized. One patient turned 15 after the first study visit but prior to randomization.

Patient characteristics were well-balanced across treatment sequences, with the exception of race and ICS use. These imbalances are acceptable.

5.1.3 Subject Disposition

Of the 364 patients screened, 298 patients were excluded, mostly due to screen failures. The remaining 66 patients were randomized, and 63 patients (95.5%) completed the study; reasons for discontinuation included physician decision (n=1), protocol violation (n=1), and subject withdrawal (n=1). Sixty-five patients received treatment with montelukast and 66 patients received treatment with placebo.

5.1.4 Analysis of the Primary Endpoint

The results for the analysis of the primary endpoint, maximum percent fall in FEV_1 after exercise challenge performed at 2 hours postdose, are provided in Table 3.

Table 3. Results for Primary Efficacy Endpoint: Maximum Percent Fall in FEV_1 After Exercise at 2 Hours Postdose Use (Completers Analysis Population, ANOVA Model)

	n	Mean	SD	LS Mean	95% CI
Montelukast	64	15.35	9.47	15.35	12.60,18.11
Placebo	64	20.00	15.75	20.00	17.25, 22.76
Comparison Between Treatments		**Difference in LS Means**		**95% CI**	**p-Value**
Montelukast vs. Placebo		-4.65		-8.55, -0.75	0.02

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 67 (Table 11-1)

Maximum percent fall in FEV_1 after exercise challenge performed at 2 hours postdose was reduced for patients treated with montelukast, as compared to placebo. The LS mean treatment difference of -4.65 percentage points was statistically significant (p=0.02).

It is noted that the size of the treatment effect (-4.65 percentage points), is smaller than the effect size described for the adult population in the product label (-9 percentage points), and smaller than the 6% magnitude anticipated, which was flagged as a potential review issue by the Division (see Section 2.2). While the effect size is of modest magnitude, the totality of the data, including the results for the secondary endpoints (Section 5.1.5), and the results for the evaluation of Singulair™ for EIB in adults (Section 5.1.1) together support the efficacy of this product for the prevention of EIB in patients 6 to 14 years of age.

5.1.5 Analysis of Secondary Endpoint(s)

The secondary endpoints evaluated in Trial 377 were:

- Maximum percent fall in FEV_1 after exercise challenge at 24 hours postdose
- Categorized maximum percent fall in FEV_1 after exercise challenge at 2 and 24 hours postdose
- $AUC_{0\text{-}60min}$ after exercise challenge at 2 and 24 hours postdose
- Time to recovery after exercise challenge at 2 and 24 hours postdose
- Rescue medication within 90 minutes after exercise challenge at 2 and 24 hours postdose

Maximum Percent Fall in FEV_1 After Exercise Challenge at 24 Hours Postdose

Results for this secondary efficacy endpoint were supportive of the results for the primary endpoint; see Table 4.

Table 4. Results for Maximum Percent Fall in FEV_1 After Exercise at 24 Hours Postdose Use (Completers Analysis Population, ANOVA Model)

	n	Mean	SD	LS Mean	95% CI
Montelukast	62	12.96	10.38	12.92	10.81, 15.04
Placebo	62	17.22	12.06	17.25	15.14, 19.36
Comparison Between Treatments		**Difference in LS Means**		**95% CI**	**p-Value**
Montelukast vs. Placebo		-4.33		-7.31, -1.34	0.005

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 71 (Table 11-2)

Categorized Maximum Percent Fall in FEV_1 (< 10%, 10-20%, > 20%) After Exercise Challenge at 2 and 24 Hours Postdose

The results for this secondary endpoint supported an effect of montelukast on decreasing the maximum percent fall in FEV_1 after exercise challenge at 2 hours, as demonstrated by a significant shift towards a lower category fall for patients on montelukast compared to placebo (p=0.034). The result at 24 hours postdose was not significant (p=0.061). Results are provided in Table 5.

Table 5. Results for Categorized Maximum Percent Fall in FEV_1 After Exercise at 2 and 24 Hours Postdose (Completer Analysis Population)

	Montelukast		Placebo	
	n/N*	%	n/N	%
2 Hours Postdose				**p=0.034#**
<10%	17/64	26.6	16/64	25.0
10-20%	32/64	50.0	20/64	31.3
>20%	15/64	23.4	28/64	43.8
24 Hours Postdose				**p=0.061#**
<10%	28/62	45.2	19/62	30.6
10-20%	22/62	35.5	23/62	37.1
>20%	12/62	19.4	20/62	32.3

***n/N=number of patients in specified category/number of patients as specified sequence and treatment**

#p-value by Cochram-Mantel-Haenszel test for the comparison between Montelukast and placebo.

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 73 (Table 11-3)

It is notable that some patients did not experience EIB when treated with placebo, which suggests some degree of within-patient variability with respect to this disease process.

Area Under the Curve for the Percent Fall From Pre-exercise FEV_1 Over 60 Minutes ($AUC_{0-60min}$) After Exercise Challenge at 2 and 24 Hours Postdose

Results for this secondary efficacy endpoint were supportive of the results for the primary endpoint; see Table 6 and Table 7.

Table 6. Results for $AUC_{0-60min}$ After Exercise Challenge at 2 Hours Postdose (Completers Analysis Population, ANOVA Model)

	n	Mean	SD	LS Mean	95% CI
Montelukast	64	294.50	278.46	294.50	221.73, 367.27
Placebo	64	415.37	375.94	415.37	342.60, 488.13
Comparison Between Treatments		**Difference in LS Means**		**95% CI**	**p-Value**
Montelukast vs. Placebo		-120.86		-223.77, -17.95	0.022

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 76 (Table 11-4)

Table 7. Results for $AUC_{0-60min}$ After Exercise Challenge at 24 Hours Postdose (Completers Analysis Population, ANOVA Model)

	n	Mean	SD	LS Mean	95% CI
Montelukast	62	229.19	233.93	227.98	160.44, 295.51
Placebo	62	349.59	315.29	350.80	283.26, 418.34
Comparison Between Treatments		**Difference in LS Means**		**95% CI**	**p-Value**
Montelukast vs. Placebo		-122.82		-218.36, -27.29	0.013

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 76 (Table 11-5)

Time to Recovery After Exercise Challenge at 2 and 24 Hours Postdose

At exercise challenge conducted 2 and 24 hours postdose, montelukast was associated with a reduced time to recovery after maximum percent fall in FEV_1 compared to placebo, but the results were not statistically significant. Results are provided in Table 8 and Table 9.

Table 8. Results for Time to Recovery from Maximum Percent Fall at 2 Hours Postdose (Completers Analysis Population, ANOVA Model)

	n	Mean	SD	LS Mean	95% CI
Montelukast	64	16.21	22.01	16.21	10.01, 22.42
Placebo	64	24.48	27.91	24.48	18.27, 30.68
Comparison Between Treatments		**Difference in LS Means**		**95% CI**	**p-Value**
Montelukast vs. Placebo		-8.27		-17.04, 0.51	0.064

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 78 (Table 11-6)

Table 9. Results for Time to Recovery from Maximum Percent Fall at 24 Hours Postdose (Completers Analysis Population, ANOVA Model)

	n	Mean	SD	LS Mean	95% CI
Montelukast	62	11.58	16.51	11.49	6.42, 16.56
Placebo	62	18.46	22.66	18.55	13.48, 23.62
Comparison Between Treatments		**Difference in LS Means**		**95% CI**	**p-Value**
Montelukast vs. Placebo		-7.06		-14.23, 0.11	0.054

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 78 (Table 11-7)

Rescue Medication Within 90 Minutes After Exercise Challenge at 2 and 24 Hours Postdose

After exercise challenge at 2 hours postdose, 1 patient on montelukast and 2 patients on placebo required medication; at 24 hours postdose, no patients on montelukast and 2 patients on placebo required rescue medication. These results were not statistically significant. See Table 10.

Table 10. Results for Rescue Medication Use Within 90 Minutes After Exercise Challenge at 2 and 24 Hours Postdose (Completers Analysis Population)

				Montelukast vs. Placebo		
	N	n	%	Point Difference (%)	95% CI*	p-Value#
2 Hours Postdose						
Montelukast	64	1	1.6	-1.6	-9.27, 5.63	1.000
Placebo	64	2	3.1			
24 Hours Postdose						
Montelukast	62	0	0.0	-3.2	-11.02, 3.06	---
Placebo	62	2	3.2			

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 80 (Table 11-8)

***95% CI computed using a continuity corrected Wilson's Score method**

#p-value by exact McNemar's test for the comparison between Montelukast and placebo

Key: N=number of patients performing the exercise challenge at specified time point in both periods; n=number of patients requiring rescue medication

6 REVIEW OF SAFETY

Safety Summary

The review of safety took into account both the safety data from Trial 377, as well as the safety data available from prior clinical trials and the extensive postmarketing experience for Singulair™, as summarized in the product label.

There were no deaths, serious adverse events, or discontinuations due to a clinical adverse event reported for Trial 377. Overall, the occurrence of any adverse event when treated with montelukast was lower (n=4, 6.2%) than that when treated with placebo (n=5, 7.6%). The proposed dose and

dosing frequency falls within current dosing recommendations for other indications approved for Singulair, and the safety profile observed in Trial 377 is consistent with the profile described in the current package insert for Singulair™. These results do not raise any new safety concerns for Singulair™.

6.1 Methods

The review of safety took into account both the safety data from Trial 377, as well as the safety data available from prior clinical trials and the extensive postmarketing experience for Singulair™, as summarized in the product label.

6.1.1 Studies/Clinical Trials Used to Evaluate Safety

A single trial (Trial 377) was conducted in support of the proposed indication. Safety assessments conducted in this trial included: adverse experiences (AEs), serious adverse experiences (SAEs), vital signs, physical exam, ECGs, and laboratory safety tests.

6.1.2 Categorization of Adverse Events

An adverse experience (AE) was defined as "any unfavorable and unintended change in the structure (signs), function (symptoms), or chemistry (laboratory data) of the body temporally associated with any use of a Merck product whether or not considered related to the use of the product" (Trial 377 Study Report, pg. 35). A serious adverse experience was defined as any adverse experience which results in death, is life threatening, results in a persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization, or is a congenital anomaly/birth defect (Trial 377 Study Report, pg. 35-36), consistent the *Code of Federal Regulations.*[1]

6.2 Adequacy of Safety Assessments

6.2.1 Overall Exposure

During each of the 2 active treatment periods (Periods II and III), patients received 1 witnessed dose of oral trial medication (either Singulair™ or placebo); exposure was comparable between the two treatments. A summary of exposure is provided in Table 11.

Table 11. Extent of Exposure

Treatment	Period II (N=66)	Period III (N=65)
	n (%)	n (%)
Singulair™ (N=65)	33 (50)	32 (49.2)
Placebo (N=66)	33 (50)	33 (50.8)

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 84 (Table 12-1)
N=Number of patients who took their assigned drug

[1] 21 CFR § 312.32(a).

Percentages are calculated based on the number of patients treated in each treatment period.

6.2.2 Routine Clinical Testing

The routine clinical testing conducted in Trial 377 was adequate and included: urine β-hCG (for postmenarchal females), hematology, serum chemistry, vital signs, physical examination, and 12-lead electrocardiogram (ECG). Regarding the safety laboratory testing, β-hCG was obtained at the start of each study period; hematology and chemistry tests were obtained only at baseline, and could be waived if the patient had documented results within the 3 months prior to Visit 1. Physical examination and 12-lead ECG were conducted at baseline; vital signs were obtained in each period.

6.3 Major Safety Results

6.3.1 Deaths

There were no deaths reported for Trial 377.

6.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events reported for Trial 377.

6.3.3 Dropouts and/or Discontinuations

There were no discontinuations due to a clinical adverse event reported for Trial 377.

6.4 Supportive Safety Results

6.4.1 Common Adverse Events

Overall, the occurrence of any adverse event when treated with montelukast was lower (n=4, 6.2%) than that when treated with placebo (n=5, 7.6%). A summary of adverse events is provided in Table 12.

Table 12. Patients with Adverse Events, Incidence > 0% in One or More Treatment Groups, by System Organ Class (All Patients as Treated Population)

	Montelukast (N=65)		Placebo (N=66)	
	n	%	n	%
Gastrointestinal Disorders	0	0	1	1.5
Abdominal discomfort	0	0	1	1.5
General Disorders and Administration Site Conditions	1	1.5	0	0
Pyrexia	1	1.5	0	0
Immune system Disorders	1	1.5	0	0
Hypersensitivity	1	1.5	0	0
Infections and Infestations	3	4.6	1	1.5
Nasopharyngitis	2	3.1	0	0.0
Pharyngitis Streptococcal	0	0.0	1	1.5
Upper Respiratory Tract Infection	1	1.5	0	0.0
Respiratory, Thoracic, and Mediastinal Disorders	1	1.5	4	6.1
Asthma	0	0.0	1	1.5
Bronchospasm	1	1.5	3	4.5

Source: NDA 20-829, September 3, 2010 Submission: Section 5.3.5.4.3, pg. 88 (Table 12-4)

The proposed dose and dosing frequency falls within current dosing recommendations for other indications approved for Singulair, and the observed safety profile is consistent with the profile described in the current package insert for Singulair. These results do not raise any new safety concerns for Singulair™.

6.4.2 Laboratory Findings

Hematology and serum chemistry testing was conducted only at baseline, and so no analyses of change are presented here.

6.4.3 Vital Signs

Vital Signs were obtained for during each treatment period. Mean changes from baseline in pulse rate, systolic and diastolic blood pressure, respiratory rate, and temperature were both small in magnitude and comparable between treatments.

6.4.4 Electrocardiograms (ECGs)

12-lead ECG was conducted only at baseline, and so no analyses of change are presented here.

7 Appendices

7.1 Literature Review/References

A literature review was not conducted by the Applicant.

A PubMed search was conducted by this reviewer on February 18, 2012, [search term: montelukast and exercise induced and safety] using the following restrictions [limits: human, clinical trial, meta-analysis, randomized clinical trial, English language], for the time period covering the past 5 years. The search yielded 14 references. Brief review of the abstracts for these references did not identify any safety concerns.

7.2 Labeling Recommendations

The Applicant's proposed labeling changes were reviewed. The revisions to Sections 1.2, 2.2, and 14.2 of the PI are included below. Final labeling is pending at this time.


(b) (4)

7.3 Advisory Committee Meeting

An advisory committee meeting was not held for this Application, since montelukast is a well-known chemical entity, and the drug product is already approved for the prevention of EIB in patients 15 years and older.

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/s/

JENNIFER R PIPPINS
02/21/2012

SUSAN L LIMB
02/21/2012