CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-952

SUMMARY REVIEW

CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Nonprescription Clinical Evaluation
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
301.796.2280

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
6/16/2008 07:00:58 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Nonprescription Clinical Evaluation
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
301.796.2280

MEMORANDUM

Date: **1/15/07**

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 loratdine was also approved.

Loratadine is marketed OTC in combination with pseudoephedrine as Claritin D 12 and Claritin –D 24 for the treatment of allergic rhinitis and nasal congestion. Claritin-D 12 contains 5 mg loratidine plus 120 mg of pseudoephedrine (PSE) and Claritin-D 24 contains 10 mg loratidine plus 240 mg PSE.

For this submission, Dr. S. Kim has reviewed the clinical pharmacology; Dr. L Lopez has reviewed the clinical safety; Dr. G. Holbert has reviewed the chemistry, and Dr. L. Sancilio has reviewed the toxicology data.

Toxicology:

No new toxicology data was provided in this 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. Kim in the Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology studies submitted to NDA 21-952, and overall found that the data from Study CL2004-02 for Claritin® Liqui-Gels™ capsules did not meet bioequivalence (BE) criteria for loratadine Cmax (90% CI = 0.7875-0.9996) but met the BE criteria for loratadine AUC as well for the Cmax and AUC of its active metabolite, desloratadine.

The bioequivalence study CL2004-02 was an open-label, single dose, randomized, crossover study in healthy volunteers under fasting conditions with a 14-day wash-out period. A total of 48 subjects were planned; 50 subjects (24 males and 26 females) were enrolled, treated, and analyzed for safety; 48 subjects completed the study and were included in the analysis of bioequivalence.The following table presents the Cmax and AUC data for loratadine and desloratadine. As can be seen, the capsule and tablet are bioequivalent for all parameters except for Cmax.

PK data for Claritin liqui-gel vs tablet (reference); fasting

Analyte Parameter	1 × 10 mg Capsule Test	1 × 10 mg Tablet Reference	Ratio (Test/Reference)	90% CI Lower	90% CI Upper
Loratadine					
AUC	6.9581	7.6683	0.9074	0.8135	1.0121
AUC_T	6.5545	7.1760	0.9134	0.8214	1.0156
C_{max}	2.4688	2.7825	0.8873	0.7875	0.9996
Desloratadine					
AUC	38.9407	42.0624	0.9258	0.8668	0.9888
AUC_T	37.6661	40.7446	0.9244	0.8647	0.9883
C_{max}	2.9756	3.2874	0.9051	0.8375	0.9783

A re-analysis was performed by the applicant after excluding subjects based on the acceptance criteria recommended by DSI and the results are consistent with the original analysis. The results of the study are not altered to any significant extent (data not shown here; please see the clinical pharmacology review for additional tables).

The next table presents the results of the food effect study. As can be seen from the results in this table, 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%. There was no significant change in desloratadine PK. However, a reference product such as Claritin tablets, was not included in the study and therefore, we do not know how the reference would have performed in this study. In previous studies of loratadine tablets, the food effect is of the order of 30-40% difference.

Food effect study

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data (N = 11)				
Parameter	Fed	Fasting	% Ratio	90% CI
Loratadine				
AUC_{0-t} (ng-hr/mL)	13.45	6.08	221.13	(191.02, 255.99)
$AUC_{0-\infty}$ (ng-hr/mL)	14.13	6.48	218.03	(187.84, 253.07)
Cmax (ng/mL)	3.91	2.55	153.06	(113.45, 206.5)
Desloratadine				
AUC_{0-t} (ng-hr/mL)	38.10	35.99	105.87	(95.98, 116.79)
$AUC_{0-\infty}$ (ng-hr/mL)	39.66	37.33	106.24	(96.3, 117.2)
Cmax (ng/mL)	3.03	3.19	94.81	(78.69, 114.24)

Overall, Dr. Kim recommends approval. She provides the following scientific rational for her recommendation (the following is taken directly from Dr. Kim's review):

1) Desloratadine is two to four times more potent than parent loratadine as shown by in vitro and preclinical animal antihistamine activity studies. Additionally, the systemic exposure to the active metabolite (AUC) is about four times that of the parent drug although both have similar Cmax.

2) Desloratadine concentrations from 5 mg Clarinex are similar to 10 mg Claritin tablet (NDA 21-165 for Clarinex Tablets – Review by Young Moon Choi, Ph.D dated 11/21/00). The test formulation is equivalent to the reference formulation in terms of the active metabolite but marginally failed equivalence criteria with respect of the Cmax of the parent drug.

3) There has been a few occasions when Claritin or Clarinex (desloratadine) formulations have failed BE and the sponsor had conducted clinical trials; those trials have been successful in beating the placebo and the NDAs were approved (for example NDA 20-704 for Claritin RediTabs and NDA 21-605 for Clarinex D-24). These examples demonstrate that even on previous occasions failed BE formulations have proven to be effective in clinical trials.

4) In one case of failed BE submitted as a 505(b) application (NDA 21-734 for Loratadine Suspension, clin pharm review by Shinja Kim, Ph. D dated 10/22/04), when sponsor repeated the BE study with more number of subjects (N increased from 43 to 70) it passed BE (NDA 21-734, clin pharm review dated 8/15/05). This may be due to high variability in the PK of loratadine.

5) Phase 2 study submitted to NDA 19-670 (Claritin-D 12 Hour) showed that 5 mg Claritin was as efficacious/superior compared to placebo and comparable to 10 mg Claritin tablet (per Sponsor).

6) The General BA/BE Guidance is currently being considered a revision with a proposal that BE should be based on relevant active moiety, which in this case will be desloratadine.

These comments address the issue of differences in the Cmax. However, they do not address the issue of food effect. Nevertheless, the food effect is striking and may lead to individuals with significantly higher serum levels of drug. Add to this the potential for drug-drug interactions that may also lead to further increases in the levels of drug[1], and there exists the potential for an increase in adverse events with this formulation, particularly drowsiness. Based on these concerns, the applicant should be asked to provide additional data supporting the safety of the drug at the levels that may be reached with food. Alternatively the applicant may repeat the food effect study with the reference product included, to assess the true differences in PK parameters.

The OCP reviewer recommends that the product be labeled to take without food. However, the label should also reflect the fact that taking the product with food may lead to additional safety issues (see discussion below).

Chemistry:

Claritin® 10 mg LiquiGels™ Capsules are clear, blue liquid-filled soft gelatin capsules printed on one side with "C10" in white ink. Each capsule contains 10 mg of loratadine and the inactive ingredients caprylic/capric glycerides, FD&C blue #1, gelatin, glycerin, pharmaceutical ink, polysorbate 80, povidone, purified water and sorbitol.

Dr. Holbert recommends approval based on the following: Adequate controls for raw materials are in place. Manufacturing processes are robust and adequately controlled. Specifications are adequate to ensure the identity, strength, quality, purity and potency of the drug product. The container/closure system is adequate to protect the drug product. The product is stable over the proposed shelf life (24 months) when stored as labeled. Labeling is acceptable. Facilities inspections are complete and acceptable.

[1] According to the loratadine (prescription) label, co-administration of Claritin and cimetidine for 10 days can lead to an increase in AUC 0-24 hours of 103% for loratadine and 6% desloratadine; co-use with erythromycin, an increase of 40% loratadine and 46% desloratadine; co-use with ketocaonazole, an increase of 307% loratadine and 73% desloratadine.

I agree with this recommendation.

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 from the single-dose relative bioavailability study (CL2004-02) assessing the proposed Claritin® liqui-gel 10 mg capsule and the currently marketed Claritin® tablet 10 mg (RLD). See comments under the clinical pharmacology section of this memorandum.

Safety Update:

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). In addition, the following were submitted to this application:

1) Safety data from bioequivalence study CL2004-02
2) Post Marketing Safety Surveillance (adverse event) data from Schering-Plough internal adverse event database from October 1, 2005 to June 28, 2006
3) World Health Organization (WHO) database from October 1, 2005 to February 2, 2006
4) Toxic Exposure Surveillance System (TESS) database from the American Association of Poison Control Centers (AAPCC) from December 1, 2005 to May 31, 2006
5) Worldwide human and pre-clinical peer-reviewed literature October 1, 2005 to July 14, 2006

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.

However, the clinical significance of the magnitude of food effect is unknown. There remains the possibility that due to the increased bioavailability of this drug, there might be an increase in adverse events. Furthermore, drug-drug interactions could lead to even further increases in systemic levels of the drug. Therefore, consumers should be informed that drowsiness may occur when this formulation is taken with food.

A t-con was held with SPHCP on November 30, 2006 in regards to the food effects and labeling. During the t-con the Division expressed the need for labeling to address the food effect and the potential for AEs, including unexpected drowsiness. It was felt that adding the statement "take on an empty stomach," as suggested by the applicant, was not sufficient to convey the potential safety concerns when taken with food. The Division felt that this statement was not informative enough to the consumer because unexpected drowsiness could be a safety issue.

The applicant may be able to remove the food effect information from the label if they can present sufficient data to either show that the food effect for this formulation is similar to the food effect for other approved Claritin formulations, or that the systemic levels that may be reached when taken with food, do not adversely affect the safety profile of their product.

Pediatrics:

The applicant is requesting a waiver 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 are appropriate for this age group such as syrup. Additional studies using the proposed capsule formulation will not offer meaningful therapeutic benefit over the existing loratadine formulations.

Labeling:

There is one labeling issue that needs to be resolved before approval. The main labeling issue concerns the appropriate information to include in the label in regards to the food effect and potential for adverse events associated with the higher systemic levels achieved should this product be taken with food. See further discussion under the "conclusion" section, below.

DMETS has no objections to the use of the "Liqui-gels™" descriptor in conjunction with the Claritin® proprietary name. In addition DMETS had the following comments on the carton labeling: *As a report from the Drug Quality Reporting System (DQRS) database indicated that the verbiage on the "Children's Claritin" packaging reading "up to 24 days of relief Children's Claritin 24 hours" was misleading as to how long the medication would last. DMETS recommends the sponsor remove the "10 capsules for 10 days of relief" to eliminate the potential for overdose from the patient/consumer taking 10 tablets at once to yield 10 days of relief.* The Division has allowed the statement "10 capsules for 10 days of relief" as we do not anticipate that consumers will use 10 tablets at one time, and the directions clearly state to take one tablet a day.

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 single 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. The OCP reviewer recommends approval. The arguments for approval are presented by the OCP reviewer and reproduced in this review (see section above on Clinical Pharmacology). I believe the main argument in favor of approval is as follows: desloratadine is two to four times more potent than parent loratadine as shown by in vitro and preclinical animal antihistamine activity studies; additionally, the systemic exposure to the active metabolite (AUC) is about four times that of the parent drug although both have similar Cmax. Therefore, the small difference in the 90% CI of the Cmax is unlikely to affect the overall efficacy of this product to any significant degree. Additional arguments for approval are previously presented.

However, the issue regarding the food effect remains problematic. The OCP reviewer recommends that the product be labeled to take without food. However, this does not fully inform the consumer, who will not understand the potential consequences of taking this product with food. Furthermore, the effects of food may be compounded by the concomitant administration of other medications some of which may also be OTC drugs (such as cimetidine).

Therefore, the label should reflect the fact that taking the product with food may lead to additional safety concerns such as drowsiness. While the safety margin for this product appears to be wide, and further, that the safety concerns are likely relatively limited (for example, drowsiness), nevertheless, the applicant should include this information in the label.

The applicant may be able to remove the food effect information from the label if they can present sufficient data to either show that the food effect for this formulation is similar to the food effect for other approved Claritin formulations, or that the systemic levels that may be reached when taken with food, do not adversely affect the safety profile of their product.

At the present time, the Division has not been able to come to agreement with the applicant on appropriate language for the label to address the food effect concerns. Therefore, I will recommend that this NDA be approvable.

Recommendations:

It is recommended that this NDA be approvable.

For approval the applicant should be requested to add information about the food effect and its potential consequences such as drowsiness, to the label.

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/s/

Joel Schiffenbauer
1/12/2007 06:33:18 AM
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