CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-830/S008

PHARMACOLOGY REVIEW(S)

JAN 27 2000

HFD-570 : DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Labeling Review

NDA No. 20-830 **Supplement No.:** S-008 **Submission Date:** 07 MAY 1999

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 27 JAN 2000

Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: Merck Research Laboratories

Drug Names: *Generic Name:* montelukast sodium *Commercial:* Singulair™

The sponsor submitted draft labeling as part of a supplement package presenting data from a pharmacokinetic study in 2- to 5-year old patients with chronic asthma to demonstrate the safety and tolerability of profiles of montelukast in this pediatric population. Montelukast is currently indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 6 years of age and older. Furthermore, a new formulation, the 4 mg chewable tablet, is proposed by the sponsor. Currently, the tablet is available in 5 mg chewable tablet and the 10 mg film-coated tablet. The new formulation 4 mg chewable tablet is an exact submultiple (80%) of the approved 5 mg chewable tablet formulation.

The sponsor's draft labeling includes pharmacokinetic data in 2- to 5-year old patients. This data demonstrated comparable AUC_{pop} values between 2- to 5-year olds administered 4 mg chewable tablets (2721 ng.hr/ml) and adults administered 10 mg tablets (2595 ng.hr/ml) and a geometric mean ratio (pediatric/adult) of 1.05. The mean exposure value following administration of the 5 mg chewable tablet in the 6 to 12 age group was 2928 ng.hr/ml). Since exposure in adults and pediatrics was nearly equivalent, ratios to human exposures are based on exposure values in adults.

The proposed labeling for the current supplement includes outdated dosage comparisons between humans and animals based upon body surface area. Labeling Reviews for NDAs 20-829 and 20-830 (Supplement S-001, dated June 12, 1998, October 9, 1998 and December 7, 1998) discuss recommended dosage comparisons between humans and animals based upon plasma drug concentrations.

It is, however, recommended that these changes be included in the current labeling to include the 2- to 5-year old pediatric population. Therefore, the following sections of the proposed label should be revised as follows with revised portions in bold lettering:

Carcinogenesis, Mutagenesis, and Impairment of Fertility
No evidence of tumorigenicity was seen in **either** a 2-year carcinogenicity study in Sprague Dawley rats, at ——————— up to 200 mg/kg/day **[estimated exposure was**

~~approximately 120 times the area under the plasma concentration versus time curve (AUC)~~ for adults and children at the maximum recommended daily oral dose], or in a 92-week ~~carcinogenicity study in mice at~~ ——— ~~up to 100 mg/kg/day (estimated exposure was~~ **approximately 45 times the AUC for adults and children at the maximum recommended daily oral dose).**

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the *in vivo* mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg **(estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose).** No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg **(estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose).** Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg **(estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).**

Pregnancy
Pregnancy Category B:
No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day **(estimated exposure was approximately 100 times the AUC for adults at the maximum recommended daily oral dose)** and in rabbits at oral doses up to 300 mg/kg/day **(estimated exposure was approximately 110 times the AUC for adults at the maximum recommended daily oral dose).** Montelukast crosses the placenta ——— in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SINGULAIR should be used during pregnancy only if clearly needed.
Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to SINGULAIR while pregnant. Healthcare providers are encouraged to report any prentatal exposure to SINGULAIR by calling the Pregnancy Registry at (800) 986-8999.

Nursing Mothers
Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINGULAIR is given to a nursing mother.

OVERDOSAGE
No mortality occurred following single oral doses up to 5000 mg/kg in mice **(estimated exposure was approximately 340 times the AUC for adults and children at the maximum recommended daily oral dose)** and rats **(estimated exposure was approximately 230 times the AUC for adults and children at the maximum recommended daily oral dose).**

No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week without clinically important adverse experiences. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

RECOMMENDATIONS

1. The proposed labeling submitted by the sponsor is acceptable, with incorporation of the suggested revisions for the labeling sections entitled: Carcinogenesis, Mutagenesis, and Impairment of Fertility, Pregnancy Category and OVERDOSAGE as indicated above. These changes reflect the labeling revisions made during the consideration of Supplement 001.

/S/ 1/27/2000

Timothy J. McGovern, Ph.D., Pharmacologist

/S/ Jan 27, 2000

Original NDA 20-830
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