CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-658/S-018
19-670/S-018
20-470/S-016
20-641/S-009
20-704/S-008

MEDICAL REVIEW

MEDICAL TEAMLEADER REVIEW
Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:	NDA 19-658, 20-704, 20-641, 19-670, 20-470	**APPLICATION TYPE:**	NDA supplements for OTC switch
SPONSOR:	Schering-Plough Pharmaceuticals	**PROPRIETARY NAME:**	Claritin tablets, RediTabs, syrup, Claritin D 12 Hour, Claritin D 24 Hour
INDICATIONS:	Hay fever, Hives	**USAN Name:**	Loratadine
CATEGORY OF DRUG:	Antihistamine	**ROUTE :**	Oral
MEDICAL REVIEWER:	Purucker	**REVIEW DATE:**	22 November 2002

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document/CDER stamp date	Document ID #:	Submission type/Comments:
25 January 2002/	N19-658 SE6-018, 020	Claritin tablets: hay fever, hives
28 January 2002	N20-704 SE6-008, 009	Claritin RediTabs: hay fever, hives
	N20-641 SE6-009, 011	Claritin Syrup: hay fever, hives
	N19-670 SE6-018	Claritin D 12 Hour, hay fever
	N20-470 SE6-016	Claritin D 24 Hour, hay fever

Overview of Application/Review: On 25 January 2002, Schering-Plough submitted five supplements in support of a switch in marketing status for its Claritin® line of products from prescription-only to OTC. The applications proposed to switch both approved prescription indications, seasonal allergic rhinitis and chronic idiopathic urticaria. While SAR (hay fever) is considered an OTC indication, CIU is not. The safety of loratadine to treat hay fever was fully supported at a joint NDAC-PADAC held 22 May 2001. A related Advisory Committee meeting held 22 April 2002 concluded that the use of loratadine for OTC treatment of urticaria was reasonable. The Committee identified "hives" as the appropriate OTC indication, defined it broadly as acute or chronic urticaria, and recommended the OTC product should have clearly worded instructions for consumer use. OTC dosages should be identical to prescription-only.

With regard to the hay fever indication, the applicant has provided sufficient primary (NDA) and secondary evidence (cross-referenced from several sources) to support the safety of loratadine in the OTC setting. Labeling specific to the hay fever indication for the five Claritin® products was found to be adequate and in compliance with 21 CFR 201.66, after the incorporation of negotiated revisions into the sponsor's proposed OTC label. In contrast, product labeling provided for the hives indication for the three loratadine-only products was found to be unacceptable and potentially misleading. A concurrently submitted label comprehension study was also considered flawed and not supportive of the proposed label.

Although the preponderance of evidence is supportive of loratadine as safe for use in the OTC setting, several issues remain. While cardiac conduction abnormalities have been a concern for antihistamines as a class, this issue has largely been resolved for loratadine. Two potential safety concerns have been identified, and will be further characterized in the post-approval setting. First, there is a relative paucity of safety data on the use of loratadine for children ≤ 5 years. Second, Swedish regulatory authorities have reported a relationship between loratadine use in early pregnancy and the occurrence of hypospadias, an observation not found in US databases. The applicant has agreed to address both of these issues by a post-marketing agreement to provide periodic information to the Agency for 3 years. Adverse events specific to the ≤ 5 year old age group will be separately identified and submitted. Periodic tracking, tabulation, and analysis of hypospadias reported in association with loratadine will likewise be submitted.

Outstanding Issues: The data and proposed labeling do not support approval of the hives indication at this time.

Recommended Regulatory Action: Efficacy Supplements: Hay fever ___X__ Approval Hives _X___ Approvable

Signed: Medical Team Leader: _____ Date: _____

Division Director: Date:

1. Overview

On 25 January 2002, Schering-Plough submitted five supplements in support of a switch in marketing status for its Claritin® line of products from prescription-only to OTC. The applicant proposed to carry over the same approved prescription doses to the OTC setting. The proposed age range also appeared to be identical, although for one product, this remains less clear (Claritin Syrup, see "4" below).

The safety of an OTC switch of the antihistamine loratadine for treatment of allergic rhinitis was previously discussed at a joint NDAC-PADAC held 22 May 2001, and overwhelmingly supported by the Committee. Although initially opposed to such a switch, Schering-Plough clearly changed their position over the ensuing months and now fully endorse it. The applicant has chosen to take the process a step further, by proposing to switch both approved prescription indications, SAR (seasonal allergic rhinitis), for which the OTC counterpart is "hay fever" and CIU (chronic idiopathic urticaria), which has no OTC counterpart. If successful, this would leave no prescription-only indication and hence the entire Claritin® line of products would become OTC.

As noted above, although allergic rhinitis/hay fever is recognized as an OTC indication, neither CIU nor "urticaria" has been considered suitable for this status. In part to address this issue, an Advisory Committee comprised of members of the NDAC, PADAC, and Dermatology Advisory Committees was convened 22 April 2002. The joint Committee reasoned that urticaria could fulfill criteria for an OTC indication because the condition is symptomatic (i.e. pruritus) and is likely to be recognizable by a consumer, particularly one who had received the diagnosis previously. Evidence was presented that OTC antihistamines have been used by consumers to self-treat urticaria without the direct intervention of a learned intermediary. Scientific evidence was presented that cellular mediators, particularly histamine, play a pivotal role in the pathophysiology of urticaria. Based on these data, the joint Committee recommended that urticaria be considered for an OTC indication and that "hives" be adopted as the OTC term encompassing both the acute and chronic conditions. Claritin was considered a reasonable candidate for this indication because of NDA data to support the indication of CIU. However, the Committee also recommended that the content and wording of the OTC label be carefully considered, given the novelty of the indication. It was felt that the consumer ought to be educated about the disease, instructed in the proper use of the product, and given the appropriate warnings in the label regarding the dangers of antihistamine monotherapy as treatment for anaphylaxis, a related condition.

In the weeks following the Advisory Committee meeting, both for administrative purposes and to take into consideration the Committee's remarks, the Division "split" the three loratadine-only supplements into six separate applications, three for "hay fever" and three for "hives." The two combination products, Claritin-D12 and Claritin–D24, carry the SAR (hay fever) indication alone, and each remained as a single supplement.

2. Contents of Application

The application was submitted entirely in paper copy. The applicant has provided data from the original NDA reviews of the five products, reference to the NDA for the active

metabolite of loratadine, desloratadine (Clarinex®, NDA 21-165), proposed labeling for the "hay fever" and the "hives" indications, and the report of the label comprehension study conducted for the hives indication. The NDA reviews cited include both the seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU) indications. Also submitted are articles from the peer-reviewed medical literature, testimonials from sponsor-identified experts in the field of Allergy (particularly urticaria), publicly available information from prior advisory committees (including May 2001 and April 2002), and adverse event reports from several post-marketing databases.

3. Safety of Loratadine in the OTC setting, SAR/Hay Fever Indication

Given that hay fever is an accepted OTC indication, the efficacy of loratadine in an OTC setting at doses supported by the original NDA's is not in dispute. The safety of loratadine in the OTC setting is supported by an Agency document authored by the Antihistamine OTC Working Group and presented at the joint NDAC-PADAC of 22 May 2001. Most of the sources utilized for the Agency document have been re-submitted by the applicant, and in fact, the document itself was cited in support of the safety of loratadine for OTC use. The literature review adds little new information. The AE database has been updated to include events reported subsequent to the May 2001 meeting. In general, the applicant provides a coherent and convincing argument for OTC loratadine for the allergic rhinitis indication.

However, there are three well-known safety concerns with antihistamines as a class, and loratadine in particular, which deserve special discussion. In general, these safety concerns have been adequately addressed, and will be summarized below.

Impact on Cardiac Conduction

Several antihistamines have been shown to prolong the QT_c, leading to the potentially lethal arrhythmia torsades de pointes. Terfenadine (Seldane®) and astemizole (Hismanil®) are examples of drugs producing this effect and were withdrawn from the US market for this reason. With regard to loratadine, *in vitro* studies have failed to provide evidence of I_{kr} interaction, and clinical PK/PD and drug interaction studies fail to demonstrate prolongation of the QT_c. A widely-quoted paper[1] that appeared to support the potential of loratadine to cause I_{kr} blockade must be read with some skepticism. Serious methodological flaws, including the post-hoc nature of the analysis, have been publicly disclosed by one of the senior authors on the paper[2]. For this reason, the totality of evidence supports the safety of loratadine in cardiac conduction.

Hypospadias/Teratogenicity Potential

A cluster of 15 loratadine-associated cases of hypospadias were reported to the Agency by the Swedish regulatory authorities in May 2002. This amounted to an elevated risk of 2.5 – 3.5 in the exposed women. The signal appeared to be unique to the Swedish pregnancy and birth registry because it had not been observed in data from the US or from other countries with similar adverse event reporting systems in use.

The report from the Swedish authorities has been reviewed by the applicant and by experts within and outside of the Agency. Questions raised include the following: 1)The inclusion of subjects whose mothers were exposed before pregnancy or at periods of gestation incompatible with the timing of development of male genitalia. 2) Selection of

a control group of women who had used antihistamines other than loratadine, because this group paradoxically showed a lower incidence of hypospadias than all parturient women. 3) The absolute numbers of cases of hypospadias was very small, and misclassification of only a few of these cases could drastically change the estimated risk ratio. 4) The hypospadias reported in Sweden in association with loratadine was not different from the sporadic form, characterized by the occurrence of the abnormal urethral opening at a relatively distal site on the penis. Increased severity of the malformation, such as a more proximal location of the urethral opening, was considered more supportive of a true teratogenic effect. 5) A pre-clinical study of pregnant female rats conducted by the applicant and reviewed by the Division failed to support loratadine as causal in hypospadias, given that the anal-urethral distance was not abnormally short. There was also no evidence of an anti-androgen effect of loratadine. Nevertheless, this same preclinical study did show other detrimental effects on the pups, and it was recommended by the Division pharm-tox group that loratadine's Pregnancy Category be changed from a ——— "C" rating.

While further surveillance of the occurrence of hypospadias is planned (see below), the evidence does not support this concern as an approvability issue for OTC loratadine. At this time, the Agency is also unconvinced that hypospadias is a labeling issue for prescription-only loratadine for the US population.

"Slow Metabolizers" and Pediatric Approval

A third issue is the significance of "slow metabolizers" of desloratadine, the active metabolite of the parent drug. This issue has been covered exhaustively in prior reviews, particularly for the Clarinex (desloratadine) NDA. Based on data from Poison Control and related databases, it appears that loratadine taken in overdose does not lead to mortality unless it is taken concomitantly with other potentially lethal agents, and the lethality does not appear to be related to the loratadine.

The relevance of this issue to the present application is a consequence of the applicant's proposal to extend the OTC age range for Claritin syrup down to 2 years. Data submitted by the applicant in response to the Agency's Written Request (WR) for pediatric studies included a total of four separate studies, two for children age 2 – 5 years and two for infants age 6 months to < 2 years. The first of each pair of studies was for PK and dose-finding, the second was intended as a safety study. These studies were submitted, and exclusivity was granted in July 2000.

In addition to the children studied to fulfill the terms of the WR, there were also data available from earlier studies conducted during the Claritin drug development program. When these children were included in the applicant's calculation of the overall pediatric exposure, there were 127 children age 2 – 5 years who received loratadine for a duration ranging from 1 day to 15 days at a dose of 5 mg per day, or one-half the adult/adolescent/older child dose. With regard to the WR, children exposed during the "safety study" appeared to tolerate loratadine with few reported AE's. The second study for this age group was conducted for PK information, and failed to show elevations in mean loratadine or desloratadine levels.

The second of the two pairs of trials conducted under the WR was for children age 6

months to < 2 years. A dose of 2.5 mg syrup per day was administered. The PK study showed elevated loratadine and desloratadine levels, particularly among the younger children (< 1 year). This finding is of concern, given that the dosage form makes it likely that Claritin syrup will be administered to children younger than 2 years of age in an OTC setting. Although overdose data from adult and older children is reassuring, it is important to consider that extrapolation of such data to very young infants may be scientifically perilous, given the variable maturity of infants' hepatic enzymes and other drug metabolizing systems.

If Claritin syrup is to be made OTC for children down to the age of 2 years, it will be important that safety data concerning the use of this product in this very young population be studied. The applicant should collect and submit all AE's for children age 5 years and younger, including children < 2 years, to the Agency on a quarterly basis for at least 3 years.

4. Safety and Efficacy of Loratadine in the OTC setting, Hives Indication

Similar to the allergic rhinitis indication, the proposed OTC hives indication recommends the same doses as presently approved for the prescription-only indication of CIU for each of the three loratadine-only products. The age range remains problematic because there is presently no labeling submitted for Claritin syrup, which is approved as a prescription-only product for ages 6 and above for CIU (see section "1" above).

In support of the efficacy and safety of loratadine for the (OTC) hives indication, the applicant has submitted data from the original supplemental NDA's for the indication of CIU. Some dose-ranging data were also provided. No controlled clinical trials that specifically recruited individuals with acute or chronic urticaria, and studied the impact of loratadine on their symptoms were provided in the submissions. There was a review of the literature on the use of antihistamines in general on acute and chronic urticaria. These publications did provide some indirect support for the efficacy of loratadine in the treatment of hives. However, assurance that the correct dose has been proposed for this indication relies heavily upon the conviction that CIU and hives are sufficiently similar that no dose adjustment would be expected.

The applicant provided tabulations of AE's according to indication. In general, a higher proportion of SAEs due to anaphylaxis were reported by patients taking loratadine for urticaria than for allergic rhinitis. While not unexpected, this finding should be considered a safety concern and included in the appropriate sections of the OTC label.

5. Labeling

For the hay fever indication, the proposed OTC doses for each of the products will be identical to the doses for the prescription-only products, as will the recommended age range. It should be noted that the age range cited in the labeling for Claritin syrup was recently (Sept. 2000) extended to include children as young as 2 years. This expansion of the pediatric age range will be carried over in the prescription labeling (see section "3", above). The two combination products containing pseudoephedrine utilize a dose that exceeds monograph limits for children under the age of 12 years, and therefore the OTC indication will include only adults and adolescents ≥12 years. This is not different

from the prescription-only products.

The applicant has supplied product labeling for the hay fever indication, which has been reviewed by this Division and by the Division of OTC products. It has been found acceptable, with minor modifications, and conforms to 21 CFR 201.66.

For the hives indication, the applicant's labeling was reviewed and found to be unacceptable. Deficiencies included format and content not in compliance with 21 CFR 201.66, confusing and potentially misleading images and statements relative to food and insect allergies, latex, and penicillin; lack of clarity on the proposed age ranges, inadequate description of anaphylaxis, absence of instructions NOT to use the product prophylactically, among other deficiencies. Due to these multiple problems, the label comprehension study accompanying the original submission was considered uninformative.

Preliminary comments were conveyed to the applicant, and the Division provided them with a face-to-face meeting on 2 August 2002. Based on the comments from the meeting, Schering submitted revised draft labeling and a draft protocol for a new Label Comprehension study on 5 September 2002. The protocol was sent to HFD-410 (DSRCS, in ODS) for review and comment, and has only recently returned to the Division (dated 5 November 2002; obtained by this reviewer 15 November 2002). OTC has not formally commented on the review at the time of this memo, however, the ODS reviewer continues to find problems with the label relating to the precise type of skin or systemic reaction that would cause the consumer to seek immediate medical attention. At the present time, the Agency is working with the sponsor to construct an acceptable product label from which an informative label comprehension study may be designed. An approvable action is recommended for the hives indication for loratadine at this time.

6. Post-marketing Agreements

Two post-marketing agreements have been arranged with the applicant. The first will include world-wide monitoring, follow-up and reporting of loratadine-associated hypospadias for a period of 3 years. The second will be to closely monitor and report all SAE's involving the use of Claritin syrup by children age 5 years and younger. Reports for children age 2 – 5 years will be separately reported from children < 2 years of age. The applicant will file quarterly reports for a period of 3 years.

References

1. Abernathy DR, Barbey JT, Franc J, Brown KS, *Clinical Pharmacology and Therapeutics* 2001; 69: 96-103.
2. Barbey JT, *Clinical Pharmacology and Therapeutics* 2002; 71: 5.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Purucker
11/22/02 12:15:18 PM
MEDICAL OFFICER

Badrul Chowdhury
11/22/02 06:07:05 PM
MEDICAL OFFICER
TL - Division Dir Memo

MEDICAL OFFICER REVIEW
Division of Pulmonary and Allergy Drug Products (HFD-570)

Application Numbers: N19-658, N20-704, N20-641, N19-670, N20-470

Application Type: NDA supplement

Sponsor: Schering Corporation

Proprietary Names: Claritin tablets, RediTabs, and syrup, Claritin D 12 Hour, Claritin D 24 Hour

Category of Drug: Antihistamine
Antihistamine/decongestant

USAN/Established Name: loratadine
loratadine/pseudoephedrine

Route of Administration: Oral

Medical Reviewer: Charles E. Lee, M.D.

Review Date: 10/25/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp:	Submission Type	Comments:
N19-658 SE6-018	1/25/02	1/25/02	NDA supplement	Claritin tablets, allergic rhinitis
N20-704 SE6-008	1/25/02	1/25/02	NDA supplement	Claritin RediTabs, allergic rhinitis
N20-641 SE6-009	1/25/02	1/25/02	NDA supplement	Claritin syrup, allergic rhinitis
N19-670 SE6-018	1/25/02	1/25/02	NDA supplement	Claritin D 12 Hour, allergic rhinitis
N20-470 SE6-016	1/25/02	1/25/02	NDA supplement	Claritin D 24 Hour, allergic rhinitis

Continued on page 2

These NDA supplements are applications for an over-the-counter (OTC) switch for the Claritin line of loratadine products. The sponsor is the Schering Corporation. The products are currently approved and marketed as prescription only. The proposed indications for the single ingredient loratadine products are (1) the relief of various symptoms of allergic rhinitis and (2) the relief and reduction of itching due to hives. The Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products have concluded that loratadine demonstrates a risk/benefit profile suitable for an OTC antihistamine. Hay fever (allergic rhinitis) is considered an OTC indication because consumers are able to self-diagnose and treat symptoms. Because of the extensive pre-approval and post-approval database for this drug, the Agency has determined that no new clinical studies would be required to support the OTC switch for the allergic rhinitis/hay fever indication. Data from clinical studies previously performed to support the original approval of these products supports the efficacy of loratadine in the treatment of symptoms of allergic rhinitis and chronic idiopathic urticaria. Data from previous clinical studies also support the efficacy of the loratadine/PSE combination products in the treatment of symptoms of allergic rhinitis. A review of the literature on the use of antihistamines in acute and chronic urticaria provides support for the efficacy of loratadine in the treatment of hives. The CDER OTC Switch Review Team previously concluded that there were no strong links between use of loratadine and significant serious safety concerns. A higher proportion of serious adverse events (SAEs) due to anaphylaxis occurred in patients taking loratadine for urticaria than for allergic rhinitis. Differences in the proportion of SAE reports due to anaphylaxis may represent a safety signal, and there may be a higher safety risk for anaphylaxis in patients who are taking loratadine for urticaria than for other indications. Swedish postmarketing data reveal a cluster of 15 cases of hypospadias associated with loratadine use in pregnancy. It is unclear that this observation can be generalized to the US population. The potential safety benefits of drug, including lack of sedation, outweigh the potential for this weak signal. The postmarketing safety database including safety data from Canada and the United Kingdom, where loratadine is available as a non-prescription product, reveal no other suggestion of safety signal. In summary, the sponsor adequately supports the efficacy and safety of loratadine and the loratadine/PSE products for OTC use. In this reviewer's opinion, the possible signals are not a barrier to the approvability of loratadine for OTC use. The sponsor must demonstrate in label comprehension studies that their product labeling effectively communicates the appropriate use and warnings of these products for the hives indication to consumers.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION:

Approval: X **Approvable: X for hives indication** **Not Approvable:**

SIGNED:

Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

SUBMISSIONS REVIEWED IN THIS DOCUMENT, continued

Application	Document Date:	CDER Stamp:	Submission Type	Comments:
N19-658 SE6-020	1/25/02	1/25/02	NDA supplement	Claritin tablets, hives
N20-704 SE6-009	1/25/02	1/25/02	NDA supplement	Claritin RediTabs, hives
N20-641 SE6-011	1/25/02	1/25/02	NDA supplement	Claritin syrup, hives
N19-658 SE6-018 C	2/12/02	2/12/02	Briefing book	Claritin tablets, CIU
N20-704 SE6-008 C	2/12/02	2/12/02	Briefing book	Claritin RediTabs, CIU
N20-641 SE6-009 C	2/12/02	2/12/02	Briefing book	Claritin syrup, CIU
N19-670 SE6-018 C	2/12/02	2/12/02	Briefing book	Claritin D 12 Hour, CIU
N20-470 SE6-016 C	2/12/02	2/12/02	Briefing book	Claritin D 24 Hour, CIU
N19-658 SE6-018 BL	3/28/02	3/29/02	Information request	Label comprehension study
N20-704 SE6-008 BL	3/28/02	3/29/02	Information request	Label comprehension study
N20-641 SE6-009 BL	3/28/02	3/29/02	Information request	Label comprehension study
N19-670 SE6-018 BL	3/28/02	3/29/02	Information request	Label comprehension study
N20-470 SE6-016 BL	3/28/02	3/29/02	Information request	Label comprehension study
N19-658 SE6-018 BM	3/28/02	3/29/02	Information request	SAEs, CIU
N20-704 SE6-008 BM	3/28/02	3/29/02	Information request	SAEs, CIU
N20-641 SE6-009 BM	3/28/02	3/29/02	Information request	SAEs, CIU
N19-670 SE6-018 BM	3/28/02	3/29/02	Information request	SAEs, CIU
N20-470 SE6-016 BM	3/28/02	3/29/02	Information request	SAEs, CIU
N19-658 N000 C	4/26/02	4/29/02	Correspondence	Hypospadias
N19-658 N000 C	5/23/02	5/24/02	Correspondence	Hives, labeling, safety
N20-704 N000 C	5/23/02	5/24/02	Correspondence	Hives, labeling, safety
N20-641 N000 C	5/23/02	5/24/02	Correspondence	Hives, labeling, safety
N19-658 SE6-018 BL	8/9/02	8/14/02	Draft labeling	Allergic rhinitis
N20-704 SE6-008 BL	8/9/02	8/14/02	Draft labeling	Allergic rhinitis
N20-641 SE6-009 BL	8/9/02	8/14/02	Draft labeling	Allergic rhinitis
N19-670 SE6-018 BL	8/9/02	8/15/02	Draft labeling	Allergic rhinitis
N20-470 SE6-016 BL	8/9/02	8/15/02	Draft labeling	Allergic rhinitis
N19-658 SE6-018 MR	9/6/02	9/9/02	Draft labeling	Label comprehension, hives
N20-704 SE6-008 MR	9/6/02	9/9/02	Draft labeling	Label comprehension, hives
N20-641 SE6-009 MR	9/6/02	9/9/02	Draft labeling	Label comprehension, hives
N19-658 SE6-018 SU	9/16/02	9/17/02	Safety update	Allergic rhinitis, hives
N20-704 SE6-008 SU	9/16/02	9/17/02	Safety update	Allergic rhinitis, hives
N20-641 SE6-009 SU	9/16/02	9/17/02	Safety update	Allergic rhinitis, hives
N19-670 SE6-018 SU	9/16/02	9/17/02	Safety update	Allergic rhinitis, hives
N20-470 SE6-016 SU	9/16/02	9/17/02	Safety update	Allergic rhinitis, hives
N19-658 SE6-018 BM	9/16/02	9/17/02	Information request	Subgroup analyses
N20-704 SE6-008 BM	9/16/02	9/17/02	Information request	Subgroup analyses
N20-641 SE6-009 BM	9/16/02	9/17/02	Information request	Subgroup analyses
N19-670 SE6-018 BM	9/16/02	9/17/02	Information request	Subgroup analyses
N20-470 SE6-016 BM	9/16/02	9/17/02	Information request	Subgroup analyses
N19-658 SE6-018 BL	9/25/02	9/26/02	Study report	Label comprehension, hives
N20-704 SE6-008 BL	9/25/02	9/26/02	Study report	Label comprehension, hives
N20-641 SE6-009 BL	9/25/02	9/26/02	Study report	Label comprehension, hives
N19-658 SE6-018 C	10/16/02	10/17/02	Correspondence	Hypospadias update, EMEA

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AERS	Adverse Event Reporting System
AR	Allergic rhinitis
AUC	Area under the curve
BID	Twice daily
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CIU	Chronic idiopathic urticaria
C_{max}	Maximum concentration
CMC	Chemistry, manufacturing, and controls
CNS	Central nervous system
CPMP	Committee for Proprietary Medicinal Products (of the EMEA)
CSO	Consumer Safety Officer
DCL	Desloratadine
DOTCDP	Division of Over-the-Counter Drug Products
DPADP	Division of Pulmonary and Allergy Drug Products
ECG	Electrocardiogram
EEU	Environmental Exposure Unit
EMEA	European Agency for the Evaluation of Medicinal Products
FD&C Act	Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
H_1	Histamine-$_1$ receptor
IND	Investigational New Drug
MAO	Monoamine oxidase
MPA	Medicinal Products Administration
NDA	New Drug Application
NDAC	Nonprescription Drug Advisory Committee
ODS	Office of Drug Safety
OTC	Over-the-counter
PADAC	Pulmonary-Allergy Drug Advisory Committee
PAR	Perennial allergic rhinitis
PMSS database	Postmarketing Safety Surveillance database
PSE	Pseudoephedrine
QD	Once daily
QID	Four times daily
SAE	Serious adverse event
SAR	Seasonal allergic rhinitis
SMBR	Swedish Medical Birth Registry
$T_{1/2}$	Half-life
TID	Three times daily
T_{max}	Time at which maximum concentration is measured
UK	United Kingdom
US	United States
WR	Written Request

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendations on approvability

The sponsor adequately supports the efficacy and safety of loratadine and the loratadine/ pseudoephedrine sulfate (loratadine/PSE) products for OTC use. From a clinical perspective, this reviewer recommends an approval action for the proposed allergic rhinitis indications for the loratadine tablet and RediTab formulations products for consumers 6 years of age and older and for the syrup formulation for consumers 2 years and age and older. This reviewer recommends an approval action for the loratadine/PSE combination products for consumers 12 years of age and older.

This reviewer recommends an approvable action for the proposed hives indication for the single ingredient loratadine products. The sponsor has not provided proposed labeling for the hives indication for the RediTab and syrup products. The sponsor also must provide evidence that their labeling effectively communicates the safe use of this product for this indication.

1.2. Recommendations on Phase 4 studies and risk management steps

The sponsor should agree to provide post-approval updates on the possible association of hypospadias with loratadine use in pregnancy. Spontaneous reports for hypospadias must be summarized in a separate section of the required quarterly periodic safety update reports and annual periodic safety update reports. This section of the annual periodic safety update reports should contain a thorough narrative discussion, analysis, and summary of any and all such events. The sponsor should provide an update on data from the Swedish Medical Birth Registry (SMBR). The sponsor should also summarize information from other sources, such as the Motherisk database, and regulatory authorities in other countries. Information from the SMBR and other sources should include data listings, summary tables, analysis, and interpretation. Reports should also include information on any regulatory action taken or any changes of the marketing status of the product worldwide as a result of these events. A summary and analysis of the worldwide literature review for loratadine and hypospadias should also accompany each required annual periodic safety report. These reports should be required for 3 years.

The sponsor should also provide additional information in periodic safety update reports on serious adverse events noted in the pediatric population with use of any of the loratadine or loratadine/PSE products. All serious adverse events (AEs) for the 2-5 year old age group need to be filed as 15-day reports. The sponsor should provide FDA forms 3500A for serious/unlabeled and serious/labeled AEs for the time period covered. A thorough narrative discussion, analysis and clinical significance of adverse events and summary needs to be provided. A summary and analysis of worldwide literature review

for this age group needs to be updated at the same frequency that periodic reports need to be filed. These reports should be required for 3 years.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief overview of clinical program

The applications for the OTC switch of loratadine and loratadine/PSE were submitted as supplements to the original NDAs for these products. The regulations recognize allergic rhinitis as an OTC indication and antihistamine drugs as appropriate treatment [21 CFR 341.3(e)], therefore permitting an approval of an OTC switch of a prescription-only antihistamine to be based upon the finding of safety of the drug. With regard to the CIU indication, the sponsor must provide adequate support for the use of the product in the OTC setting because CIU alone is not included in the monograph as an OTC indication. At a meeting in May 2001, the Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products concluded that loratadine demonstrates a risk/benefit profile suitable for an OTC antihistamine. Because of the extensive pre-approval and post-approval database for this drug, the Division has determined that no new clinical studies would be required to support this application for the indication of allergic rhinitis.

The sponsor originally proposed to "switch" both prescription indications for the single ingredient loratadine products (i.e. both allergic rhinitis and chronic idiopathic urticaria or CIU). A Nonprescription Drug Advisory Committee (NDAC) meeting was held on 4/22/02 to discuss CIU as an OTC indication. The consensus of the Advisory Committee was that urticaria was an appropriate OTC indication and that the urticaria indication should be broad and should not be restricted to the specific diagnosis of CIU. The committee's opinion was that the appropriate term to use in OTC labeling would be "hives." Accordingly, the sponsor has changed the proposed indication for urticaria from CIU to hives.

2.2. Efficacy

The sponsor adequately supports the efficacy of loratadine and the loratadine/PSE products for OTC use for the proposed indications. Data from clinical studies submitted with the original NDA support the efficacy of loratadine in the treatment of symptoms of allergic rhinitis and CIU. Data from clinical studies also support the efficacy of the loratadine/PSE combination products in the treatment of symptoms of allergic rhinitis. The sponsor's literature review supports of the efficacy of loratadine for the treatment of symptoms of allergic rhinitis and chronic idiopathic urticaria (CIU). In support of the "hives" indication, the sponsor submitted a review of the literature on the use of antihistamines in acute and chronic urticaria. There is little actual evidence from clinical studies to support the efficacy of H1 antihistamines, including loratadine, in the treatment acute urticaria. However, histamine is a mediator that is involved in both acute and chronic urticaria and antihistamines are not only currently used for treatment of acute urticaria, but their use is accepted as the standard of care. In this context, the sponsor's review of the literature provides additional support for, and no evidence against, the efficacy of loratadine in the treatment of urticaria. The sponsor's application acceptably supports efficacy of loratadine for the treatment of hives. The sponsor has yet to

demonstrate in label comprehension studies that their product labeling effectively communicates the appropriate use and warnings of these products for the hives indication to consumers.

2.3. Safety

The sponsor adequately supports the safety of loratadine and the loratadine/PSE products for OTC use for the proposed indications. The CDER OTC Switch Review Team previously concluded that there were no strong links between use of loratadine and significant serious safety concerns. Adverse events in clinical trials of loratadine tablets, RediTabs, and syrup were similar in character and frequency to that of the placebo. AEs for the loratadine/PSE combination products were comparable to those of loratadine, with the exception of those expected from PSE alone, including insomnia, dry mouth, nervousness, and dizziness. Postmarketing patient exposure to all formulations of loratadine is extensive. In general, the types of AEs that were noted in the postmarketing safety database for loratadine are similar to those noted in clinical trials, such as somnolence, headache, dizziness, and nausea. Reports of dysphagia and esophageal obstruction for loratadine 10 mg/PSE 240 mg (D-12) were related to the size and coating of the tablet and there have not been any such serious advents reported for the new formulation since the size and coating were changed in December 1998. Postmarketing safety data from Canada and the United Kingdom, where loratadine is available as a non-prescription product, reveal no safety signal.

The safety database for the allergic rhinitis indication does not reveal evidence for a safety signal in children from 2 to 6 years of age. It is important to point out, however, that the entire NDA database for this age group is comprised of 231 children, most of whom were exposed to loratadine for duration between 8 and 15 days [Dr. Susan Johnson, Medical Officer Review, NDA 20-641 SE5-007, 9/21/00]. The sponsor's application supports an allergic rhinitis indication for children ages ≥2 to < 6 years at the currently approved Claritin syrup dose of 5 mg once daily.

A higher proportion of serious adverse events (SAEs) due to anaphylaxis occurred in patients taking loratadine for urticaria than for allergic rhinitis. Differences in the proportion of SAE reports due to anaphylaxis may represent a safety signal, and there may be a higher safety risk for anaphylaxis in patients who are taking loratadine for urticaria than for other indications. Swedish postmarketing data reveal a cluster of 15 cases of hypospadias associated with loratadine use in pregnancy. The association of hypospadias with loratadine use has been noted only in Sweden. Most of the cases in the Swedish database were mild, and the incidence of hypospadias among exposed cases in this database is low. It is unclear that this observation can be generalized to the US population. The potential safety benefits of drug, including lack of sedation, outweigh the potential for this weak signal. The sponsor will be asked to agree to provide updates for 3 years on the possible association of hypospadias with loratadine use in pregnancy. These updates should include follow-up on the Swedish data as well as postmarketing data from other countries.

2.4. Dosing

The sponsor's proposed OTC dosing for the loratadine and loratadine/PSE combination products is the same as that of the currently approved prescription products. There was no safety or efficacy data that suggest that OTC dosing should be different from the currently approved prescription dosing.

The proposed OTC dose of the single ingredient loratadine products is one 10 mg tablet or RediTab, or 2 teaspoonfuls (10 mg) of syrup once daily for adults and children 6 years of age and over. This dose is the same as the recommended dose for the currently approved prescription product in adults and children 6 years of age and older. The tablet is an acceptable dosage form for consumers 6 years of age and older, according the OTC monograph.

The proposed OTC dose of the single ingredient loratadine products for children ages 2 to 6 years of age is one teaspoonful (5 mg) of syrup once daily. This dose is the same as the recommended dose for the currently approved prescription product in children 2 to 6 years of age.

The proposed directions for the RediTabs instructs the consumer to place one RediTab on the tongue and advises the consumer that the tablet disintegrates rapidly, with or without water. Current prescription labeling for the RediTabs includes the same instructions.

The proposed OTC dose of the loratadine/PSE 12-hour product is 1 tablet every 12 hours, not to exceed 2 tablets in a 24-hour period. Proposed labeling instructs the consumer not to divide, crush, chew, or dissolve the tablet. The loratadine/PSE 12-hour product is not for use in children under 12 years of age.

The proposed OTC dose of the loratadine/PSE 24-hour product is 1 tablet daily, not to exceed 1 tablet in a 24-hour period. The label instructs consumers to take the tablet with a full glass of water. Proposed labeling instructs the consumer not to divide, crush, chew, or dissolve the tablet. The loratadine/PSE 24-hour product is not for use in children under 12 years of age.

The proposed doses for the loratadine/PSE combination products are the same as the recommended dose of the currently approved prescription products for patients 12 years of age and older. This dose of PSE is not acceptable for consumers less than 12 years of age. The daily PSE dose is the same as that specified by the monograph for these ages [21 CFR 341.80(d)(i)].

2.5. Special populations

AUC and C_{max} of loratadine and desloratadine (DCL) in subjects ≥65 years of age are approximately 50% greater than those observed in studies of younger subjects. The mean elimination $T_{1/2}$ in subjects ≥65 years is 18.2 hours for loratadine and 17.5 hours for DCL, compared with 8.4 hours for loratadine and 28 hours for DCL in younger subjects. Despite these differences, clinical experience has not revealed differences in efficacy or safety of loratadine between elderly and younger patients. There is no dose adjustment in

this group recommended in the current prescription labeling for loratadine products. The sponsor's proposed OTC labeling appropriately makes no special recommendations for dosing for healthy consumers 65 years of age and greater and appropriately addresses use of the products in this population.

The approval of loratadine syrup in children as a prescription product was based on pharmacokinetic comparability of doses in children and adults and an extrapolation of the demonstrated efficacy of loratadine in adults with allergic rhinitis and CIU and the consideration that the disease course, pathophysiology, and the drug's effect is substantially similar in children and adults. Placebo controlled trials of loratadine in children and worldwide postmarketing data reveal that the types and relative frequencies of AEs for loratadine and the loratadine/PSE combinations in the pediatric population are similar to those noted for all spontaneous AEs. The sponsor has completed pediatric studies for loratadine in children down to 6 months of age to answer the Agency's Written Request for pediatric studies (WR). The studies of children age 2 to <6 years of age support the approval of loratadine as a prescription product in children down to the age of 2 years. The supplement submitted to support an indication for children between the ages of 6 months and 2 years was not approved, and language was added to the label stating its use was not recommended in this age group. The sponsor's submission supports the OTC use of loratadine for the allergic rhinitis indication for children down to 2 years of age. The sponsor has not provided proposed labeling for the hives indication for the syrup product. The sponsor still must also provide evidence that their labeling effectively communicates the safe use of loratadine for the hives indication in children.

The amount of PSE in the combination products is not appropriate for children under the age of 12 years, and the sponsor's labeling appropriately notes that the loratadine/PSE products should not be used in children under 12 years of age. The sponsor appropriately addresses use of the loratadine/PSE combination products in the pediatric population.

There are to no gender-related efficacy or safety issues with these products. The AUC and C_{max} for desloratadine (DCL) is higher in subjects of Black race than in subjects of Caucasian race, and subjects of Black race are more likely to be slow metabolizers of DCL than subjects of Caucasian race. However, plasma concentrations noted in pharmacokinetic studies in this subpopulation were lower than those noted in studies in normal subjects where 40-mg doses were shown to be safe and well tolerated. There are no differences in the safety profiles of normal and fast metabolizers. There are no known efficacy or safety issues related to race for these products.

Compared with normal individuals, patients with hepatic impairment have increased C_{max}, AUC, and $T_{1/2}$ for loratadine and patients with renal impairment have increased $T_{1/2}$ for loratadine. No dosage adjustment for patients with liver or kidney disease is included in the label, but the sponsor has proposed the text, "Ask a doctor before use if you have liver or kidney disease." The sponsor's proposed OTC labeling for single ingredient loratadine products and loratadine/PSE products instructs consumers with liver disease or kidney disease to ask a doctor before use and advises the consumer that a different dose may be needed. The sponsor appropriately addresses use of the product in consumers

with hepatic and renal impairment. The sponsor's recommendations for consumers with liver or kidney disease are appropriate and acceptable for the OTC setting.

There was a cluster of 15 cases of hypospadias associated with loratadine use during pregnancy in Sweden. These data show an incidence of hypospadias in women exposed to loratadine during pregnancy of approximately 0.05% to 0.06%. The incidence is elevated approximately 2.5 to 3.5-fold over the expected baseline incidence of hypospadias in Sweden. Most of these cases were mild. It is unclear if this observation can be generalized to the US population. The potential safety benefits of drug, including lack of sedation, outweigh the potential for this weak signal. In this reviewer's opinion, this signal is not a barrier to the approvability of loratadine for OTC use. The sponsor's proposed OTC labeling instructs consumers who are pregnant to ask a health professional before using the product. The sponsor's recommendation to pregnant consumers is appropriate.

The sponsor's proposed OTC labeling instructs consumers who are breast feeding to ask a health professional before using the product. The sponsor's recommendations for use of the single ingredient loratadine and the loratadine/PSE combination products in breast feeding consumers are appropriate. The maximum dose of loratadine and DCL that would be ingested by a 4-kg infant would be at most 1.1% of the loratadine dose received by the mother on a mg/kg basis.

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

These NDA supplements are applications for an OTC switch for the Claritin line of loratadine products. The sponsor is the Schering Corporation. The products and their NDA application numbers follow:

- NDA 19-658, SE6-018, Claritin tablets (loratadine 10 mg), allergic rhinitis indication
- NDA 20-704, SE6-008, Claritin RediTabs (loratadine 10 mg), allergic rhinitis indication
- NDA 20-641, SE6-009, Claritin Syrup (loratadine 5 mg/5 mL), allergic rhinitis indication
- NDA 19-670, SE6-018, Claritin D 12-Hour tablets (loratadine 5 mg/pseudoephedrine HCl 120 mg), allergic rhinitis indication
- NDA 20-470, SE6-016, Claritin D 24-Hour tablets (loratadine 10 mg/pseudoephedrine HCl 240 mg), allergic rhinitis indication
- NDA 19-658 SE6-020, Claritin tablets (loratadine 10 mg), hives indication
- NDA 20-704, SE6-009, Claritin RediTabs (loratadine 10 mg), hives indication
- NDA 20-641, SE6-011, Claritin Syrup (loratadine 5 mg/5 mL), hives indication

The products are currently approved and marketed as prescription only. The proposed indications for the single ingredient loratadine products are (1) the relief of various symptoms of allergic rhinitis and (2) the relief and reduction of itching due to hives. The single ingredient tablets and RediTabs are proposed for OTC use in adults and children 6 years of age and older for the treatment of allergic rhinitis and hives. The syrup is proposed for use in children 2 years of age and older for the treatment of allergic rhinitis and for use in adults and children 6 years of age and older for the treatment of hives.

The proposed indication for the combination loratadine/pseudoephedrine (PSE) products is the relief of various symptoms of allergic rhinitis, including nasal congestion and relief of sinus pressure, among others. The combination loratadine/PSE products are proposed for OTC use in adults and children ages 12 years and older, the same ages for which the currently marketed prescription products are indicated.

1.2. State of Armamentarium for Indications

Antihistamines are first-line agents in the treatment of symptoms due to allergic rhinitis. There are various antihistamines currently marketed as OTC products in the US. Some of these are OTC monograph drugs, such as brompheniramine, chlorpheniramine, diphenhydramine, and doxylamine. There are also antihistamines marketed OTC in the US that were approved as NDA products, such as clemastine. These products are indicated for the treatment of symptoms of "hay fever or other upper respiratory allergies

(allergic rhinitis)" [21 CFR 341.72]. These OTC antihistamines all have a tendency to cause sedation.

There are also antihistamines currently approved in the US for the treatment of symptoms of allergic rhinitis that are prescription products. Some of these prescription antihistamines also have a tendency to cause sedation, such as hydroxyzine and cyproheptadine. Cetirizine, fexofenadine, and loratadine are more recently approved prescription antihistamines that are less likely to cause sedation than the OTC antihistamines and older prescription antihistamines. Sedation from antihistamines is a significant public health concern. Allergic rhinitis is a common condition, and many consumers need to perform tasks requiring mental alertness in the course of their day. The availability of a less-sedating antihistamine in the OTC marketplace would represent a great public health benefit that would come from the approval of this application.

There currently are no OTC products approved in the US for the treatment of CIU, urticaria, or itching due to hives. CIU, urticaria, and itching due to hives also are not OTC monograph indications. A Nonprescription Drug Advisory Committee (NDAC) meeting was held on 4/22/02 to discuss CIU as an OTC indication. The consensus of the Advisory Committee was that urticaria was an appropriate OTC indication, and that the appropriate language to be used in labeling for this OTC indication was "hives."

1.3. Important Milestones in Product Development

Loratadine is a tricyclic antihistamine, and is one of the second-generation antihistamines. Second generation antihistamines tend to be less sedating and are less likely to have anticholinergic side effects than first generation antihistamines. There has been much recent public interest in a switch for loratadine from prescription status to OTC status. The California Blue Cross submitted a Citizen's Petition requesting OTC status for "non-sedating" (second generation) antihistamines, including loratadine. The petition was based on a review of approximately 300 relevant publications, and included meta-analyses of data extracted from these publications. In addition, the Agency solicited information from the public on the regulation of OTC drug products at a recent Public Hearing on over-the-counter drug products [Docket 00N-1256, 6/28/00-6/29/00, http://www.fda.gov/ohrms/dockets/dockets/00n1256/00n1256xx.htm].
The Agency also heard opinions on the suitability of second generation antihistamines such as loratadine for OTC switches in a joint meeting of the Nonprescription Drugs and Pulmonary and Allergy Drugs Advisory committees on 5/11/01 [http://www.fda.gov/ohrms/dockets/ac/cder01.htm]. The Advisory Committee concluded that loratadine demonstrated a risk/benefit profile suitable for an OTC antihistamine.

Information regarding the safety and efficacy of loratadine for these indications has been previously submitted to the approved NDAs. The sponsor points out in their cover letter that they are supportive of the switch only if both indications and all dosage forms are approved for OTC marketing. There were no pre-IND, End-of-Phase 2, or pre-NDA meetings for these applications, although the sponsor met with Drs. Temple, Meyer, Ganley, and Mann on 12/20/01 to discuss the submission.

A Nonprescription Drug Advisory Committee (NDAC) meeting was held on 4/22/02 to discuss CIU as an OTC indication. Selected members of the Pulmonary-Allergy Drugs Advisory Committee also participated in this meeting. The consensus of the Advisory Committee was that urticaria was an appropriate OTC indication. The committee also advised that the urticaria indication should be broad and should not be restricted to the specific diagnosis of CIU. The committee's opinion was that the appropriate term to use in OTC labeling would be "hives." Although the committee felt that the sponsor presented sufficient data to support a switch for CIU, they did not feel that there was sufficient information to support the more general indication for hives. The committee suggested that the sponsor conduct a literature review of studies in acute hives and a label comprehension study to support a more general hives indication. It was suggested that labeling should maximize warning statements about anaphylaxis, include pictures as examples of hives, and include a list of reasons to consult a doctor, among others.

A meeting between the sponsor and the Division of Pulmonary and Allergy Drug Products (DPADP) and the Division of Over-the-Counter Drug Products (DOTCDP) was held on 8/2/02, at which labeling for the more general hives indication was discussed. The sponsor was provided comments and guidance to guide their choice of labeling to be tested in planned label comprehension studies.

1.4. Other Relevant Information

The five dosage forms of loratadine (tablets, RediTabs, syrup, loratadine/PSE 12 Hour tablets, loratadine/PSE 24 Hour tablets) are marketed worldwide. In most countries, the single ingredient loratadine products are indicated for the relief of symptoms of seasonal and perennial allergic rhinitis (SAR and PAR), allergic skin disorders, and chronic idiopathic urticaria (CIU). Loratadine tablets and RediTabs are indicated for patients 6 years of age and older; loratadine syrup is indicated in patients 2 years of age and older. The loratadine/PSE combination products are generally indicated for the treatment of symptoms of SAR in patients 12 years of age and older [NDA 19-658, Volume 1.1, Section 3.C., page 3].

The number of countries in which each of the products is approved for prescription and non-prescription use is displayed in Table 1.

Table 1. Worldwide marketing of loratadine products [NDA 19-658, Volume 1.1, Section 3.C., page 3].

Formulation	Number of Countries approved (marketed)			
	Prescription		Non-prescription	
Loratadine, 10 mg tablets	114	(102)	30	(28)
Loratadine, 10 mg RediTabs	35	(15)	7	(3)
Loratadine, 1 mg/mL syrup	92	(80)	22	(20)
Loratadine/PSE 12 Hour tablets	74	(51)	10	(7)
Loratadine/PSE 24 Hour tablets	34	(15)	4	(3)

Loratadine was first introduced as a prescription product in Belgium in 1988 and as a non-prescription product in Canada in 1988. In most countries where loratadine tablets and syrup are available as a non-prescription products, it is indicated for AR, allergic skin disorder, and CIU indications, including the UK, Canada, and Australia [NDA 19-658, Volume 1.1, Section 3.C., pages 3-4].

In the US, Claritin tablets (NDA 19-658) were approved for SAR in April 1993 and for CIU in September 1995. Claritin syrup (NDA 20-641) was approved in the US for patients 6 years of age and older in October 1996 and in patients ages 2 to 6 years in September 2000. Claritin RediTabs (NDA 20-704) were approved in the US in December 1996. Claritin D 12 Hour tablets (NDA 19-670) were approved in the US in November 1994 and Claritin D 24 Hour tablets (NDA 20-470) were approved in August 1996 [NDA 19-658, Volume 1.1, Section 3.C., page 4].

1.5. Important Issues with Pharmacologically Related Agents

As noted above, all OTC antihistamines have a tendency to cause sedation. Some of the prescription antihistamines, such as cyproheptadine, hydroxyzine and promethazine, also have a tendency to cause sedation. Sedation from antihistamines is a significant public health concern and the OTC availability of a less-sedating antihistamine such as loratadine would represent a great public health benefit.

Two less-sedating antihistamines previously approved in the US, terfenadine and astemizole, have been removed from the market because of association with fatal cardiac arrhythmias due to their tendency to provoke prolongation of the QTc interval and torsades des pointes. These serious events were associated with co-administration of the drugs with inhibitors of cytochrome P450 3A4, which resulted in increased systemic exposures, and/or with administration of greater than recommended doses. The three less-sedating antihistamines currently approved in the US as prescription products, cetirizine, fexofenadine, and loratadine, do not provoke significant prolongation of the QTc interval at normal or greater than normal systemic exposures, and have not been shown to be associated with similar cardiac events.

2. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

Clinically relevant information other disciplines are summarized below.

2.1. Chemistry, Manufacturing and Controls

The Chemistry, Manufacturing and Controls (CMC) information for the single ingredient loratadine products were incorporated by reference into the applications from the original NDA submissions for Claritin tablets (NDA 19-658), Claritin RediTabs (NDA 20-704), and Claritin syrup (NDA 20-641) [NDA 19-658, Volume 1, 3.D., pages 28, 14, 14]. The Chemistry, Manufacturing and Controls (CMC) information for the loratadine/PSE combination products were incorporated by reference into the applications from the original NDA submissions for Claritin D 12-Hour (NDA 19-670), and Claritin D 24-Hour (NDA 20-470) [NDAs 19-670 and 20-470, Volume 1.3.D., pages 2, 8].

Loratadine is a white to off-white powder not soluble in water, but very soluble in acetone, alcohol, and chloroform. It has a molecular weight of 382.89, and empirical formula of $C_{22}H_{23}ClN_2O_2$; its chemical name is ethyl 4-(8-chloro-5, 6-dihydro- 11 *H*

-benzo[5,6]cyclohepta [1,2- *b*]pyridin-11-ylidene)-1-piperidinecarboxylate [Volume 1, 3.C., page 83].

CLARITIN Tablets contain 10 mg micronized loratadine, an antihistamine, to be administered orally. It also contains the following inactive ingredients: corn starch, lactose, and magnesium stearate [Volume 1, 3.C., page 83].

CLARITIN Syrup contains 1 mg/mL micronized loratadine, an antihistamine, to be administered orally. It also contains the following inactive ingredients: citric acid, edetate disodium, artificial flavor, glycerin, propylene glycol, sodium benzoate, sugar, and water. The pH is between 2.5 and 3.1[Volume 1, 3.C., page 83].

CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) contain 10 mg micronized loratadine, an antihistamine, to be administered orally. It disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water. CLARITIN REDITABS (loratadine rapidly-disintegrating[1] tablets) also contain the following inactive ingredients: citric acid, gelatin, mannitol, and mint flavor [Volume 1, 3.C., page 83].

Pseudoephedrine sulfate is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine and is classified as an indirect sympathomimetic amine. The empirical formula for pseudoephedrine sulfate is $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$; the chemical name is [S-(R*,R*)]-a-[1(methylamino)ethyl] benzenemethanol sulfate (2:1) (salt) [Volume 1, 3.C., page 92]

CLARITIN-D 12 HOUR Extended Release Tablets contain 5 mg loratadine in the tablet coating for immediate release and 120 mg pseudoephedrine sulfate, USP equally distributed between the tablet coating for immediate release and the barrier-coated extended release core. The inactive ingredients for CLARITIN-D 12 HOUR Extended Release Tablets are acacia, butylparaben, calcium sulfate, carnauba wax, corn starch, lactose, magnesium stearate, microcrystalline cellulose, neutral soap, oleic acid, povidone, rosin, sugar, talc, titanium dioxide, white wax, and zein [Volume 1, 3.C., page 83].

CLARITIN-D® 24 HOUR (loratadine and pseudoephedrine sulfate, USP) Extended Release Tablets contain 10 mg loratadine in the tablet coating for immediate release and 240 mg pseudoephedrine sulfate, USP in the tablet core which is released slowly allowing for once-daily administration. The inactive ingredients for oval, biconvex CLARITIN-D 24 HOUR Extended Release Tablets are calcium phosphate, carnauba wax, ethylcellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, povidone, silicon dioxide, sugar, titanium dioxide, and white wax [Volume 1, 3.C., page 101].

---

[1] "Rapidly disintegrating tablets" is the dosage form of the currently marketed product. The name of the dosage form is to be changed to "orally disintegrating tablets" in the proposed OTC product.

2.2. Animal Pharmacology and Toxicology

The sponsor's applications reference pharmacology and toxicology studies previously submitted to INDs and NDAs for loratadine and desloratadine (DCL; approved as Clarinex® 12/21/01) [Volume 1, 3.E., page 1].

Schering conducted an additional non-clinical study of loratadine to address the issue of hypospadias after a cluster of cases was noted in the Swedish Medical Birth Registry (SMBR). The Swedish Medicinal Products Administration (MPA) agreed with the sponsor's proposed protocol design for this non-clinical study [NDA 19-658, N-000 C, 4/26/02, Attachment 4]. In this preclinical study, 100 mated female rats were exposed to 4, 12, or 24 mg/kg of loratadine from day 7 of gestation to day 4 of lactation, the androgen-sensitive period of genital development. Anogenital distance and presence of nipples in males and females were assessed, which are both indicators of anti-androgenic activity in the rat. In addition, the presence of hypospadias, age at preputial separation, organ weights of seminal vesicles and prostate in males were evaluated, additional indicators of sensitivity to anti-androgenic effects. The sponsor states that maternal body weight gain and mean pup body weight were lower at the 24 mg/kg dose, but that no effects were noted at the other doses. There were no effects on male genital tract in offspring at any dose, according to the sponsor.

Dr. Sancilio, pharmacology reviewer for this Division, reviewed the sponsor's non-clinical information submitted with this application and reviewed non-clinical data on file for loratadine and desloratadine (DCL). Data on file from loratadine and DCL INDs and NDAs showed no evidence of teratogenic effects in offspring of female rats and rabbits given loratadine or DCL during gestation. There was no evidence of antiandrogenic effects in offspring of female rats exposed to loratadine and DCL during the androgen-sensitive period of genital development. There was no delay in the day of preputial separation, no decrease in anogenital distance, and no nipple retention, all sensitive indicators of an anti-androgenic effect. These markers have been successful in identifying drugs known to have such a risk, such as flutamide, bicalutamide, and finasteride.

There was some evidence of reproductive toxicity of loratadine and DCL in adult male rats, as indicated by decreased epididymal prostate, and testis weights in rats and for loratadine in cynomolgous monkeys, and indicated by hypoplastic juvenile changes in the testes and secondary sex organs. The changes in the adult animals are not markers for hypospadias, however. He concluded that loratadine and DCL are not anti-androgenic in newborn male rats. He concluded that loratadine and DCL are not anti-androgenic in newborn male rats. His findings are summarized in the minutes for an internal meeting of DPADP, ODS, and DOTCDP on 10/4/02 at which the possible signal of hypospadias with loratadine was discussed.

2.3. Microbiology

No microbiology review was necessary for these applications.

2.4. Statistics

No statistics review was necessary for these applications.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

There were no new pharmacokinetics or pharmacodynamics studies performed to support the sponsor's application. This section of the review briefly summarizes pertinent human pharmacokinetics and pharmacodynamics information regarding loratadine.

3.1. Pharmacokinetics

Loratadine is rapidly absorbed following oral administration of 10-mg tablets, with a T_{max} of about 1 to 2 hours. It is extensively metabolized and excreted in approximate equal amounts in the urine and feces. After absorption, loratadine is metabolized to the pharmacologically active metabolite desloratadine (DCL), predominantly by cytochrome P450 3A4 and to a lesser extent by cytochrome P450 2D6. The AUC of DCL is about 8.6-fold higher than that of loratadine in normal subjects. Loratadine is 97-99% bound to plasma protein. DCL is 73-77% bound to plasma protein [Volume 1, 3.F., pages 2-3].

The mean $T_{1/2}$ for loratadine in normal subjects is 8.4 hours, and ranges from 3 to 20 hours. The mean $T_{1/2}$ for DCL in normal subjects is 28 hours, and ranges from 8.8 to 92 hours. As reflected in the range for $T_{1/2}$, 9.5% of normal subjects are slow metabolizers of DCL, and have approximately 5-fold elevated exposure and prolonged $T_{1/2}$ (>50 hours). Subjects of Black race are more likely to be slow metabolizers of DCL than subjects of Caucasian race. There have been no differences in safety profiles noted between normal and fast metabolizers [Volume 1, 3.F., pages 3-4].

The mean C_{max} and AUC for loratadine are similar for tablet and RediTab formulations and 45-67% higher for the syrup. The sponsor notes that these differences are not expected to be clinically relevant. Food increases loratadine exposure and delays absorption, but has no effect on loratadine C_{max}. There is no food effect on C_{max} and AUC of DCL. Differences in exposure due to food effects are also not considered to be clinically relevant. Administration of the RediTab formulation with water increases loratadine AUC by 26%, but no effect on DCL bioavailability. This difference is also not thought to be clinically important [Volume 1, 3.F., page 4].

The pharmacokinetic profile of loratadine in children 2 to 12 years of age is similar to that of adults. The AUC and C_{max} for loratadine and DCL is 29-93% higher in females than in males. The AUC and C_{max} for DCL are higher in subjects of Black race than in subjects of Caucasian race. However, plasma concentrations noted in pharmacokinetic studies in subpopulations were lower than those noted in studies in normal subjects where 40-mg doses were shown to be safe and well tolerated [Volume 1, 3.F., pages 5-6].

AUC and C_{max} of loratadine and desloratadine (DCL) in healthy subjects 66 to 78 years of age were approximately 50% greater than those observed in studies of younger subjects. The mean elimination $T_{1/2}$ in these subjects was 18.2 hours for loratadine and 17.5 hours for DCL, compared with 8.4 hours for loratadine and 28 hours for DCL in

younger subjects [Volume 1, 3.F., pages 5-6]. The AUC and C_{max} of loratadine in patients with chronic alcoholic liver disease were found to be twice that of normal subjects. No substantial change in DCL levels was noted. The mean $T_{1/2}$ in these patients for loratadine was 24 hours and for DCL was 37 hours, compared with normal subjects, who had a mean $T_{1/2}$ for loratadine of 8.4 hours and for DCL of 28 hours. The AUC and C_{max} increased 73% for loratadine and 120% for DCL patients with chronic renal impairment and creatinine clearances of ≤30 mL/min. The mean $T_{1/2}$ for loratadine (7.6 hours) and DCL (23.9 hours) were similar to values in normal subjects. [Volume 1, 8.F., pages 5-6].

The sponsor has conducted studies in which loratadine has been co-administered with therapeutic doses of erythromycin, cimetidine, and ketoconazole. Increased plasma concentrations of loratadine and/or DCL were observed after co-administration of loratadine with each of these drugs. There were no clinically relevant changes in ECGs, laboratory tests, vital signs or AEs. There was no significant effect on QTc intervals, and no reports of sedation or syncope. Plasma levels of erythromycin decreased 15%; no effects on plasma levels of cimetidine or ketoconazole were noted [Volume 1, 3.F., pages 6-7].

3.2. Pharmacodynamics

The sponsor states that loratadine was found to be safe and well tolerated when administered to adults at 40 mg once daily for 90 days or as a single dose up to 160 mg. No clinically significant increases were seen in the QTc interval or ECGs in these studies [Volume 1, 3.F., page 4].

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

These applications were paper NDA submissions. The initial applications for the loratadine products are identical and consist of 63 paper volumes. Some of the data are also submitted in electronic form. The initial applications for the loratadine/PSE products are identical and consist of 61 paper volumes. Some of the data are also submitted in electronic form. The submissions for the loratadine products and the loratadine/PSE products are essentially identical, except for 2 additional volumes in the loratadine application, which contain information supporting the OTC switch of the CIU indication.

Data for clinical review in these applications included summaries of efficacy and safety data from clinical trials conducted to support the approval of the original US and foreign applications. The sponsor also submitted summaries of efficacy and safety data from clinical trials conducted after the approval of the applications. The sponsor submitted tabulations and summaries of worldwide postmarketing safety data, including postmarketing safety data for OTC loratadine use from Canada and the United Kingdom.

During the course of the review, the sponsor provided additional information that addressed the hives indication and a cluster of 15 cases of hypospadias in Sweden that was associated with loratadine use during pregnancy. This information is reviewed in the Integrated Review of Efficacy and Integrated Review of Safety sections of this document.

4.2. Overview of Clinical Trials

There were no new clinical trials performed to support these applications. There were no clinical study reports included in these applications.

4.3. Postmarketing Data

As noted above, the sponsor submitted tabulations and summaries of worldwide postmarketing safety data, including postmarketing safety data for OTC loratadine use from Canada and the United Kingdom

4.4. Literature Review

The sponsor's applications included a review of the medical literature of the efficacy of orally administered loratadine, a review of the medical literature on the use of antihistamines in acute and chronic urticaria, and a literature review of safety data covering the period since the completion of the CDER OTC Switch Review Team's literature review in April 2000. These literature reviews are discussed in the Integrated Review of Efficacy and the Integrated Review of Safety sections of this document.

5. CLINICAL REVIEW METHODS

A summary of review methods follows, and includes a description of the conduct of the review and an assessment of data quality.

5.1. Conduct of the review

The bulk of this review focuses in depth on data included in the sponsor's Integrated Summary of Efficacy and Integrated Summary of Safety. As noted above, there were no new clinical trials performed to support the switch of these products. The Agency has previously determined that these products are safe and effective as prescription drugs for their respective indications. The Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products have previously concluded that loratadine demonstrates a risk/benefit profile suitable for an OTC antihistamine [http://www.fda.gov/ohrms/dockets/ac/cder01.htm, Pulmonary-Allergy Drugs Advisory Committee]. The sponsor performed label comprehension studies to support these applications. These label comprehension studies are not reviewed in this document but have been reviewed by DOTCDP. Other points of focus for this clinical review include information supporting the "hives" indication, and information addressing a cluster of 15 cases of hypospadias in Sweden that was associated with loratadine use during pregnancy.

5.2. Data Quality and Integrity

DSI audit was not requested for these applications because the applications included no new clinical data.

5.3. Ethical Standards

As noted above, no new clinical studies were performed to support these applications, and no original study reports were included in the applications. Therefore there was no debarment certification or any Statement of Good Clinical Practice.

5.4. Financial Disclosure

A financial disclosure statement was not required because no new clinical studies were performed to support these applications, and no original study reports were included in the applications.

6. INTEGRATED REVIEW OF EFFICACY

A review of the sponsor's information provided in support of efficacy follows below.

6.1. Summary and conclusions

The applications for the OTC switch of loratadine and loratadine/PSE were submitted as supplements to the original NDAs for these products. The regulations recognize allergic rhinitis as an OTC indication and antihistamine drugs as appropriate treatment [21 CFR 341.3(e)], therefore permitting an approval of an OTC switch of a prescription-only antihistamine to be based upon the finding of safety of the drug. With regard to the CIU indication, the sponsor must provide adequate support for the use of the product in the OTC setting because CIU alone is not included in the monograph as an OTC indication. As noted earlier in this review, the Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products previously concluded that loratadine demonstrates a risk/benefit profile suitable for an OTC antihistamine. Because of the extensive pre-approval and post-approval database for this drug, the Division of Pulmonary and Allergy Drug Products (DPADP) has determined that no new clinical studies would be required to support this application.

The sponsor provided an Integrated Summary of Efficacy that included reviews of efficacy data for loratadine products from clinical studies and from the medical literature. Data from clinical studies support the efficacy of loratadine in the treatment of symptoms of allergic rhinitis and CIU. Data from clinical studies support the efficacy of the loratadine/PSE combination products in the treatment of symptoms of allergic rhinitis. The sponsor's literature review also supports of the efficacy of loratadine for the treatment of symptoms of allergic rhinitis and CIU. In support of the "hives" indication, the sponsor submitted a review of the literature on the use of antihistamines in acute and chronic urticaria. There is little actual evidence from clinical studies to support the efficacy of H1 antihistamines, including loratadine, in the treatment acute urticaria. However, histamine is a mediator that is involved in both acute and chronic urticaria. Antihistamines are not only currently used for treatment of acute urticaria, but their use is accepted as the standard of care. In this context, the sponsor's review of the literature provides some additional support for, and no evidence against, the efficacy of loratadine in the treatment of urticaria. In summary, the sponsor adequately supports the efficacy of loratadine and the loratadine/PSE products for OTC use. A detailed review of the sponsor's Integrated Summary of Efficacy follows below.

6.2. Content

The sponsor's Integrated Summary of Efficacy included the following data [Volume 2, 8.G., pages 5-7]:

- Review of efficacy data from clinical studies performed by the sponsor to support the respective NDAs for
  - Loratadine tablets (Claritin® tablets)
  - Loratadine syrup (Claritin® syrup)
  - Loratadine RediTabs (Claritin® RediTabs®)
  - Loratadine-pseudoephedrine (PSE) 12-hour tablets (Claritin D 12-Hour tablets)
  - Loratadine-PSE 24-hour tablets (Claritin D 24-Hour tablets)
- Summary of efficacy in special populations
- Overview of results of a review of the medical literature of orally administered loratadine

In support of the general "hives" indication, the sponsor submitted the following [N19-658 SE6-018, N20-704 SE6-008, and N20-641 SE6-009, Correspondence, 5/23/02]:

- Review of the literature on the use of antihistamines in acute and chronic urticaria

Review of these efficacy data supporting these applications follows below.

6.3. Efficacy data from clinical studies

The sponsor notes that approximately 100,000 subjects have been treated with loratadine in controlled or uncontrolled clinical studies since 1984 [Volume 2, 8.G., page 7]. The sponsor's summary of efficacy data from clinical studies that supported the applications is reviewed below.

6.3.1. Efficacy data from clinical studies, loratadine tablets

6.3.1.1. Efficacy, SAR

The NDA for loratadine tablets (NDA 19-658) for SAR included 10 randomized, double blind, placebo controlled, multicenter, parallel group studies. There was one randomized, double blind, multicenter, parallel group study that was not placebo-controlled. Four of the clinical studies were pivotal for the approval of the application. Each of the four studies included adults and adolescents ≥12 years of age and was 14 days in duration. Enrollment in these studies ranged from 123 to 356. Evaluation of efficacy was based primarily on assessments of total and individual symptoms of SAR. Total symptom scores included both nasal and non-nasal symptoms of SAR. The difference between loratadine 10 mg and placebo in change from baseline in percent improvement in total symptom score at endpoint ranged from 11% to 26% in each of the studies and was statistically significant ($p < 0.05$) for three of the four studies. The difference between loratadine 10 mg and placebo in change from baseline in percent improvement in total symptom score at first assessment (Day 7 in one study and Day 3 in the remaining three studies) ranged from 12% to 25% and was statistically significant ($p < 0.05$) for all four studies. Loratadine 10-mg tablets were approved for marketing in the US in April 1993

based on the efficacy results from the four pivotal and seven supporting clinical studies [Volume 2, 8.G., pages 7-10].

6.3.1.2. Efficacy, PAR

The sponsor did not submit an application for loratadine for the PAR indication in the US. However, the loratadine 10-mg tablets have been approved for the relief of symptoms of PAR in 110 countries outside of the US. The sponsor's PAR program for loratadine 10-mg tablets consisted of six multicenter, randomized, placebo controlled, parallel group studies ranging from 28 days to 3 months in duration. Three of the studies were pooled and considered to be a single study for analysis. There was one multicenter, randomized, active controlled, parallel group study of 6 months duration. Each of the studies included adults and adolescents ≥11 years of age. Enrollment ranged from 140 to 453 patients. Evaluation of efficacy was based primarily on assessments of total and individual symptoms of PAR. Total symptom scores included both nasal and non-nasal symptoms of PAR.

For the 28-day study, the difference at endpoint between loratadine and placebo in change from baseline in percent improvement in the total symptom score was 32% and 17% at first evaluation and was statistically significant at both time points ($p < 0.05$). In the three remaining placebo controlled studies, differences between loratadine and placebo in change from baseline in percent improvement in total symptom score ranged from 0% to 12% at endpoint and –4% to 8% at first evaluation. None of these differences were statistically significant. Two of the three remaining placebo controlled studies numerically favored loratadine over placebo. One study showed no difference between loratadine 10 mg and placebo. Each of these studies had large improvements from baseline in the placebo group, which obscured evidence of efficacy in the loratadine group. The improvements from baseline the placebo groups ranged from 31% to 54%. The remaining active controlled study showed no difference between loratadine 10-mg QD and clemastine 1-mg BID. These data were sufficient to form the basis for approval for the PAR indication in countries outside the US [Volume 2, 8.G., pages 10-12].

Reviewer comment:
The large improvements in the placebo groups interfered with the demonstration of efficacy in three of the four pivotal placebo controlled PAR studies. Loratadine was favored numerically in two of the remaining three studies. These data provide evidence that the drug is efficacious in PAR, particularly in light of clear evidence of efficacy for 10-mg loratadine in SAR, and given that the pathophysiology of PAR is similar to that of SAR. The OTC indication is for allergic rhinitis (hay fever) alone, and does not distinguish between seasonal and perennial allergic rhinitis.

6.3.1.3. Efficacy, CIU

The sponsor conducted seven randomized, double blind, parallel group, clinical studies of the efficacy of loratadine 10-mg tablets in treatment of symptoms of CIU. Each of the studies included adults and adolescents ≥14 years of age. Enrollment ranged from 45 to 203 patients. Evaluation of efficacy was based on assessments in severity scores for individual signs and symptoms of CIU. Differences at endpoint between loratadine and

placebo in the change from baseline in percent improvement in symptom scores ranged from 9% to 38% in each of the studies and were statistically significant ($p < 0.05$) for four of five studies. Differences at Day 7 between loratadine and placebo in change from baseline in percent improvement in symptom scores ranged from 12% to 48% and were statistically significant ($p < 0.05$) for all seven studies. Based on the results of these studies, loratadine 10-mg tablets were approved in September 1995 for marketing in the US for relief of symptoms of CIU in adults and adolescents ≥12 years of age [Volume 2, 8.C., pages 13-16].

6.3.2. Efficacy data from clinical studies, loratadine syrup

Efficacy data for approval of loratadine syrup (NDA 20-641) in children 6 to <12 years of age consisted of 11 randomized, double blind, parallel group studies with loratadine syrup (seven studies) or suspension (four studies). Seven of these studies were conducted in subjects with SAR and four were conducted in subjects with chronic skin disorders. Six of the 11 studies were placebo controlled. Treatment duration was seven days in two studies and 14 days in nine studies. The sponsor states that the effectiveness of loratadine was numerically superior to placebo in the placebo controlled studies and comparable to active comparator in the active controlled studies. These studies formed the basis for approval of loratadine syrup in children 6 to <12 years of age at a daily dose of 10 mg in October 1996.

Two additional studies of the safety of loratadine syrup in children <6 years of age have been performed. One study was conducted in children 2 to <6 years of age with SAR or CIU. The other study was in children 6 months to 2 years of age with a personal or strong family history of allergies. The studies of children age 2 to <6 years of age support the approval of loratadine as a prescription product in children down to the age of 2 years. Loratadine syrup was approved for the treatment of SAR and CIU in children 2 to <6 years of age in December 2000. This approval was based on an extrapolation of the demonstrated efficacy of loratadine in adults with these conditions and the consideration that the disease course, pathophysiology, and the drug's effect is substantially similar in children and adults. The approved daily dose of loratadine for children 2 to <6 years of age is 5 mg. The supplement submitted to support an indication for children between the ages of 6 months and 2 years was not approved, and language was added to the label stating its use was not recommended in this age group. [Volume 2, 8.C., pages 16-18].

6.3.3. Efficacy data from clinical studies, RediTabs

The sponsor conducted three double blind, randomized, active and placebo controlled, parallel group studies in subjects with SAR to support the loratadine RediTab application (NDA 20-704). Treatment duration was two weeks. Subjects were ≥12 years of age. Enrollment in these studies ranged from 319 to 530 patients. The total symptom score was the primary efficacy endpoint. Both nasal and non-nasal symptoms were included in the total symptom score. One of the three studies had statistically significant treatment by investigator interactions, which made interpretation impossible. The difference between loratadine and placebo at endpoint in change from baseline in percent improvement in total symptom score was 5% in one study and 10% in the other. The 10% difference was statistically significant ($p < 0.05$). Differences between loratadine and placebo in change

from baseline in percent improvement in total symptom score at Day 3 were 7% in one study and 8% in the other. Both of these values were statistically significant ($p < 0.05$). The magnitude of change from baseline for loratadine 10-mg RediTabs was similar to that noted in the loratadine 10-mg tablet active control arms of these studies. Loratadine RediTabs were approved in the US for treatment of symptoms of SAR in December 1996 [Volume 2, 8.G., pages 18-20].

6.3.4. Efficacy data, loratadine/PSE 12-hour formulation

The application for the loratadine/PSE 12-hour formulation (NDA 19-670) was supported by the results of five studies in subjects ≥12 years of age with SAR. These were randomized, double blind, placebo controlled, parallel group studies of loratadine 5 mg/PSE 120 mg given twice daily. Four of the five studies were also active controlled. Enrollment in these studies ranged from 264 to 442 patients. Four of the studies had a duration of 14 days and one had a duration of 28 days. The total and individual symptom scores were the primary efficacy assessments. Nasal and non-nasal symptoms were included in the total symptom score. In all studies, the loratadine 5 mg/PSE 120 mg combination was more effective than placebo at Day 4 and at endpoint. The difference between loratadine 5mg/PSE 120 mg and loratadine 5 mg in change from baseline in percent improvement in total symptom score at endpoint ranged from 7% to 19%. The difference between loratadine 5mg/PSE 120 mg and loratadine 5 mg in change from baseline in percent improvement in total symptom score at Day 4 ranged from 2% to 20%. The combination product was superior to the individual components alone in reducing total symptoms of SAR. In three of the four studies, the loratadine 5 mg/PSE 120 mg combination product was statistically significantly more effective in reducing nasal stuffiness than placebo and was more significantly more effective than loratadine alone. The loratadine 5 mg/PSE 120 mg tablets were approved in the US in November 1994 for the treatment of SAR in adults and adolescents ≥12 years of age [Volume 2, 8.G., pages 23-26].

6.3.5. Efficacy data, loratadine/PSE 24-hour formulation

The application for the loratadine/PSE 24-hour formulation (NDA 20-470) was supported by the results of three studies in subjects ≥12 years of age with SAR. These were randomized, double blind, active and placebo controlled, parallel group studies of loratadine 10 mg/PSE 240 mg given QD. Two of these studies were active controlled. Enrollment in these studies ranged from 466 to 874 patients. The duration of these studies was 14 days. Two of these studies had total symptom scores as the primary efficacy assessment. One of these studies evaluated only nasal stuffiness.

In one study, the difference between the combination product and loratadine alone in the total symptom score was 4% at Day 4 and 7% at endpoint. The difference at endpoint was statistically significant. In another study, the difference between the combination product and loratadine alone in the end-of-dosing interval nasal stuffiness was 4% at Day 4 and 5% at endpoint. The difference at endpoint was statistically significant. The difference between the combination product and placebo in the end-of-dosing interval nasal stuffiness was 13% at Day 2 and 6% at endpoint. Both of these differences were statistically significant. The results showed that the loratadine 10 mg/PSE 240 mg

product was more effective than placebo and more effective than its components in relieving the signs and symptoms of SAR, including nasal stuffiness. The loratadine 10 mg/PSE 240 mg combination was approved for marketing in the US for treatment of symptoms of SAR in adults and adolescents ≥12 years of age in August 1996 [Volume 2, 8.G., pages 26-29].

6.4. Efficacy in special populations

The sponsor submitted a summary of efficacy of loratadine by age, gender, and race [NDA 19-658, SE6-018 BM, 9/16/02]. This summary is reviewed below. Efficacy in the pediatric population was discussed in the preceding section of this document.

There were too few patients ≥65 years of age in the controlled trials of loratadine for AR and CIU to assess subgroup efficacy. The sponsor performed uncontrolled studies of loratadine in SAR and PAR that showed loratadine tablets to be similarly effective in patients <65 years and ≥65 years of age. Regarding the CIU diagnosis, the sponsor notes that the disease process is similar in patients <65 years and ≥65 years of age and that the response to loratadine is expected to be similar in these groups. The approval of loratadine syrup in children was based on pharmacokinetic comparability of doses in children and adults and an extrapolation of the demonstrated efficacy of loratadine in adults with these conditions and the consideration that the disease course, pathophysiology, and the drug's effect is substantially similar in children and adults [NDA 19-658, SE6-018 BM, 9/16/02, pages 1-2].

Reviewer comment:
It would also be expected the RediTabs and the regular tablets would be similarly effective for the AR and CIU diagnoses in consumers ≥65 years of age. It is likely that loratadine is similarly effective in children under of 12 years of age as in consumers 12 years of age and older.

There were no consistent differences in the changes from baseline in symptom scores between patients of Caucasian and non-Caucasian races or between males and females in the pivotal clinical trials of loratadine tablets and RediTabs for the AR diagnosis or for loratadine tablets for the CIU diagnosis [NDA 19-658, SE6-018 BM, 9/16/02, pages 1-2].

6.5. Review of the medical literature, efficacy of loratadine

The sponsor conducted a comprehensive literature search to identify publications addressing the efficacy of loratadine in the treatment of SAR, PAR, CIU, and of the loratadine/PSE combination in the treatment of symptoms of SAR. The sponsor conducted the searches with their own in-house database (——— and several commercial databases (———————). Searches were restricted to articles reporting results of placebo controlled trials. The sponsor excluded review articles and abstracts [Volume 8.G., pages 29-33]. Abstracts of articles identified in the searches were included in the application.

There were more articles identified addressing the SAR indication than for the PAR and CIU indications. Studies identified in this search included natural exposure efficacy

studies for AR, efficacy studies for CIU, as well as EEU (Environmental Exposure Unit) and nasal challenge studies, skin test suppression studies. Many studies had active control arms. Active controls in these studies included prescription antihistamines such as cetirizine, fexofenadine, and astemizole, OTC antihistamines such as chlorpheniramine, brompheniramine, clemastine, and diphenhydramine, as well as nasal corticosteroids such as beclomethasone, fluticasone, and triamcinolone [Volume 8.G., pages 33-262].

This reviewer examined the information submitted by the sponsor and agrees with the sponsor that the results of these studies are supportive of the efficacy of loratadine. The studies support the efficacy of loratadine in the treatment of the symptoms of SAR, PAR, and CIU. The results of the studies also support the efficacy of the loratadine/PSE combination in the treatment of the symptoms of SAR. Loratadine was consistently more effective than placebo. In active controlled studies, nasal corticosteroids showed greater efficacy in the treatment of symptoms of AR than loratadine. In light of the proposed OTC switch, it is important to note that in active controlled studies, loratadine demonstrated efficacy similar to that of other antihistamines, both prescription and OTC.

6.6. Literature review, use of antihistamines for acute and chronic urticaria

A Nonprescription Drug Advisory Committee (NDAC) meeting was held on 4/22/02 to discuss CIU as an OTC indication. Selected members of the Pulmonary-Allergy Drugs Advisory Committee also participated in this meeting. The consensus of the Advisory Committee was that urticaria was an appropriate OTC indication and that the urticaria indication should be broad and should not be restricted to the specific diagnosis of CIU. The committee's opinion was that the appropriate term to use in OTC labeling would be "hives."

The original application addressed the CIU indication. In support of the general "hives" indication, the sponsor submitted a literature review consisting of a compilation of 24 articles on the use of antihistamines for acute and chronic urticaria [N19-658 SE6-018, N20-704 SE6-008, and N20-641 SE6-009, Correspondence, 5/23/02]. The search engine or search strategy was not noted. Most of the articles were review articles; only a few were primary references. The sponsor concluded that there is substantial documentation of the recognized efficacy of antihistamines in the treatment of symptoms of chronic and acute urticaria.

This reviewer examined these articles. The articles uniformly suggest that H_1 antihistamines are effective for all types of urticaria. However, the authors of these articles also agree that there little actual evidence from clinical studies to support this opinion. Data needed to support a "hives" indication was discussed at two internal meetings between the Division of Pulmonary and Allergy Drug Products (DPADP) and the Division of Over-the-Counter Drug Products (DOTCDP) on 6/7/02 and 7/19/02. Dr. Temple, the Director of the Office of Medical Policy, attended the first meeting. At these meetings, there was agreement that there was little actual clinical data supporting the use of antihistamines in general, or loratadine in specific, for the treatment of acute urticaria. However, it was pointed out that both acute urticaria and chronic urticaria are associated

with the release of histamine, that antihistamines are currently used for treatment of acute urticaria, and that their use for this condition is accepted as the standard of care. Accordingly, it was determined that no additional clinical studies would be required, but that additional label comprehension studies would be necessary to support the proposed "hives" indication. In this reviewer's opinion, and in this context, the sponsor's review of the literature provides some additional support for and no evidence against the efficacy of loratadine in the treatment of urticaria.

7. INTEGRATED REVIEW OF SAFETY

Integrated review of safety data supporting these applications follows below.

7.1. Summary and conclusions

At a joint meeting on 5/11/01, the Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products determined that loratadine has a safety profile acceptable for OTC marketing [http://www.fda.gov/ohrms/dockets/ac/cder01.htm, Pulmonary-Allergy Drugs Advisory Committee]. The focus of this section of this document focuses on the case that the sponsor has made for the safety of loratadine and the loratadine/PSE combination products for the OTC market.

The sponsor provided an integrated review of safety that included information from the CDER OTC Switch Review Team, safety data from clinical trials and postmarketing databases, bioequivalence studies, and review of the published medical literature. The CDER OTC Switch Review Team concluded that there were no strong links between use of loratadine and significant serious safety concerns. Adverse events in clinical trials of loratadine tablets, RediTabs, and syrup were similar in character and frequency to that of placebo. AEs for the loratadine/PSE combination products were comparable to those of loratadine, with the exception of those expected from PSE alone, including insomnia, dry mouth, nervousness, and dizziness. Postmarketing patient exposure to all formulations of loratadine is extensive. In general, the types of AEs that were noted in the postmarketing safety database for loratadine are similar to those noted in clinical trials, such as somnolence, headache, dizziness, and nausea. Reports of dysphagia and esophageal obstruction for loratadine 10 mg/PSE 240 mg (Claritin D-24 Hour tablets) were related to the size and coating of the tablet. There have not been any such serious advents reported for the new formulation since the size and coating were changed in December 1998. Postmarketing safety data from Canada and the United Kingdom, where loratadine is available as a non-prescription product, reveal no safety signal. The safety database for children from 2 to 6 years of age for the allergic rhinitis indication does not reveal evidence for a safety signal.

A higher proportion of SAEs due to anaphylaxis occurred in patients taking loratadine for urticaria than for allergic rhinitis. Differences in the proportion of SAE reports due to anaphylaxis may represent a safety signal, and there may be a higher safety risk for anaphylaxis in patients who are taking loratadine for urticaria than for other indications. Swedish postmarketing data reveal a cluster of 15 cases of hypospadias associated with loratadine use in pregnancy. The association of hypospadias with loratadine use has been noted only in Sweden. Most of the cases in the Swedish Medical Birth Registry (SMBR)

database were mild, and the incidence of hypospadias among exposed cases in this database is low. Is unclear that this observation can be generalized to the US population. The potential safety benefits of drug, including lack of sedation, outweigh the potential for this weak signal. The sponsor should be asked to agree to provide updates for 3 years on the possible association of hypospadias with loratadine use in pregnancy. These updates should include follow-up on the Swedish data as well as postmarketing data from other countries.

In summary, the sponsor's integrated review of safety supports the proposed indication of their products. In this reviewer's opinion, the possible signals are not a barrier to the approvability of loratadine for OTC use, but may need to be addressed in labeling. The sponsor should address anaphylaxis in their proposed labeling for the hives indication and provide evidence supporting their labeling in label comprehension studies. Input from Division of Over-the-Counter Drug Products will be important in drafting any precautions for product labeling.

7.2. Content

The sponsor included the following information in their Integrated Summary of Safety:

- Summary of CDER OTC Switch Review Team
- Safety data from controlled clinical trials of loratadine
- Literature review covering the period from completion of the CDER Switch Review Team's review (April 2000) until 9/3/02
- Worldwide postmarketing safety data
- Postmarketing safety data for OTC loratadine use from Canada and the United Kingdom

The sponsor also submitted safety data regarding the following:

- Pediatric subjects
- Geriatric subjects
- Gender
- Race
- Pregnancy
- Drug-drug interactions
- Drug-disease interactions
- Overdose and abuse potential

The sponsor also submitted a safety update covering the period since the cutoff for the submission of the NDA, from 12/17/02 to 9/6/02.

These data were reviewed in preparation of this overview of safety.

7.3. Summary of CDER OTC Switch Review Team

The sponsor included information from the CDER OTC Switch Review Team to support the safety of the OTC use of loratadine for the proposed indications [Volume 3, 8.H., pages 16-19]. The CDER OTC Switch Review Team conducted a review of worldwide safety information to determine whether there were safety concerns that would prevent