

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as
amended**

**Singulair, Singulair AR, Montelukast MSD, Airathon
(Montelukast)**

PL/W/0002/pdWS/001

**Marketing Authorisation Holder:
Merck Sharp & Dohme**

Rapporteur:	Poland
Start of the procedure (day 0):	21.09.2010
Date of this report:	22.11.2010
Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR)(day 70):	30.11.2010
Deadline for CMS's comments:	15.12.2010
Finalisation procedure (day 90)	20.12.2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Singulair 5 mg Chewable Tablets Singulair AR 5 mg Chewable Tablets Montelukast MSD 5 mg Chewable Tablets Airathon 5 mg Chewable Tablets
INN (or common name) of the active substance(s):	Montelukast
MAH:	Merck Sharp & Dohme
Currently approved Indication(s)	The treatment of mild to moderate persistent asthma The prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.
Pharmaco-therapeutic group (ATC Code):	R03D C03
Pharmaceutical form(s) and strength(s):	Chewable tablets, 5 mg
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I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed

II. RECOMMENDATION¹

No further action required

III. INTRODUCTION

On September 8th 2010 the MAH submitted a completed paediatric study for Singulair 5 mg Chewable Tablets, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Singulair 5 mg Chewable Tablets and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

According to the study protocol it was planned to use montelukast 4-mg Chewable Tablets (CT) and 5-mg CT formulations, as approved for use in the EU Member States for the respective age ranges (4-mg CT: patients aged 4 and 5 years; 5-mg CT: patients aged 6 to 14 years). However, because there were no 4- or 5-year-old patients randomized into this study; only the 5-mg CT formulation was administered to patients in the study.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

Prot. No. 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.

2. Clinical study(ies)

Prot. No. 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.

¹ The recommendation from section V can be copied in this section
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➤ Description

➤ Methods

- Objective(s)

The primary objective was to determine the effect of a single oral dose of montelukast, compared with placebo, on exercise-induced bronchoconstriction as measured by the maximal percent fall in Forced Expiratory Volume in 1 second (FEV₁) after exercise challenge performed 2 hours postdose in paediatric patients aged 4 to 14 years.

- Study design

A multicenter, multinational, randomized, placebo-controlled, double-blind crossover study

- Study population /Sample size

The study protocol required that patients be aged 4 to 14 years with a history of EIB or wheeze and/or shortness of breath with exercise, with or without a diagnosis of persistent asthma, required to have a baseline FEV₁ ≥70%, and decrease in FEV₁ of at least 20% from prechallenge baseline after a standardized exercise challenge. 364 patients were recruited. A total of 66 patients met the inclusion criteria and were randomized into the study.

- Treatments

Montelukast was administered as a chewable tablet (CT). Patients received a single dose montelukast CT, 5mg, or matching-image placebo. After a 3- to 7-day washout period each patient crossed over to the next treatment. Patients previously assigned to receive montelukast received placebo and patients previously assigned to receive placebo received montelukast

- Outcomes/endpoints

Efficacy was assessed by spirometric measurement before and after exercise challenge. The principle efficacy endpoint in this study was the maximum percent fall from pre-exercise baseline in FEV₁. Additional efficacy endpoints included AUC_{0-60 min} (area under the curve for FEV₁ percent change from pre-exercise baseline during the 60 minutes following exercise challenge), time to recovery of FEV₁ to within 5% of baseline, and the proportion of patients requiring rescue with short-acting beta-agonist within the 90 minutes following exercise.

- Statistical Methods

Power analysis:

For the primary endpoint of maximum percent fall in FEV₁, a sample size of 60 completed patients was needed to detect a treatment difference of 6 percentage points between montelukast and placebo with 90% power with $\alpha=0.050$, two-sided test, and assumed standard deviation of difference of 14 percentage points.

- Efficacy

The maximum percent fall in FEV₁ after exercise at 2 hours postdose was analyzed using an Analysis of Variance (ANOVA) model with terms for patient, treatment, and period effects. Treatment comparison was performed using adequate contrast within the ANOVA model. In addition, least-squares (LS) means and corresponding 95% confidence intervals (CIs) were computed for each treatment, as well as the difference in LS means and the corresponding 95% CIs. To further explore the assumption of no differential carryover effect, an ANOVA model with terms for sequence, treatment, period, and patient nested within sequence was used. A mixed model that includes all available information at both 2 and 24 hours postdose was used as an additional sensitivity analysis with terms for treatment, time, treatment by time and period, and unstructured variance/covariance. Centers were not included in the ANOVA and mixed models for the efficacy analyses.

➤ **Results**

- Recruitment/ Number analysed

Of the 66 patients randomized, 63 (95.5%) of the patients completed the study. Sixty-five of the 66 patients took montelukast. Patients were randomized to one of two treatment sequences; 1) montelukast followed by placebo; 2) placebo followed by montelukast.

- Baseline data

Data from the study support the efficacy of montelukast in the prevention of EIB after acute (single-dose) administration in paediatric patients. The treatment effect is apparent as early as 2 hours and the duration of effect as long as 24 hours postdose. Moreover, montelukast demonstrated significant prevention of EIB.

- Efficacy results

A single 5-mg dose of montelukast significantly reduced the maximum percent fall in FEV₁ (Least Square [LS] mean difference = -4.65%, p=0.020), compared with placebo, after exercise challenge at 2 hours postdose. Montelukast treatment significantly shifted the maximum percent fall in FEV₁ toward a lower fall category (i.e., toward a less severe fall in FEV₁) (p=0.034), compared with placebo, at 2 hours postdose. Most of the difference between montelukast and placebo was found in the proportion of patients achieving maximum percent fall in FEV₁ ≥10% and ≤20%. The proportion of patients achieving maximum percent fall in FEV₁ <10% was similar between montelukast and placebo. A single dose of montelukast significantly reduced the AUC_{0-60min} for percent fall in FEV₁ after exercise challenge, compared with placebo (LS mean difference = -120.86%•min, p=0.022). On the secondary endpoint of maximum percent fall in FEV₁ after exercise challenge at 24 hours postdose, a single oral 5-mg dose of montelukast provided significant benefit compared with placebo (LS mean difference = -4.33%, p=0.005). The categorized response (maximum percent fall in FEV₁ <10%, 10% to 20%, >20%) on montelukast and placebo after exercise was similar for the two treatments (p=0.061); however, there was a numerical increase in the proportion of patients achieving maximum percent fall in FEV₁ <10% (i.e., “no or minimal” response to exercise challenge) on montelukast compared with placebo (45.2% vs. 30.6%).

- Safety results

Safety and tolerability were assessed by statistical and/or clinical review of all adverse experiences. Clinical adverse experiences were reported by 8 (12.1%) of the 66 randomized patients; 4 (6.2%) patients on montelukast treatment and 5 (7.6%) patients on placebo treatment. One patient reported adverse experiences on both treatments. No clinically meaningful differences were noted in any adverse experiences between treatments. The two most common AEs were bronchospasm (montelukast 1 [1.5%], placebo 3 [4.5%]), and nasopharyngitis (montelukast: 2 [3.1%], placebo 0 [0%]). No drug-related adverse experiences, serious adverse experiences, or discontinuations due to an adverse experience were reported. There were no patient deaths, pregnancies or overdoses (accidental or intentional) reported. No laboratory adverse experiences were reported.

3. Discussion on clinical aspects

As far 2 studies (PNs 040 and 911) were conducted in paediatric patients aged 6 to 14 years, during which montelukast was administered chronically. In both studies montelukast demonstrated a significant protective effect against EIB. In PN 40 montelukast was compared to placebo and in PN 911 montelukast was compared to salmeterol.

Three studies (PNs 270, 275, 316) of montelukast with single-dose administration were conducted in adults and adolescents where montelukast provided significant protection against EIB.

The study no. 377 revealed that a single oral dose of montelukast, compared with placebo significantly reduces the maximum percent fall in FEV₁ after exercise in patients aged 4 - 14 years. No new safety concerns for montelukast were identified. The results of this paediatric EIB study are consistent with the results of previous montelukast EIB studies, both in terms of efficacy and safety.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The results of this paediatric EIB study are consistent with the results of previous montelukast EIB studies, both in terms of efficacy and safety. No SmPC and PL changes are required.

➤ Recommendation

No further action required

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable