CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-830

CORRESPONDENCE

MEMORANDUM

TO: NDA 20-829/20-830 (montelukast sodium)

FROM: Peter Honig, MD
Medical Team Leader
Division of Pulmonary Drug Products (HFD-570)

(S) 5/19/97

RE: Proprietary Name for Montelukast

DATE: May 19, 1997

This memo is written in response to the Merck submission in which the sponsor requests that DPDP revisit the acceptability of the trademark name Singulair. The sponsor acknowledges that there does not appear to be a "sound-alike" problem with other currently marketed drugs. This is always the major concern for the Agency and is not a factor in this case. The major objections of the LNC focused around potential future changes in the dosing regimen which would make the name Singulair an unreliable proprietary name for dosing recommendations and the potential for the name to allow the sponsor to promote the drug as the only drug needed for asthma.

The sponsor responds by indicating that, for scientific as well as marketing reasons, the once-daily dosing regimen will not be modified. Due to its pharmacokinetic and receptor binding characteristics, it is highly unlikely that the drug will be used more often than once daily. Furthermore, for marketing purposes, a once-daily regimen is optimal for the company.

The sponsor responds to the potential promotional misuse of the name Singulair by indicating that Merck his an internal medical-legal review process that will ensure appropriate use of the trademark. The sponsor also states that the trademark review and promotional review are separate issues, and the trademark should not be rejected based upon speculation involving future, yet to be prepared, promotional material.

Reviewer recommendation: This response has been evaluated by the montelukast review team and, after consideration of the sponsor's response, there was no objection to the trademark Singulair. This has been discussed with Drs. Jenkins and Bilstad who concur.

cc:
NDA 20-829/20-830/Division file
HFD-570/MO/Honig/Kwong
HFD-570/Pharm/Williams
HFD-570/Chem/Leak/Poochiakian
HFD-570/PM/Kuzmik
HFD-530/Boring

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-830

FEB 20 1998

Merck Research Laboratories
Sumneytown Pike
P.O. Box 4
West Point, PA 19486

Attention: William G. Roberts, M.D.
Director, Regulatory Affairs

Dear Dr. Roberts:

Please refer to your new drug application (NDA), dated and received February 21, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Singulair (montelukast sodium) Chewable Tablets.

We also refer to your submissions dated March 18, April 11, May 1, June 13, 17, and 19, July 3, 10, and 31, September 5, 23, and 29, October 14, 16, and 29, November 7, 13, 14, 18, 21, 25, and 26, and December 4 and 11, 1997, and January 13, 20, 26, and 28, and February 2, 3, 5, 6, 9, 12, and 20, 1998. The user fee goal date is February 21, 1998.

This new drug application provides for the use of Singulair Chewable Tablets for the prophylaxis and chronic treatment of asthma in pediatric patients ages 6 to 14.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician labeling and patient package insert submitted on February 20, 1998, and mock-up carton and container labels submitted on November 25, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-830." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated February 2, 1998.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of the commitment in your annual report to this NDA. The status summary should include the number of patients entered in the study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to the Phase 4 commitment must be clearly designated "Phase 4 Commitment." The protocol for this study should be submitted within 3 months of the date of this letter and the study should be initiated within 6 months of the date of this letter.

We also strongly recommend that you pursue additional dose-ranging efficacy trials in pediatric patients to further evaluate the optimally effective pediatric dose and to validate your plans to use the pharmacokinetic dose extrapolation model for dose selection in the 2-5 year age group.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Pulmonary Drug Products and two copies of both the promotional material and the package insert directly to the following:

Food and Drug Administration
Division of Drug Marketing, Advertising,
and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Within 30 days of the date of this letter, please submit a labeling supplement revising the PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility and Pregnancy subsections, and OVERDOSAGE section so that the dosage comparison between humans and animals is based on plasma drug concentrations rather than body surface area.

If you have any questions, please contact Ms. Betty Kuzmik, Project Manager, at (301)827-1051.

Sincerely,

/S/

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: February 9, 1998

TO: NDA 20-829, NDA 20-83 /S/ 2/9/98

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products HFD-570

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 20-829, for Singulair (montelukast sodium) Tablets, and NDA 20-830, for Singulair (montelukast sodium) Chewable Tablets, were originally submitted by Merck Research Laboratories on February 21, 1997. NDA 20-829 seeks an indication in adolescents and adults and NDA 20-830 seeks an indication in children and young adolescents. The current user fee goal date for NDA 20-829 and NDA 20-830 is February 21. 1998.

Clinical

NDA 20-829:

The sponsor proposes that Singulair Tablets be indicated for chronic, maintenance treatment of asthma in patients 15 years of age and older. In support of this indication, the sponsor submitted several large, randomized, double-blind, placebo-controlled trials in patients with asthma, including patients not previously maintained on inhaled corticosteroids (ICS) and patients previously maintained on ICS. Please refer to the medical officer review prepared by Dr. Honig for a more detailed review of the studies submitted by the sponsor. Selected important trials which support the proposed indication and which are reflected in the draft labeling will be briefly discussed in this memorandum. Note that in the pivotal trials Singulair was dosed at 10-mg once-daily in the evening. The sponsor submitted the results of several Phase 2 dose-ranging studies, which supported a conclusion that doses above 10-mg once-daily did not provide any additional clinical benefit.

Study 31 and Study 20 were similarly designed 12-week clinical trials in patients with mild to moderate persistent asthma at baseline. The major difference in the two trials was the inclusion of a low-dose beclomethasone (400 mcg/day ex-valve from a non-US formulation which delivered 100 mcg/puff ex-valve, a spacer device was also used) active control arm in Study 20. In both studies the primary endpoints were FEV_1 assessed at each clinic visit and daytime asthma symptom scores recorded by patients in a diary. Numerous other secondary endpoints were also specified in the protocol. In Study 31, the mean percent change in FEV_1 averaged over the 12-week treatment period was 4.22% and 13.05% for placebo and montelukast, respectively. During the three-week, single-blind washout period, patients who remained on montelukast continued to demonstrate improvement in FEV_1, while patients

randomized from montelukast to placebo demonstrated a fall in mean FEV_1 toward the placebo values. In this trial, montelukast was also significantly better than placebo for daytime asthma symptom scores, rescue beta-agonist use, morning PEFR, and nocturnal asthma symptom score. In Study 20, the mean percent change in FEV_1 averaged over the 12-week treatment period was 1.07%, 7.49%, and 13.30% for placebo, montelukast, and beclomethasone, respectively. While montelukast was significantly more effective than placebo for FEV_1, daytime asthma symptom score, and most of the secondary endpoints, beclomethasone was consistently significantly more effective than montelukast on these same endpoints.

Study 31 and Study 20 clearly demonstrate that montelukast is more effective than placebo in patients with mild to moderate asthma; however, Study 20 strongly suggests that low-dose beclomethasone is more effective than montelukast for these patients groups.

Study 15 was a 4-week, randomized, double-blind, placebo-controlled trial in asthmatic patients with a documented history of aspirin sensitivity. The design of this trial and the pre-specified endpoints were very similar to those employed for Study 31 and Study 20. The mean percent change in FEV_1 averaged over the 4-week treatment period was -1.74% and 8.55% for placebo and montelukast, respectively. Montelukast was also significantly more effective than placebo for daytime asthma symptom scores and most other secondary endpoints. While this trial supports the effectiveness of montelukast in asthmatics with a documented history of aspirin sensitivity, cross-study comparisons of the treatment effect size for montelukast versus placebo indicate that montelukast is not uniquely more effective in this group than in the broader population of asthmatics. Importantly, this trial did not assess the response to aspirin in patients treated with montelukast.

Study 42 was a 12-week, randomized, placebo-controlled trial in patients with asthma and a documented clinically significant fall in FEV_1 in response to exercise. Exercise challenges were performed at baseline and periodically throughout the course of the 12-week trial to assess the impact of chronic montelukast therapy on the response to exercise. The exercise challenges were performed near the end of the dosing interval (i.e., at 20-24 hours after the preceding dose). Exercise challenges were not performed at any other time in the dosing interval. Over the course of the 12-week trial, montelukast was significantly more effective than placebo in decreasing the mean FEV_1 $AUC_{0\text{-}60\ min}$, mean maximum percent fall in FEV_1, and time to recovery to within 5% of pre-exercise baseline FEV_1. While these results suggest that chronic therapy with montelukast blunts the response to exercise in patients with documented exercise induced bronchospasm, careful analysis of the mean maximum percent fall in FEV_1 and a post-hoc categorical analysis of this endpoint call into question the clinical significance of these findings. The mean maximum percent fall in FEV_1 for the montelukast group at baseline was 38.3% and decreased to 22.26%, 20.33%, and 20.91% at weeks 4, 8, and 12, respectively. Thus, the mean maximum percent fall in FEV_1 remained above 20% (the traditional cutoff for defining a positive response to exercise), indicating that a significant number of the patients treated with montelukast continued to have a clinically significant decline in FEV_1 in response to exercise. A post-hoc, categorical analysis of the maximum percent fall in FEV_1 for individual patients revealed that 52% of montelukast patients had

>20% fall in FEV_1 while on therapy (versus 72% of placebo patients). Based on these results, and similar results for shorter-term crossover trials, I believe that montelukast should not be approved for a specific indication of exercise induced bronchospasm. Further, I believe that the categorical analysis of FEV_1 described above should be included in the labeling and that the labeling should clearly state that patients with EIB who are on montelukast therapy should continue to use their usual regimen of prophylactic beta-agonist prior to exercise (unless otherwise directed by their physician) and should continue to have a short-acting beta-agonist available for rescue use during exercise.

Study 46 employed a complex study design in which patients who were receiving various doses and formulations of ICS were enrolled into a lead-in period during which their ICS dose was tapered by protocol toward their lowest effective dose. The patients were then randomized to a 12-week, double-blind, placebo-controlled period. During the double-blind period, the patient's ICS doses were titrated based on protocol defined criteria with the primary endpoint being the last tolerated ICS dose as a percent change from baseline. It is worthwhile to note that patients entered this study on a wide variety of ICS formulations (both MDIs and DPIs), many of which are not available in the US. The study is also somewhat flawed by the fact that there was an implicit assumption that the nominal doses of ICS were equi-effective. These design flaws serve to limit the interpretation of the results of this trial to a qualitative rather than a quantitative level. Over the course of the double-blind period, the montelukast group demonstrated a 46.73% decrease in ICS requirement from baseline versus a decline of 30.27% for the placebo group. In perhaps a more clinically meaningful analysis, 40.2% of montelukast patients were able to be titrated completely off ICS and remained off ICS at the end of the 12 week treatment period versus 29.2% for placebo. This study supports a conclusion that addition of montelukast to patients already receiving ICS for treatment of asthma may allow the ICS dose to be tapered without significant loss of asthma control. It is not clear; however, whether the results of this study can be generalized to all patients receiving ICS or to patients receiving oral corticosteroids.

Study 29 also employed a complex study design to assess whether the combination of montelukast and beclomethasone provided added clinical benefit over beclomethasone or montelukast alone in patients previously maintained on low-dose ICS (beclomethasone 336 mcg/day). The results of this study demonstrated that the combination of montelukast and beclomethasone was significantly better than beclomethasone alone or placebo for FEV_1 averaged over the last ten weeks of the 16-week double-blind treatment period. Also notable from this study was the observation that beclomethasone alone was more effective than montelukast alone. This finding serves to validate the observations from the beclomethasone versus montelukast comparison noted above from study 20; i.e., the NDA contains two studies which demonstrate that low-dose beclomethasone is clinically superior to montelukast. This finding provides important data for clinicians as they determine where montelukast should fit into the treatment regimen for individual patients and, therefore, should be included in the labeling.

(Note: The sponsor had previously been informed by the Division that the active comparison

arm of Study 20 would not support any comparative claims for promotion or labeling since the beclomethasone active control arm in that study was a non-US formulation. This decision was based on the fact that the comparison would have little meaning to US prescribers since the comparator formulation was not available in the US and it was impossible to state how the beclomethasone formulation used in Study 20 compared to available US formulations. I now believe that it is appropriate to represent the active control arm of Study 20 in the US labeling for montelukast for two primary reasons; 1) the findings in Study 29, in which a US formulation of beclomethasone was used, provide confirmation of the findings of Study 20, and 2) it is important that these comparative findings be available to US clinicians as they incorporate montelukast into their treatment armamentarium for asthma.)

The safety profile of montelukast in patients 15 years of age and older was generally benign with adverse events occurring at a rate greater than for placebo primarily limited to non-serious gastrointestinal signs and symptoms. There was also a signal that montelukast may result in elevation of hepatic transaminases in a small percentage of patients. No cases of severe elevations or drug-induced hepatitis occurred in the NDA database and it appeared that the frequency of hepatic transaminase elevations decreased with time suggesting that any liver toxicity is not related to cumulative dose. There was no evidence in the NDA database for the type of eosinophilic vasculitis syndromes, including Churg Stauss Syndrome, which have been reported for zafirlukast, another leukotriene receptor antagonist. While this provides some comfort, it should be noted that the majority of cases reported in patients receiving zafirlukast have occurred in patients who were being tapered from oral corticosteroids; a patient group that was not studied in the montelukast NDA database.

NDA 20-830:

The sponsor proposes that Singulair Chewable Tablets be indicated for the chronic, maintenance treatment of asthma in patients 6 to 14 years of age. Please refer to the medical officer review prepared by Dr. Trontell and the Medical Team Leader Memorandum prepared by Dr. Honig for more complete details of the clinical program conducted by the sponsor in patients 6-14 years of age. The sponsor chose the proposed 5 mg once-daily dose for the chewable tablets in children based on pharmacokinetic comparisons to the plasma concentrations of montelukast demonstrated to be safe and effective in adults in clinical trials using a 10-mg once-daily dose. The sponsor then conducted Study 49, an 8-week, double-blind, randomized, placebo-controlled trial in patients with mild to moderate asthma 6-14 years of age to validate the efficacy and safety of the 5-mg once-daily dose. The results of Study 49 demonstrated that the mean change from baseline in FEV_1 averaged over the 8-week treatment period was 4.16% and 8.71% for placebo and montelukast, respectively ($p<0.001$). Montelukast was also numerically more effective than placebo on secondary endpoints such as rescue beta-agonist requirements, morning PEFR, daytime asthma symptom scores, and nocturnal asthma symptom scores.

A second clinical trial, Study 40, evaluated the efficacy of the 5-mg once-daily dose in patients 6-14 years of age with a documented history of exercise induced bronchospasm. In this

crossover study, montelukast was significantly more effective than placebo in decreasing the response to exercise as measured by FEV_1 $AUC_{0\text{-}60\ min}$ and by the mean maximum percent fall in FEV_1 post exercise. While the clinical significance of these findings are suspect for the same reasons described above for the adult EIB studies, these findings do support that the 5 mg once-daily dose is effective through the end of the dosing interval since the exercise challenges were performed at or near the end of the dosing interval (i.e., 20-24 hours after the preceding dose).

Post-hoc cross-study comparisons of the treatment effect size observed for montelukast in pediatric patients suggest that the effect size of the 5-mg dose may be smaller than that seen with the 10-mg dose in adults. This observation, combined with the fact that no dose-ranging trials were done in pediatric patients, raises the question of whether the 5 mg once-daily dose is the optimal dose for pediatric patients. While the 5-mg once-daily dose has been shown to be more effective than placebo, the sponsor should be urged to conduct Phase 4 dose-ranging trials in pediatric patients to better characterize the optimal dose in this age group.

The safety profile of montelukast pediatric patients was generally similar to that observed in adults.

There are no outstanding clinical issues and both NDAs are approvable from a clinical perspective once a few remaining issues related to representations of the clinical trial data in the package insert are agreed between the division and the sponsor.

Pre-clinical

The sponsor conducted an extensive battery of in vitro and animal studies designed to evaluate the pharmacologic and toxicologic profile of montelukast. Please refer to the pharmacology/toxicology review prepared by Dr. Williams and the Team Leader Memorandum prepared by Dr. Sun for more complete details of the results of these studies. Montelukast was not teratogenic in rats or rabbits, although impairment of fertility was observed in female rats. These findings support a Pregnancy Category B statement in the labeling. Montelukast was not genotoxic in a battery of in vitro and in vivo assays and was not carcinogenic in lifetime studies conducted in rats and mice.

There are no outstanding issues and both NDAs are approvable from a preclinical perspective with acceptable labeling.

CMC

Singulair Tablets are film coated and contain 10.4-mg montelukast sodium, equivalent to 10

mg of the free acid. Singulair Chewable Tablets contain 5.2-mg montelukast sodium, equivalent to 5 mg of the free acid. Please refer to the reviews prepared by Dr. Leak for a more detailed description of the CMC sections of the NDAs.

There are no outstanding issues and both NDAs are approvable from a CMC perspective with acceptable labeling.

Clinical Pharmacology and Biopharmaceutics

Montelukast is a selective cysteinyl leukotriene receptor antagonist. The sponsor submitted PK information for both the 10-mg film-coated tablet and the 5-mg chewable tablet. For a more detailed discussion of the clinical pharmacology and biopharmaceutics data submitted to these NDAs please refer to the review prepared by Dr. Chen. Summary PK parameters for the 10 mg tablet include a T_{max} of 3-4 hours, mean oral bioavailability of 64%, linear pharmacokinetics up to a dose of 50 mg, and a mean plasma half-life of 2.7-5.5 hours. Summary PK parameters for the 5-mg chewable tablet include a T_{max} of 2-2.5 hours, mean oral bioavailability of 73% in the fasted state, and mean oral bioavailability of 63% in the fed state. Montelukast is extensively metabolized by the liver by cytochrome P450 3A4 and 2C9 and the primary route of elimination of the parent compound and its metabolites is in the bile. The sponsor submitted data to show that the pharmacokinetic profile of the 5 mg chewable tablet in children 6-14 years of age was similar to that observed for the 10-mg tablet in adolescents and adults 15 years of age and older. As noted above, this pharmacokinetic comparison was the basis for the sponsor's dose selection for the 5-mg tablet in children 6-14 years of age; no dose ranging trials were conducted. The sponsor conducted a battery of drug interaction studies and found no significant effect of montelukast on the PK of warfarin, theophylline, digoxin, terfenadine, fexofenadine, oral contraceptives, prednisone, or Phenobarbital, a hepatic enzyme inducer, caused a 40% decrease in montelukast AUC.

There are no outstanding clinical pharmacology and biopharmaceutics issues and the application is approvable with appropriate labeling.

Data Verification

The Division of Scientific Investigations performed audits of four clinical sites involved in the pivotal clinical trials for these NDAs (3 sites for NDA 20-829, 1 site for NDA 20-830). Two of the three sites audited for NDA 20-829 received an NAI rating by the DSI reviewer, the third site received a VAI rating. The minor discrepancies noted at the VAI rated site were carefully reviewed and analyzed by Merck and Dr. Honig, including a full audit of all the sites for that study conducted by Merck and a reanalysis of the study results based on the revised database. There were no significant differences noted between the two analyses. Further, the DSI auditor was provided with clinical data from the NDA by the medical reviewer that was compared to source data at the three audited sites. There were no discrepancies noted.

The one clinical site audited by DSI for NDA 20-830 received an NAI rating. The audit report was reviewed by Dr. Trontell who agreed that the deficiencies noted by the inspector were not of concern with regard to database integrity.

Based on the results of the DSI audits, and based on the limited auditing of the NDA performed by the two medial reviewers, there are no reasons to suspect any serious data integrity problems with the NDA databases.

Labeling

The trademark "Singulair" was reviewed by the Labeling and Nomenclature Committee and found to be acceptable. The trademark is also acceptable to the division. The package insert, carton, and container labeling are nearing completion. There are a few outstanding issues related to the representation of some of the clinical trial efficacy results that remain to be agreed between the agency and the sponsor. Otherwise the labeling had been reviewed by the various disciplines and has been found to accurately reflect the data submitted to the NDAs.

Conclusion

There are a few remaining labeling issues that need to be agreed to between the sponsor and the agency. Otherwise there are no outstanding issues and the sponsor should receive an APPROVAL letter for both NDAs. The sponsor will be reminded in the approval letter for NDA 20-830 of their commitment

The sponsor will also be strongly encouraged in the same action letter

cc:
NDA 20-829
NDA 20-830
HFD-570 Division Files
HFD-570/Jenkins
HFD-570/Kuzmik
HFD-570/Honig

APPEARS THIS WAY
ON ORIGINAL