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MEMORANDUM

Date: **6/16/08**

From: **Joel Schiffenbauer, M.D.**
Deputy Director, DNCE

Subject: **NDA 21-952; Claritin® liqui-gel**

Sponsor: **Schering-Plough**

Background:

Claritin first became available as a nonprescription drug in the US in 2002. The sponsor is seeking OTC approval to market Claritin® Liqui-gel. These are tablets containing 10 mg of loratadine to be dosed once a day. The indication is for the temporary relief of symptoms of runny nose, itchy eyes, sneezing and itching of the nose or throat due to hay fever or to upper respiratory allergies in adults and children 6 years of age and older.

Currently Claritin 10 mg tablets and Claritin 10 mg RediTabs orally disintegrating tablets are approved OTC for once a day dosing of adults and children for the same indication. Recently Claritin RediTabs 12 hour tablets containing 5 mg loratadine was also approved.

This NDA was originally submitted in 2006 and received an approvable letter on 1/12/2007. At that time a review of the clinical pharmacology data demonstrated a food effect. The administration of Claritin® Liqui-Gels™ Capsules (loratadine 10 mg) with food increased the loratadine Cmax by 53%, AUC0-t by 121%, and AUC0-∞ by 118%. Of additional note, there was no food effect for the active metabolite desloratadine. However, a reference product such as Claritin tablets, was not included in the study. In previous studies of loratadine tablets, the food effect was of the order of 30-40% difference. Based on these results and results from previous studies demonstrating the occurrence of drowsiness at doses exceeding 20 mg, the applicant was requested to add a bulleted statement to the label stating “take on an empty stomach. Taking with food may

cause drowsiness." The applicant chose to not include this statement, and rather, perform an additional PK study to compare the proposed product with an approved 10 mg Claritin tablet under fed conditions.

The present submission therefore, is a complete response to the approvable letter that was issued 1/12/2007. Dr. Lolita Lopez reviewed the safety update and Dr. Sandra Suarez reviewed the PK study. Marina Chang reviewed the labeling.

Toxicology:

No new toxicology data was provided in the original NDA. Reference was made to the information in NDA 19-658 (original NDA) for the active ingredient loratadine. The levels of all excipients in the liqui-gel formulation are considered acceptable by Dr. Sancilio.

Clinical Pharmacology:

Dr. Suarez the clinical biopharmacology reviewer notes that the Claritin LiquiGel capsule was not bioequivalent to the Claritin 10 mg tablet in the presence of food since the loratadine Cmax 90% CI (94.4-143.8) did not meet BE acceptance criteria. In the presence of a high fat meal, the mean Cmax (geometric mean) of loratadine was about 16% greater for the Liqui-Gel formulation compared to the tablet formulation (see table in appendix).

She also comments that although the Claritin tablet and liquiGel formulations for claritin were not bioequivalent, the 16% higher loratadine Cmax observed for the liquiGel formulation in the presence of food compared to that for the Claritin tablet in the presence of food may not be clinically relevant, and provides the following reasons:

1) There were two subjects taking Claritin Tablet with food whose Cmax values were higher than the highest value of Cmax observed for the subject taking the liquiGel formulation with food.
2) Loratadine is classified as a highly variable drug. For this kind of drug, bioequivalence is usually assessed using a replicated design. This suggests that if a replicate design would have been used for this drug, the tablet and the liquiGel formulations may have been bioequivalent in the presence of food.
3) Based on the package insert for the prescribed Claritin Tablets, drowsiness is observed after doses of Claritin tablets of 20 mg and higher.

Therefore, Dr. Suarez believes that no additional directions (such as "take on an empty stomach. Taking with food may cause drowsiness") are needed to advise consumers of the safe and effective use of this product. I agree with her recommendations. Even those

few individuals who may have a Cmax at the extreme end of the range (143%) would still be below the 20 mg level at which drowsiness appears to occur based on the package insert.

Chemistry:

There was no new chemistry information submitted with this complete response. The reader is referred to Dr. Holbert's review of the original submission. There are no chemistry issues noted.

Efficacy:

In this 505(b)(1) application, there were no efficacy trials conducted, and reference is made by the sponsor to their previously submitted NDA 19-658 (Claritin® 10 mg tablets Rx-to-OTC switch application) for clinical and pre-clinical information. Efficacy of this product is extrapolated from PK data. See also comments under the clinical pharmacology section of this memorandum.

Safety Update:

Please see the safety discussion for submission of the original NDA 21-952. The applicant relies on the safety information being referenced from their previously submitted NDA 19-658 (Claritin® tablets 10 mg Rx-to-OTC switch application) and the safety data submitted to the recently approved NDA 21-891 (Claritin® chewable tablets 5 mg).

Dr. Lopez notes that the combination of postmarketing data, previous clinical trials, literature review and adverse events information from the bioavailability studies conducted by the applicant do not raise any new safety concern. No new safety issues were identified that would preclude approval of this formulation. I agree with Dr. Lopez's recommendation.

Pediatrics:

The applicant is requesting a waiver of studies for children less than 6 years of age and I agree that this request should be granted. Loratadine is already labeled for use in children two years and older. Furthermore, there are other currently marketed loratadine formulations that have been studies and are appropriate for this age group such as syrup. Additional studies using the proposed capsule formulation if performed would not provide information that would support a meaningful therapeutic benefit over the existing loratadine formulations.

This NDA was discussed at a PERC meeting on May 28, 2008, and it was agreed that studies could be waived for children less than 2 years of age and that the product was adequately labeled for children 2 and above. The label states "ask a doctor" for children less than 6 years of age, and this was felt to be appropriate because it allows a physician to direct how an age appropriate formulation will be used, if needed.

Labeling:

There were no additional labeling recommendations in the original approvable letter dated 1/12/2007, except for the food effect issue, which is the focus of this complete response. Based on the new data provided, Marina Chang, the labeling reviewer recommends approval and has no additional labeling recommendations except for the removal of the flag "new" after 6 months. I agree with her recommendation.

Conclusions:

The sponsor is seeking OTC approval to market Claritin liqui-gel. These are tablets containing 10 mg of loratadine to be dosed once a day. The indication is for the temporary relief of symptoms of runny nose, itchy eyes, sneezing and itching of the nose or throat due to hay fever or to upper respiratory allergies in adults and children 6 years of age and older.

No efficacy studies were submitted. The applicant is relying on PK data to address efficacy. The results of the new PK study demonstrate bioequivalence for the liqui-gel and tablet formulations for AUC and Cmax for desloratadine and for AUC for loratadine, but not for Cmax. In the presence of high fat meal, the mean Cmax (geometric mean) of loratadine was about 16% greater for the Liqui-Gel formulation compared to the tablet formulation The OCP reviewer recommends approval without any additional directions or warnings and provided several reasons for her conclusion (see above). I agree with her assessment.

Recommendations:

It is recommended that this NDA be approved

Appendix

Table: Geometric means, point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of loratadine and desloratadine following single administration of the treatments

Parameter	Test	Reference	% ratio	90% CI
	Loratadine			
AUCt	10421	10318.84	100.99	90.11, 113.19
AUCinf	11102.52	11097.47	100.05	89.3, 112.08
Cmax	3338.16	2864.8	116.52	94.42, 143.8
	Desloratadine			
AUCt	43569.34	44347.17	98.25	(93.35, 103.4)
AUCinf	44593.38	45408.58	98.20	(93.37, 103.29)
Cmax	3946.90	3697.23	106.75	(95.89, 118.85)

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/s/

Joel Schiffenbauer
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MEDICAL OFFICER