the use of loratadine, cetirizine, and fexofenadine in the OTC setting. Results of this review were presented at a joint meeting of the Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products on 5/11/01. The Advisory Committee 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 sponsor points out that the CDER Switch Review Team's findings support the OTC use of loratadine. The review team noted that a review of all available safety data for loratadine failed to identify conclusive evidence of a causal relationship between use of loratadine and SAEs. Although potential safety signals were noted for ventricular arrhythmias and hepatic failure, the data were inconclusive and suggested that that these events are extremely unusual, if causally related to loratadine. The team noted a potential association between loratadine use and seizures, which was consistent with information in the package insert and was consistent with an antihistamine class effect. The team pointed out that the less sedating antihistamines may offer safety advantages over the currently available OTC antihistamines. The team concluded that there were no strong links between use of loratadine and significant serious safety concerns. This information provides support for the safety of loratadine in the OTC setting for the proposed indications.

7.4. Safety data from controlled clinical trials of loratadine

Adverse events in clinical trials of loratadine tablets, RediTabs, and syrup were similar in character and frequency to that of the placebo. Somnolence and fatigue were reported more frequently in subjects treated with clemastine than with loratadine or 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. The small number of adverse events in the loratadine groups in these studies of children from ages 6 months to <6 years were similar to those noted in the placebo groups and did not reveal a signal specific for this population. Laboratory studies in clinical trials provided no evidence of a safety signal for these products.

7.4.1. Exposure, clinical trials

Over 100,000 subjects have been exposed to loratadine in clinical trials since 1984. Of these subjects, 90,000 are subjects ≥12 years of age who were treated with loratadine 10-mg tablets in controlled and uncontrolled clinical trials. There have been approximately 500 subjects who have received loratadine RediTabs in clinical trials. In clinical trials of loratadine in children, there have been approximately 300 subjects ages 6 to <12 years who received loratadine 10 mg once daily, 231 subjects ages 2 to <6 years who received loratadine 5 mg once daily, and 111 subjects 6 months to <2 years of age who received loratadine 2.5 mg once daily. The duration of clinical trials in children ranged from 8 to 15 days [Volume 3, 8.H., page 20; Dr. Susan Johnson, Medical Officer review, NDA 20-641 SE5-007, 9/21/00].

Over 12,000 subjects ≥12 years of age have been treated with formulations of loratadine/PSE in controlled and uncontrolled clinical trials. There have been approximately 10,000 subjects who received the loratadine/PSE 12 hour formulation twice daily for up to one month in clinical trials. There have been approximately 600

subjects who received the loratadine/PSE 24-hour formulation once daily for up to two weeks in clinical trials.

7.4.2. Adverse events, clinical trials

There were 1926 subjects ≥12 years who received loratadine 10 mg once daily in placebo controlled trials. Headache (12% loratadine, 11% placebo), somnolence (8% loratadine, 6% placebo), and fatigue (4% loratadine, 3% placebo) were the most frequently reported AEs for loratadine-treated subjects in these studies. The profile and frequencies of AEs for loratadine and placebo were similar. Somnolence and fatigue were reported more frequently in subjects treated with clemastine than with loratadine or placebo [Volume 3, 8.H., pages 24-25].

There were 495 subjects 12 to 72 years of age that received loratadine RediTabs, 10 mg once daily in clinical trials. Headache (25% RediTabs, 29% placebo), pharyngitis (6% RediTabs, 6% placebo), and somnolence (5% RediTabs, 3% placebo) were the most frequent AEs noted in these studies. The profile and frequencies of AEs for loratadine RediTabs, loratadine tablets, and placebo were similar [Volume 3, 8.H., page 26-27].

There were 1023 subjects who received the loratadine 5 mg/PSE 120 mg combination (D-12) in placebo controlled clinical trials. The most frequently reported AEs in the D-12 group were headache, insomnia, dry mouth, somnolence, and nervousness. AEs that were more frequently reported for D-12 and PSE than for placebo included insomnia (15% D-12, 18% PSE, 3% placebo), dry mouth (14% D-12, 9% PSE, 3% placebo), nervousness (5% D-12, 7% PSE, 2% placebo), and dizziness (4% D-12, 5% PSE, 2% placebo). AEs were comparable to those of loratadine, with the exception of those expected from PSE alone, including insomnia, dry mouth, nervousness, and dizziness [Volume 3, 8.H., pages 26-27].

There were 604 subjects who received the loratadine 10 mg/PSE 240 mg combination (D-24) in placebo controlled clinical trials. The most frequent AEs noted in the D-24 group were headache, dry mouth, and somnolence. AEs that were reported more frequently for D-24 and PSE than for placebo included dry mouth (8% D-24, 7% PSE, 2% placebo), somnolence (6% D-24, 5% PSE, 4% placebo), insomnia (5% D-24, 9% PSE, 1% placebo), dizziness (4% D-24, 3% PSE, 2% placebo), and nervousness (3% D-24, 4% PSE, 1% placebo). AEs were comparable to those of loratadine, with the exception of those expected from PSE alone, including insomnia, dry mouth, nervousness, and dizziness [Volume 2, 8.H, pages 27-28].

There were 276 subjects who were treated with loratadine 10-mg tablets once daily in placebo controlled clinical trials of loratadine for the treatment of CIU. The most frequent AEs reported by subjects taking loratadine occurred at similar frequency to those reported by subjects taking placebo. These AEs included headache (15% loratadine, 12% placebo), somnolence (4% loratadine, 3% placebo), nausea (3% loratadine, 3% placebo), and fatigue (2% loratadine, 3% placebo). Somnolence was noted most frequently with hydroxyzine (47%), followed by clemastine (6%), loratadine (4%), placebo (3%), and terfenadine (<1%) [Volume 3, 8.H., pages 28-29].

A total of 188 children 6 to <12 years of age were treated with loratadine syrup 10 mg daily in placebo controlled trials. Adverse events were similar in character and frequency to those noted in the adult population, and were similar to those noted in the placebo group. There were 60 children 2 to <6 years of age were treated with loratadine syrup 5 mg daily in a single placebo controlled trial. There were 111 children 6 months to <2 years of age were treated with loratadine syrup 5 mg daily in a single placebo controlled trial. The small number of adverse events in the loratadine groups in these studies were similar to those noted in the placebo groups, and were not different than those noted in children 6 to <12 years of age [Volume 3, 8.H., pages 29-32].

7.4.3. Serious adverse events, clinical trials

The sponsor reviewed included SAEs occurring in clinical trials in the same database that included postmarketing AEs. SAEs are reviewed in the section of this document that examines the postmarketing safety database.

7.4.4. Laboratory data, clinical trials

No clinically meaningful changes in median laboratory values or trends of changes were noted in subjects treated with loratadine in clinical trials. There were few individual subjects with sporadic laboratory values outside of the normal ranges that were of clinical significance in clinical trials [Volume 3, 8.H., page 34].

7.5. Literature review of safety

The CDER OTC Switch Review Team conducted a review of worldwide safety information to determine whether there were safety concerns that would prevent the use of loratadine, cetirizine, and fexofenadine in the OTC setting. This review was completed in April 2000, and included a literature review of safety. The findings of the team are summarized in an earlier section of this document "Summary of CDER OTC Switch Review Team." The sponsor submitted a literature review regarding the safety of loratadine and loratadine/PSE covering the period from completion of the CDER OTC Switch Review Team's review in April 2000 until 9/3/02. The sponsor used their in-house database, [redacted] to perform the search. The sponsor identified three publications that were of note. These are summarized below.

There was one case report of a 43-year old woman who was reported as having torsades des pointes 90 minutes after taking a single 10-mg loratadine tablet.[2] She had a prior history of a transient episode of QT prolongation and non-sustained ventricular tachycardia that occurred shortly after the insertion of an automatic implantable defibrillator. The defibrillator was inserted prophylactically because she had a history of mitral valve prolapse and a sister who died suddenly, presumably as a result of a cardiac arrhythmia. The sponsor disputes the interpretation of the ECG, and concludes that the woman's episode of non-sustained ventricular tachycardia was not related to the loratadine.

[2] Kuchar DL, Walker BD, and Thornburn CW. Med J Aust 2002; 176(9):429-430.

The second article was a case report of a 6-year old child who ingested 300 mg of loratadine who had only minor elevations of blood pressure and heart rate and who was managed with supportive care.[3] The third article described the results of a clinical pharmacology study, in which a prolongation of the QTc interval in subjects taking loratadine and nefazodone.[4] The sponsor cites methodologic flaws in the study and disputes the conclusions. The sponsor concludes that there was no new safety information revealed in publications identified in this search.

Reviewer comments:
Predisposition to increased QTc and ventricular tachycardia is likely to be a significant confounder for the woman who had cardiac arrhythmia. It is unclear why QTc prolongation was noted in the clinical study where none was noted in other drug interaction studies where loratadine and DCL levels were much higher. It is important to note that the results of this study have been questioned by one of its co-authors.[5] The weight of the evidence from the other drug interaction and cardiac safety studies is that elevated loratadine and DCL levels do not produce QTc and QT interval prolongation. The literature review does not provide evidence for any new safety signal.

7.6. Worldwide postmarketing safety data

Patient exposure to all formulations of loratadine is extensive, and estimated to be [redacted] treatment days since introduction of the product in February 1988. In general, the types of AEs that were noted in the postmarketing safety database are similar to those noted in clinical trials, such as somnolence, headache, dizziness, and nausea. Palpitation, tachycardia, and rash with loratadine were noted in this database, but were not prominent AEs noted in the clinical trials. Insomnia, nervousness, tachycardia, palpitations, and dry mouth were noted for the loratadine/PSE combinations. These are AEs that would be expected based on the PSE content of the combinations. 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.

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. There appears to be no conclusive evidence of a causal relationship between use of loratadine and cardiovascular and hepatic SAEs, and rare SAEs for seizures have previously been noted and are likely to represent a class effect of antihistamines. The worldwide postmarketing safety database supports the proposed OTC marketing of the loratadine products. The sponsor should address anaphylaxis in their proposed labeling for the hives indication and provide evidence supporting their labeling in label comprehension studies.

---

[3] Cobb DB, Watson MA, Fernandez MC. Vet Human Toxicol 2001; 43(3):163-164.
[4] Abernethy DR, Barbey JT, Franc J, et. al. Clin Pharmcol Ther. 2001 69(3):96-103.
[5] Barbey JT. Clin Pharmacol Ther 2002; 71:403.

7.6.1. Exposure, worldwide postmarketing safety data

Patient exposure to all formulations of loratadine is estimated to be ——— treatment days since introduction of the product in February 1988 [Volume 3, 8.H., page 39].

7.6.2. Spontaneous adverse events, postmarketing safety data

As of 12/17/01, there were 10,852 spontaneous AE reports in the sponsor's Postmarketing Safety Surveillance (PMSS) safety database. These included 8371 spontaneous AE reports for single ingredient loratadine formulations, and 2481 reports for loratadine/PSE formulations [Volume 3, 8.H., page 40].

The most frequent AEs in the sponsor's worldwide postmarketing safety database are summarized below in Table 7.6.1. In general, the types of AEs that were noted in the postmarketing safety database are similar to those noted in clinical trials, such as somnolence, headache, dizziness, and nausea. Palpitation, tachycardia, and rash with loratadine were noted in this database, but were not prominent AEs noted in the clinical trials. Insomnia, nervousness, tachycardia, palpitations, and dry mouth were noted for the loratadine/PSE combinations, and are AEs that would be expected based on the PSE content of the combinations [Volume 3, 8.H., page 41].

The loratadine 10 mg/PSE 240 mg combination was associated with many reports of dysphagia, and esophageal obstruction shortly after its introduction to the market in 1996. The problem was thought to be related to the size and coating of the tablet. The size and coating were changed in December 1998 and there have not been any serious advents reported for the new formulation [Volume 3, 8.H., page 40].

The sponsor examined the types and relative frequencies of AEs by indication and in the pediatric population. The types and relative frequencies of AEs for loratadine and the loratadine/PSE combinations were similar to those noted for all spontaneous AEs [Volume 3, 8.H., pages 44-45].

There was slightly higher rate of dyspepsia in patients treated with loratadine for CIU (4%) than for allergic rhinitis (1%) and for all spontaneous AEs (2%). Increased hepatic enzymes were noted in patients treated with loratadine for CIU (3%) compared with all spontaneous AEs (1%). The sponsor states that most had confounding factors that prevent a causal association with loratadine [Volume 3, 8.H., pages 41-47].

Table 7.6.1. Most frequent spontaneous AEs for loratadine, D-12, and D-24 for any indication [Volume 3, 8.H., page 41].

Loratadine[1] N = 8371			D-12[2] N = 1649			D-24[3] N = 832		
Adverse event	**Number[4]**	**%[5]**	**Adverse event**	**Number**	**%**	**Adverse event**	**Number**	**%**
Therapeutic response decreased	1477	18	Insomnia	267	16	Insomnia	143	17
Somnolence	452	5	Therapeutic response decreased	199	12	Therapeutic response decreased	142	17
Headache	445	5	Palpitation	132	8	Dysphagia	62	7
Dizziness	388	5	Dizziness	105	6	Palpitation	62	7
Palpitation	357	4	Nervousness	97	6	Nervousness	52	6

Loratadine[1] N = 8371			D-12[2] N = 1649			D-24[3] N = 832		
Nausea	283	3	Somnolence	93	6	Dizziness	49	6
Tachycardia	250	3	Tachycardia	80	5	Headache	49	6
Fatigue	237	3	Headache	75	5	Esophageal obstruction	44	5
Rash	236	3	Nausea	75	5	Nausea	35	4
Insomnia	195	2	Mouth dry	65	4	Tachycardia	30	4

[1] Includes loratadine 10-mg tablets, loratadine 10-mg RediTabs, and loratadine syrup 1mg/mL
[2] Loratadine 5 mg/PSE 120 mg tablets
[3] Loratadine 10 mg/PSE 240 mg tablets
[4] N represents number of unique patients with AE reports.
[5] % represents number of individual AEs/N X 100

Reviewer comments:
The significance of palpitation and tachycardia AEs in patients treated with single ingredient loratadine products is unclear. The frequency of elevated hepatic enzymes was fairly similar in CIU patients and in all patients reporting AEs. The CDER OTC Switch Review Team, which included members of CDER's Office of Drug Safety, performed a thorough review of all available safety information and did not identify any conclusive evidence of a causal relationship between use of loratadine and SAEs. The Review Team also noted that the reporting rate for hepatotoxicity with loratadine was lower than the background rate, but that a potential safety signal could not be ruled out. The team concluded that there were not strong links between the use of loratadine and any significant serious safety concerns. It is possible that the elevated hepatic enzyme AEs may be due to confounding factors, and not loratadine.

This reviewer checked the AERS database for reports of esophageal obstruction and dysphagia occurring after the reformulation of the product in December 1998. There was a single report of esophageal obstruction reported on 5/3/99 that occurred on 4/7/00 (— #325692). It was not known if the tablet was the initial or revised formulation. There were no other reports in the AERS of similar events occurring since January 1999.

7.6.3. Serious adverse events, postmarketing safety data

There were 1041 SAE reports in the sponsor's database for single ingredient loratadine products and 293 SAE reports for the loratadine/PSE combination products. SAEs for cardiovascular, hepatic, CNS, and anaphylaxis are reviewed separately in a later section of this document.

7.6.3.1. Overall SAEs, postmarketing data

The most common SAE for loratadine was "no adverse reaction" which were generally associated with cases of overdose in which no untoward effects were observed. Prior to 2/1/98, any report of overdose was considered to be serious, regardless of the presence or absence of adverse effects. The most common SAE for loratadine 5 mg/PSE 120 mg was dyspnea. SAEs are summarized in Table 7.6.2. SAEs due to dyspnea were also noted for loratadine single ingredient products. The sponsor reported that dyspnea appeared to be related to the patient's underlying condition, allergic reaction, or exacerbation of underlying conditions. Most of the SAEs for loratadine 10 mg/PSE 240 mg (D-24) were associated with the approximately 70 cases of esophageal obstruction. These included dysphagia, dyspnea, esophagitis, vomiting, and throat obstruction. Insomnia, tachycardia,

hypertension, and anxiety in patients taking D-12 and D-24 would be likely to be due to the PSE component of the combination. The sponsor states that a definite causal attribution to loratadine or loratadine/PSE was unclear in most cases [Volume 3, 8.H., pages 48-49].

Table 7.6.2. Most frequent SAEs for loratadine, D-12, and D-24 for any indication [Volume 3, 8.H., page 48].

Loratadine[1] N = 1041			D-12[2] N = 154			D-24[3] N = 139		
Serious adverse event	**Number[4]**	**%[5]**	**Serious adverse event**	**Number**	**%**	**Serious adverse event**	**Number**	**%**
No adverse reaction	72	7	Dyspnea	16	10	Esophageal obstruction	44	32
Tachycardia	69	7	Tachycardia	15	10	Dysphagia	39	28
Syncope	64	6	Dizziness	13	8	Throat obstruction	23	17
Convulsions	62	6	Headache	13	8	Dyspnea	16	12
Dizziness	61	6	No adverse reaction	13	8	Convulsions	9	6
Dyspnea	57	5	Hypertension	11	7	Esophagitis	8	6
Palpitation	52	5	Drug interaction	10	6	Palpitation	7	5
Drug interaction	47	5	Nausea	10	6	Vomiting	7	5
Nausea	46	4	Palpitation	10	6	Hypertension	6	4
Somnolence	45	4	Anxiety	8	5	Insomnia	6	4

[1] Includes loratadine 10-mg tablets, loratadine 10-mg RediTabs, and loratadine syrup 1mg/mL
[2] Loratadine 5 mg/PSE 120 mg tablets
[3] Loratadine 10 mg/PSE 240 mg tablets
[4] N represents number of unique patients with SAE reports.
[5] % represents number of individual SAEs/N X 100

7.6.3.2. Anaphylaxis SAEs in postmarketing data

The sponsor summarizes SAEs occurring in patients with CIU who were treated with loratadine [Volume 3, 8.H., pages 50-51, 55-57]. The proportion of SAEs due to anaphylaxis was higher in patients taking loratadine for urticaria than in patients taking loratadine for allergic rhinitis (14%, 5/37 vs. 2%, 4/222) [Charles E. Lee, M.D., Medical Officer Reviews, 4/1/02 and 4/4/02, NDA 19-658 SE6-018 BM, 3/28/02]. The 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 consumers who are taking loratadine for urticaria than for other indications. The one case in which the patient self-medicated for a condition related to urticaria and perceived as appropriate resulted in fatality, making consumer self-selection and de-selection an important safety issue. The difference in the proportions of other SAE reports in CIU patients and allergic rhinitis patients may be due to chance and the small numbers of SAEs.

In response to an information request, the sponsor submitted copies of reports for each of the SAEs in patients with CIU [N19-658 SE6-018 BM, 3/28/02]. These reports were reviewed, and with the exception of the anaphylaxis SAEs, did not provide evidence for a safety signal [Charles E. Lee, M.D., Medical Officer Reviews, 4/1/02 and 4/4/02, NDA 19-658 SE6-018 BM, 3/28/02]. The anaphylaxis SAEs reports raise concerns about use of loratadine for the prevention or treatment of anaphylaxis and that similar events might occur more frequently if loratadine were to be aggressively marketed for the proposed OTC indication, "itching and rash due to chronic hives." Including an additional report from AERS of anaphylaxis in a patient with was noted by the Joyce Weaver, Office of Drug Safety, [PID # D020159] the proportion of SAEs due to anaphylaxis in patients

taking loratadine for urticaria is 16% (6/38) compared with 2% (4/222) for allergic rhinitis. Some of the cases of anaphylaxis were in patients attempting to treat urticaria, which may have been an early manifestation of anaphylaxis.

Reviewer comment:
The differences in the proportion of SAE reports for anaphylaxis may represent a safety signal, and there may be a higher safety risk for anaphylaxis in consumers who are taking loratadine for urticaria than for other indications. In labeling of their product for the "hives" indication, the sponsor should make the following points and provide evidence supporting their labeling in label comprehension studies [Charles E. Lee, M.D., Medical Officer Review, 6/6/02, N19-658 SE6-018, 5/23/02]. These points have been communicated to the sponsor at a meeting with DPAPD and DOTCDP on 8/2/02]:

-
-
-
-
-
-

7.6.3.3. Cardiovascular SAEs in postmarketing data

There were 315 cardiovascular SAEs in the sponsor's postmarketing database for single ingredient loratadine products and 80 for the loratadine/PSE products. Tachycardia, palpitation, atrial and ventricular tachycardia, atrial fibrillation, ventricular fibrillation, cardiac arrest were noted in the loratadine single ingredient products and in either or both of the loratadine/PSE combination products. SAEs due to hypertension represented a higher proportion of all SAEs in the D-12 (22%) and D-24 (20%) products than for single ingredient loratadine products (6%). The sponsor noted that serious arrhythmias such as ventricular tachycardia, ventricular fibrillation, and QT or QTc prolongation occurred predominantly in patients with cardiovascular disease, who were taking concomitant medications that could be associated with arrhythmia, and/or who had electrolyte abnormalities. No definite causal relationship to loratadine was evident. The sponsor

points out that loratadine may have been prescribed more frequently in patients with known cardiovascular risks because of known concerns with ventricular arrhythmias with astemizole and terfenadine, and therefore these patients may have had a higher baseline risk for such events [Volume 3, 8.H., pages 51-53].

Reviewer comment:
As noted before, the CDER OTC Switch Review Team did not identify any conclusive evidence of a causal relationship between use of loratadine and SAEs, including cardiovascular SAEs. Cardiovascular disease and other risk factors were also noted in the cases reviewed by the team. The team concluded that there were no strong links between the use of loratadine and any significant serious safety concerns. This reviewer concurs with the sponsor that during the period that astemizole and terfenadine were marketed, some of these cases may have had loratadine prescribed instead of astemizole or terfenadine because of known cardiovascular risks. These confounding factors would also have resulted in a higher background rate of such events.

7.6.3.4. Hepatic SAEs in postmarketing data

Rare hepatic SAEs have been reported with loratadine, including abnormal hepatic function, jaundice, hepatitis, and hepatic necrosis, and this information is noted in the current loratadine labeling. There are 75 hepatic SAEs in the sponsor's database for the single ingredient loratadine products and 7 for the loratadine/PSE combination products. There were 7 cases of hepatic failure, including 5 for loratadine and 1 each for D-12 and D-24. As with cardiovascular SAEs, the sponsor states that most of these cases do not appear to be related to loratadine because of confounding factors. Confounding factors included concomitant medications, recent foreign travel, pre-existing hepatic disease, and lack of temporal association with loratadine treatment [Volume 3, 8.H., pages 53-54].

Reviewer comment:
The CDER OTC Switch Review Team could not rule out the possibility that the hepatic events noted in their review were causally associated with loratadine. Importantly, however, as the sponsor points out, the team also noted that the reporting rate of hepatic failure for loratadine was lower than the calculated expected background rate. In this reviewer's opinion, given the confounding factors noted by the sponsor and the opinion of the CDER OTC Switch Review Team, these hepatic events are most likely to be related to the background rate. At this time there is no conclusive evidence of a casual relationship of hepatic events to loratadine.

7.6.3.5. Central nervous system (CNS) SAEs in postmarketing data

Seizures (coded as convulsions) were the most common serious CNS AE for loratadine single ingredient products and the D-24 combination, and the second most common SAE for the D-12 combination. Current prescription labeling for loratadine products notes that seizures have been reported rarely during their marketing [Volume 3, 8.H., pages 54-55].

Reviewer comment:
Seizure is likely to represent an AE common to the antihistamine drug class, and as the sponsor notes, the possible association of rare AEs due to seizure with loratadine has previously been noted [Volume 3, 8.H., page 18]. These events are rare and appear to be associated with other antihistamines. Considering of the potential benefits of the loratadine products due to their lack of sedation, in this reviewer's opinion, this rare association is not incompatible with OTC marketing of loratadine drug products.

7.6.3.6. Deaths in postmarketing data

There were 64 SAE reports with an outcome of death at the time of the submission of the application. Most were cardiac in nature. Cardiac SAEs have been discussed previously in this document. The sponsor also notes that this is a small number of deaths given the extensive worldwide exposure to loratadine. The sponsor notes that a causal relationship between loratadine exposure and death was not demonstrated in their analysis of these data [Volume 3, 8.H., page 57-58].

7.7. Postmarketing safety data from OTC use, Canada and the United Kingdom

The sponsor compared postmarketing safety data from Canada and the United Kingdom (UK) with that from the US. Loratadine was approved for prescription use in Canada in June 1988 and became a nonprescription product in December 1989. Loratadine became a nonprescription product in the UK in January 1993. Loratadine is a nonprescription product in Canada and the UK for both AR and allergic skin conditions. The types of AEs noted for single ingredient loratadine in the Canada and UK were similar to those noted in the US and in the overall worldwide postmarketing databases, and in general, to those noted in the clinical trials. AEs for "therapeutic response decreased" represented a higher proportion of AEs in Canada (43%) compared with the US (17%) and the UK (9%). Somnolence was noted in a higher proportion of AEs in the UK (9%) and Canada (7%) compared with the US (4%). Of the two D-12 and D-24 combination products, only the D-12 product is available as an OTC product in Canada only. As with the single ingredient product, "therapeutic response decreased" comprised a higher proportion of AEs in Canada (22%) than in the US (9%). The sponsor notes that a review of the cases of "therapeutic response decreased" did not reveal an explanation for these apparent differences. Insomnia was noted in a higher proportion of AEs in Canada (24%) compared with the US (9%). Somnolence was noted in a higher proportion of AEs in Canada (9%) compared with the US (3%). Many of the other AEs noted for the D-12 product represented events that would be expected in a product containing PSE, such as insomnia, palpitation, and nervousness [Volume 3, 8.H., pages 64-65].

Reviewer comment:
The significance of these differences between Canada, the UK, and the US is unclear. It is possible that these differences may be related to AE reporting in the OTC setting, rather than the drug itself, as the sponsor points out. These data are not inconsistent with the proposed OTC indications for the loratadine products.

7.8. Pediatric subjects

As noted in the earlier sections of this review, adverse events in placebo controlled trials of loratadine in children were similar in character and frequency to those noted in the adult population, and were similar to those noted in the placebo group [Volume 3, 8.H., pages 29-32]. Worldwide postmarketing data showed that the types and relative frequencies of AEs for loratadine and the loratadine/PSE combinations in the pediatric population were also similar to those noted for all spontaneous AEs [Volume 3, 8.H., pages 44-45].

Reviewer comment:
Claritin syrup was approved on 12/4/00 as a prescription product in the US for use in children from ≥2 to <6 years for the SAR and CIU indications. The product has been approved in the US for this population for almost two years. The safety database for the allergic rhinitis indication for loratadine does not reveal evidence for a safety signal in this population. It was not approved for use in children between 6 months and 2 years of age, however. The sponsor's submission supports the OTC use of loratadine syrup down to 2 years of age for the allergic rhinitis indication. Use of the product in children under 2 years of age is not appropriate.

7.9. Geriatric subjects

The sponsor did not conduct clinical trials specifically in geriatric subjects, and clinical studies did not include sufficient numbers of subjects ≥65 years of age to determine whether they respond differently from younger subjects. The sponsor notes that other reported clinical experience has not revealed differences in responses between the elderly and younger patients. The sponsor conducted a clinical pharmacology study that included 12 healthy subjects 66 to 78 years of age. AUC and C_{max} of loratadine and desloratadine (DCL) 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. The sponsor notes that dose selection for an elderly consumer should be cautious reflecting the greater frequency of concomitant disease in the elderly [Volume 3, 8.H., pages 33, 77].

Reviewer comment:
The sponsor conducted a two-week multicenter trial of loratadine in the treatment of SAR that examined AEs and laboratory values for patients stratified by age, <65 years versus ≥65 years. There were 2877 patients <65 years of age and 242 patients ≥65 years of age in this trial. In general, the types and incidences of AEs were similar in patients ≥65 years (3%) than in patients <65 years. Somnolence was slightly less frequent in patients ≥65 years (3%) than in patients <65 years (5%). A similar proportion of patients <65 years (65%) and ≥65 years (70%) rated loratadine as being "effective."[6] These data would indicate that geriatric consumers might not experience somnolence even though they experience higher systemic exposures. Accordingly, there is no dose adjustment in

[6] Lorber RR, Danzig MR, Ludwig G, et. al. J Allergy Clin Immunol 1994; 93(1 Part 2):163.

this group recommended in the current prescription labeling for loratadine products. The sponsor's proposed OTC labeling appropriately recommends that consumers with liver or kidney disease contact a health care provider before use, and appropriately makes no special recommendations for dosing for healthy geriatric consumers.

7.10. Gender

The sponsor provided a subgroup summary of safety by gender [NDA 19-658 SE06-018 BM, 9/16/02, page 4]. In clinical trials for AR, for loratadine tablets and RediTabs, the overall frequency of adverse events in females receiving both active drug and placebo were more common than in males. There were no clinically important differences between the active and placebo groups within subgroups. The types and frequencies of AEs were similar in males and females in the loratadine syrup clinical program for AR. In clinical trials of loratadine tablets for CIU, the overall frequency of adverse events in females receiving both active drug and placebo were more common than in males. There were no clinically important differences between the active and placebo groups within subgroups. There were no clinical trials with the RediTabs or controlled trials of the syrup for the CIU indication. It would be expected that a similar pattern of AEs in males and females would be noted for the for the hives indication with the RediTabs and syrup.

7.11. Race

The sponsor provided a subgroup summary of safety by race [NDA 19-658 SE06-018 BM, 9/16/02, page 5]. In the AR clinical trials of the tablet, RediTab, and syrup formulations of loratadine, 82-93% of patients were of Caucasian race, making meaningful comparisons difficult. The types of AEs in patients of Caucasian and non-Caucasian races were similar. In the CIU clinical trials of the tablet formulation of loratadine, 87% of patients were of Caucasian race. The types of AEs in patients of Caucasian and non-Caucasian races were similar. There were no clinical trials with the RediTabs or controlled trials of the syrup for the CIU indication. It would be expected that a similar pattern of AEs in consumers of Caucasian and non-Caucasian races would be noted for the for the hives indications with the RediTabs and syrup.

7.12. Pregnancy and lactation

The sponsor's information on loratadine use in pregnancy and lactation is discussed below.

7.12.1. Clinical studies and postmarketing data, pregnancy

The sponsor reports that there have been no loratadine studies conducted in pregnant women. Women who became pregnant during clinical trials were discontinued from study and every attempt was made to follow the pregnancies to conclusion. Any data collected was entered into the sponsor's safety database [Volume 3, pages 33].

The sponsor's current package insert notes that there was no evidence of teratogenicity in studies performed in rats and rabbits at oral doses of loratadine up to 96 mg/kg. This dose represents about 75 times the maximum recommended human dose on a mg/m^2 basis in the rat model, and about 150 times the maximum recommended human dose on a mg/m^2

basis in rabbits. The current package insert notes that studies of the loratadine/PSE combination product at the same ratio (1:24) revealed no evidence of teratogenicity in reproduction studies at oral doses up to 150 mg/kg in rats and 120 mg/kg in rabbits, 5 and 8 times the maximum recommended human daily dose on a mg/m^2 basis. Loratadine-containing products are currently labeled as Pregnancy Category B [Volume 3, 8.H., pages 33-34].

The sponsor notes that as of the cut-off date of 12/17/01, their safety database for loratadine included 169 cases of pregnancy or maternal exposure and 20 cases for loratadine/PSE products. The most common AE term noted was "maternal drug exposure," which was used to indicate exposure with no accompanying AE noted. For loratadine products, there were 8 fetal deaths, five cases of hypospadias, 6 cases of ear malformations, and 5 cases of large for gestational age. The possible association of loratadine with hypospadias is discussed in greater detail below. Except for "maternal drug exposure" and "no adverse reaction," no individual AE was reported more than once for the loratadine/PSE containing products. The sponsor points out that there have been an estimated ——— courses of treatment of loratadine over the 13 years of marketing, and that the reports of birth defects have been rare and appear to be similar to the expected background rate for such events [Volume 3, pages 62-63]. The sponsor's proposed OTC labeling instructs the breast feeding consumer to ask a health professional before using the product [Volume 1, Section 2., pages 1-40, NDA 19-658, SE6-018 BL, 8/6/02].

7.12.1.1. Hypospadias

The sponsor has been in contact with Swedish authorities since 1999 regarding a possible association of loratadine and hypospadias noted in the Swedish Medical Birth Registry (SMBR). The sponsor received an updated report of SMBR data in December 2001. The sponsor's application included information on the SMBR reports and the sponsor's analysis of the reports. Dr. McCloskey, of the Agency's Office of Drug Safety (ODS), and Dr. Anthony Scialli, an expert in teratology and evaluation of pregnancy outcome data, also examined the SMBR data.

There were 15 cases of hypospadias associated with loratadine use during pregnancy in the SMBR. The SMBR 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. Exposure to loratadine occurred outside of the critical period of genital development in many of these cases, however, and most of the cases were mild in severity. Additional evidence against a true signal includes the absence of a similar signal in other countries, including the US AERS database. Furthermore, there is no non-clinical evidence of a direct anti-androgenic effect of loratadine, a proposed mechanism for the development of hypospadias. The sponsor also provided a summary of a small case control study in Sweden that did not suggest an association of hypospadias with loratadine use in pregnancy. Dr. McCloskey of ODS concludes that the SMBR data represent a signal that hypospadias may be associated with exposure to loratadine in early pregnancy and that the signal warrants further study and observation. Dr. Scialli, the

expert teratology consultant, speculated that loratadine could cause hypospadias by a potential indirect effect in pregnancy. In his opinion, the association of hypospadias with loratadine exposure during pregnancy is not random. The EMEA (European Agency for the Evaluation of Medicinal Products) has been following this issue and has concluded that no regulatory action or major change in labeling is required at this time. The SMBR data, information provided by the sponsor, and reviews of Dr. McCloskey, Dr. Scialli, and the EMEA are reviewed in depth below.

Reviewer comment:
The association of hypospadias with loratadine use has been noted only in Sweden. Most of the cases in the SMBR 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. Dr. Sancilio, pharmacology reviewer for this Division, reviewed the sponsor's non-clinical information submitted with this application and non-clinical data on file for loratadine and desloratadine. He concludes that there is no evidence of antiandrogenic effects in offspring of female rats exposed to loratadine and DCL during the androgen-sensitive period of genital development. The potential safety benefits of drug, including lack of sedation, outweigh the potential for this possible 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 should be asked to provide periodic updates on hypospadias for 3 years, including follow-up on the Swedish data and including postmarketing data from other countries.

7.12.1.1.1. Swedish Medical Birth Registry (SMBR) data

Dr. Bengt Källén of the Tornblad Institute, completed an initial evaluation of the SMBR data in February 1999 [NDA 19-658, N-000 C, 4/26/02, Attachment 1, Attachment 5]. Practically all births in Sweden have been registered in the SMBR since 1973. The database has been computerized since July 1994. The registry is based on copies of medical documents from the antenatal care service, delivery, and pediatric examination of the newborn infant. Midwives interview pregnant women at antenatal care visits and ask what drugs had been used since becoming pregnant. The first visit at for the antenatal care service takes place at about week 10-12 of pregnancy.

Dr. Källén's initial evaluation of the data included 1020 infants exposed to loratadine in first trimester. There were 30 infants with congenital malformations. There was a suggestion of a safety signal only for hypospadias. There were 7 cases of hypospadias (including one set of twins; 6 cases if twins were counted as one case). These data indicate an incidence of 0.069% or about 7/1000 (0.059% or 6/1000 if the twins are counted as one case). The background incidence of hypospadias from the SMBR in Sweden is 0.02% to 0.027%, or about 2/1000 to 2.7/1000 (historical data). The incidence for of hypospadias in women exposed to other antihistamines (excluding loratadine) was 0.013% or about 1/1000 (concurrent data). Dr. Källén noted that the increased incidence

of hypospadias associated with loratadine was statistically significant, but acknowledges that if a causal association was present, the risk was very low, 1:150 instead of 1:500.

Dr. Källén, presented an updated report in April 1999 after there was one additional case of hypospadias associated with loratadine noted [NDA 19-658, N-000 C, 4/26/02, Attachment 5]. At this time there were 1115 infants, and 8 cases of hypospadias (7 counting the twins as one case). These data indicate an incidence of 0.072% or about 7/1000 (0.063% or 6/1000 if the twins are counted as one case). Dr. Källén noted that the exposure time data for most of the cases were not clear and that the amount used was not clear from the individual reports. He also remarked that in at least 2 cases the mother stopped use of drug before the critical period of genital development began. Although he speculated that loratadine could cause hypospadias through an anti-androgenic effect, he also notes that there were no anti-androgenic effects observed in the sponsor's non-clinical studies.

Dr. Källén provided a follow-up report in November 2001 [NDA 19-658, N-000 C, 4/26/02, Attachment 5]. As of November 2001, there were 15 cases of hypospadias (14 counting the twins as one) among 2780 exposures to loratadine during pregnancy. This represents an incidence of 0.054% or about 5/1000 (0.050%, or 5/1000 if the twins are counted as one case). Since the updated report of April 1999, there were 7 additional cases in 1760 exposures, which represents an incidence of 0.040% or 4/1000. Dr. Källén acknowledges that the cases may represent a random phenomenon, but also notes that a confounding association due to co-existent allergic disease is not likely because hypospadias was not associated with antenatal exposure to other antihistamines.

Reviewer comment:
It is not appropriate to use the incidence for all cases noted through November 2001 (5/1000) to confirm the earlier signal, because the initial cases are included in both incidences. If one examines the data from November 2001 to confirm the signal noted in the updated initial report from April 1999, one should compare the incidence from the initial report (6/1000) with the incidence for the cases occurring since the initial report (4/1000). This noted, the incidence during both of these periods is greater than the expected historical background rate of 2/1000 to 2.7/1000 in this population.

7.12.1.1.2. Schering's analysis of SMBR data

The Swedish MPA requested that the sponsor comment on the data included in Dr. Källén's report. The sponsor completed an evaluation of the SMBR data in April 1999 [NDA 19-658, N-000 C, 4/26/02, Attachment 3]. The sponsor's evaluation included a review of pharmacovigilance and nonclinical data and an analysis of the 8 cases of hypospadias in the April 1999 report.

The sponsor's review of pharmacovigilance data showed no additional cases of hypospadias associated with loratadine use. This review included the sponsor's corporate worldwide database, the [redacted] database, and information from authorities from UK, Finland, and Austria. The sponsor reviewed their existing non-clinical data on loratadine. These data included studies performed in rats, which are known to be

sensitive to anti-androgenic effects in utero. The sponsor reports that these data showed no indication of adverse effects on fetal development.

The sponsor noted that there was an unknown time and amount for many of the 8 cases in the Dr. Källén's report of April 1999. The sponsor noted that in 2 of cases, less than 3 tablets were taken, 2 cases were actually not exposed during pregnancy, and 2 cases were exposed before the critical period for genital development. In one of the cases there were only 3 tablets taken and exposure occurred before the critical period.

After the April 1999 report, Schering conducted a non-clinical study of loratadine to address the issue of hypospadias. The Swedish 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 reports that maternal body weight gain and mean pup body weight were lower at the 24 mg/kg dose, but no effects were noted at the other doses. The sponsor reports that there were no effects on male genital tract in offspring at any dose.

The sponsor provided a table summarizing each of the 15 cases of hypospadias noted in the SMBR as of 1/18/02 [NDA 19-658, N-000 C, 4/26/02, Attachment 8]. Most of the cases were mild in severity. Of these 15 cases, 10 are noted to be mild, glandular, or coronal, and 5 do not describe the severity. Over 75% to 80% of cases of hypospadias are be expected to be mild [NDA 19-658, N-000 C, 4/26/02, Attachment 5, Attachment 11].

Reviewer comment:
There does not appear to be a higher proportion of severe hypospadias among the Swedish cases. The percentage of cases with mild hypospadias in the Swedish data is similar to the percentage in spontaneously occurring cases, and provides some indirect support to the possibility that the Swedish observation may be due to chance.

The sponsor also referred to a case control study performed by Professor Anders Ekbom of the Karolinska Institute in Sweden [NDA 19-658, N-000 C, 4/26/02, Attachment 7]. This study compared confirmed hypospadias cases in [redacted] with a random sample of non-hypospadias births in the same regions from the year 2000 to November 2001. Confirmed cases of hypospadias were also compared with confirmed cases of cryptorchidism diagnosed at [redacted] from the year 2000 to January 2001. Cryptorchidism was chosen as a control because it is a similar type of birth defect that has no likely association with loratadine. The odds ratio for loratadine exposure was 0.85 for hypospadias cases compared with non-hypospadias controls, and 0.93 with hypospadias cases compared

with cryptorchidism controls. These data indicate that the hypospadias cases had no excess risk associated with loratadine exposure during pregnancy.

Reviewer comment:
Dr. Sancilio, pharmacology reviewer for the DPADP, reviewed the sponsor's non-clinical information submitted with this application and reviewed non-clinical data on file for loratadine and desloratadine (DCL). These data included studies that examined the appropriate endpoints for evaluation of the potential for hypospadias. He concluded that there is no evidence of antiandrogenic effects in offspring of female rats exposed to loratadine and DCL during the androgen-sensitive period of genital development. 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.

7.12.1.1.3. FDA Office of Drug Safety review

Dr. McCloskey of ODS completed a review of hypospadias associated with loratadine use during pregnancy [Medical Officer Review, PID# D020137, Carolyn McCloskey, M.D, 5/3/02]. In her review, she notes that the Agency's Adverse Event Reporting System (AERS) database contained 14 reports of hypospadias with loratadine as the suspect drug. One of these reports was from France. The remaining reports were from Sweden. There were 9 cases of hypospadias associated with other antihistamine exposure during or before pregnancy. There were no clinical trials of loratadine use during pregnancy. She noted that the incidence of hypospadias in the US is about 3/1000 and varies among geographic areas, from 0.9/1000 for Hispanics in California to 3.6/1000 in New York. Her review of the medical literature revealed no reports of antihistamines associated with congenital GU abnormalities and no reports of antihistamines having anti-androgenic effects. She notes that there is no other information supporting the association of hypospadias and loratadine use during pregnancy and acknowledges that this association may be due to chance, or may not be generalizable to US population. She does conclude, however, that the Swedish data represent a signal that hypospadias may be associated with exposure to loratadine during early pregnancy and that the signal warrants further study and observation.

7.12.1.1.4. Dr. Anthony Scialli's review

Dr. Anthony Scialli, an expert in teratology and evaluation of pregnancy outcome data was consulted by the Agency to comment on the possible association of hypospadias with loratadine use during pregnancy. His review is summarized below, and is appended in entirety in Section 12 of this document [Appendix 2, Dr. Anthony Scialli's review: Loratadine and hypospadias].

Dr. Scialli reviewed Dr. Källén's data, Dr. McCloskey's ODS review, and FDA pharmacology reviews of desloratadine (DCL), the active metabolite of loratadine. He did not have an opportunity to review Schering's analysis of the SMBR data. Regarding Dr. Källén's data, he noted that the proportion of exposed children with hypospadias is significantly different than an appropriate comparison population, but that the timing is not appropriate for a direct effect of loratadine on the production of hypospadias in at

least seven of the 15 cases. Dr. Scialli suggests that if loratadine is causally associated with hypospadias, it is likely to be an indirect effect, such as an effect on testicular androgen production. He noted that FDA reviews of DCL showed that administration of DCL to adult male rats was associated with a decrease in testicular and accessory sex organ weight at the high dose (24 mg/kg/day) and the intermediate dose (12 mg/kg/day). Dr Scialli concludes that the association of loratadine and hypospadias is non-random, and postulates that loratadine could cause hypospadias indirectly by an effect on the fetal testis. Dr. Scialli recommends that the sponsor investigate anti-androgenic effects in animal models and in adult men. He recommends that non-clinical studies should evaluate anogenital distance of rodents to assess the potential for loratadine or DCL to interfere with external genital differentiation.

Reviewer comment:
The studies reviewed by Dr. Sancilio, pharmacology reviewer for this Division, used the same endpoints that Dr. Scialli recommends. These studies showed no evidence of antiandrogenic effects in offspring of female rats exposed to loratadine and DCL during the androgen-sensitive period of genital development.

7.12.1.1.5. EMEA reviews

The EMEA (European Agency for the Evaluation of Medicinal Products) has also been following the association of hypospadias with loratadine use during pregnancy. A review of the data and were completed for the EMEA by the ——————, in June 2002 and by the Co-Rapporteur, ——————, in August 2002.

The Rapporteur considers the risk-benefit evaluation of loratadine and desloratadine to be favorable, and that there is not enough evidence to take any regulatory action [NDA 19-658, N-000 C, 10/16/02, Attachment 1, pages 27-30]. The Rapporteur considers the reported association to be a weak signal because of:

- Lack of biologic basis to explain the finding
- Mild severity of most cases
- Small odds ratio of 2.3
- Uncertainties in timing of exposure and number of doses taken
- Uncertainties regarding confounding factors
- Statistical analysis issues, including selection and observation bias and multiplicity
- Lack of a similar signal in other sources of data

The Co-Rapporteur notes that the SMBR data is a robust signal, and that reasonable biases cannot explain the occurrence of the signal, and concludes the signal is either chance or a true drug effect [NDA 19-658, N-000 C, 10/16/02, Attachment 2, pages 11-13]. The Co-Rapporteur notes that the preclinical data argue against a true drug effect, as does the lack of a similar signal in other databases. The Co-Rapporteur considers the public health impact to be limited, even if the signal represents a true drug effect. The Co-Rapporteur does not recommend any regulatory action or any major changes to the labeling.

Both the Rapporteur and the Co-Rapporteur agree that the sponsor should continue to monitor the SMBR signal and to investigate other methods to generate new data on the signal.

The EMEA has requested a small change in the sponsor's desloratadine (DCL) labeling. The sponsor has agreed to this change (change in italics), "Desloratadine was not teratogenic in animal studies. The safe use of the drug during pregnancy has not been established. . the use of <invented name> during pregnancy is therefore not recommended." Final labeling for DCL is still to be discussed with the CPMP (Committee for Proprietary Medicinal Products of the EMEA), and once finalized, the sponsor will make amendments to worldwide labeling for loratadine and DCL to ensure consistency. The Rapporteur finds the sponsor's change in DCL labeling to be acceptable and the Co-Rapporteur considers a similar labeling statement to be appropriate for loratadine:

[NDA 19-658, N-000 C, 10/16/02, Attachment 1, page 30, Attachment 2, page 9, Attachment 3, page 2].

The EMEA has asked the sponsor to declare its plan for monitoring the signal in the future, to provide further information possibilities of generating new data from other sources, and to consider conducting a study to generate data outside of Sweden on this possible link [NDA 19-658, N-000 C, 10/16/02, Attachment 1, page 30, Attachment 2, page 9, Attachment 3, page 2].

Reviewer comment:
The EMEA's conclusion and proposed actions are similar to those of this reviewer. There is no need for regulatory action or major changes in labeling at this time. The sponsor should provide updates on this signal in the future.

7.12.2. Clinical studies and postmarketing data, lactation

Loratadine and DCL are excreted into breast milk and achieve concentrations in breast milk similar to those of plasma. Current labeling of the prescription single ingredient loratadine products notes that loratadine and its metabolite, desloratadine, pass easily into breast milk and achieve concentrations that are equivalent to plasma levels with an AUC_{milk}/AUC_{plasma} ratio of 1.17 and 0.85 for loratadine and desloratadine (DCL), respectively. Following a single oral dose of 40 mg, a small amount of loratadine and desloratadine (DCL) was excreted into the breast milk (approximately 0.03% of 40 mg over 48 hours). The prescription label notes that decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother, and that caution should be exercised when loratadine is administered to a nursing woman [Volume 3, 8.H., page 79].

In addition to the above information, the loratadine/PSE combination product prescription labels note that pseudoephedrine is excreted into human breast milk, and that pseudoephedrine concentrations in milk are consistently higher than those in plasma. The

total amount of drug in milk as judged by the area under the curve (AUC) is 2 to 3 times greater than in plasma. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4% to 0.7%. The current product label for the prescription products advises that a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother [Volume 3, 8.H., page 98].

A search performed by this reviewer of PubMed with search terms "loratadine" and "breast milk" revealed one study of excretion of loratadine in breast milk.[7] The study was performed by the sponsor in women who took a single 40-mg dose of loratadine. The authors estimate that 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.

The sponsor's proposed OTC labeling appropriately instructs the breast feeding consumer to ask a health professional before using the product [Volume 1, Section 2., pages 1-40, NDA 19-658, SE6-018 BL, 8/6/02].

7.13. Drug-drug interactions

The sponsor has conducted studies in which loratadine has been co-administered with therapeutic doses of erythromycin, cimetidine and ketoconazole. Erythromycin, cimetidine, and ketoconazole are inhibitors of cytochrome p450 3A4, and when co-administrated with the antihistamines terfenadine and astemizole, have been associated with QT interval prolongation. The current prescription labeling for the loratadine products notes that 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.

Because of they contain PSE, the loratadine/PSE combination products are contraindicated in consumers taking monoamine oxidase (MAO) inhibitors and for 2 weeks after discontinuation of MAO inhibitors [Volume 3, 8.H., page 36].

Reviewer comment:
The OTC Switch Review Team noted the possibility of drug interaction of loratadine with warfarin and anticonvulsants. There were only a few cases, eight for warfarin, six for carbamazepine, four for phenytoin, and four for valproic acid or divalproex. Given the extensive use of the loratadine products world-wide, even considering that underreporting is likely, the small number of cases is not likely to be a signal for a significant drug interaction.

[7] Hilbert J, Radwanski E, Affrime E, et. al. J. Clin Pharmacol 1988; 28(3):234-9.

A recent study reported an increase in loratadine (38%) and DCL (12%) levels were noted when loratadine was co-administered with nefazodone. An increase in QTc was noted (7.8 msec) with the increase in plasma loratadine and DCL levels.[8] It is unclear why QTc prolongation was noted in this study when none was noted in other drug interaction studies in which loratadine and DCL levels were much higher. It is important to note that the results of this study have been questioned by one of its co-authors.[9] The weight of the evidence from the other drug interaction and cardiac safety studies is that elevated loratadine and DCL levels do not produce QTc and QT interval prolongation.

7.14. Drug-disease interactions

The current prescription labels for loratadine products include recommendations for dosage adjustment in patients with hepatic and renal disease. These recommendations are based on results of clinical pharmacology studies that were performed in patients with chronic liver disease and chronic renal impairment.

The sponsor's study of seven patients with chronic alcoholic liver disease demonstrated an increase in AUC and C_{max} of loratadine were twice that of normal subjects. No substantial change in DCL levels was noted. The mean $T_{1/2}$ for 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 current prescription label recommends a dose of one tablet (10 mg) once daily for the single ingredient products. The sponsor recommends that the loratadine/PSE products be avoided in consumers with hepatic insufficiency because hepatic insufficiency results in a greater decrease in loratadine clearance than for PSE [Volume 3, 8.H., pages 36, 77, 81, 90].

The sponsor conducted a clinical pharmacology study in 12 patients with chronic renal impairment and creatinine clearances of ≤30 mL/min. The AUC and C_{max} increased 73% for loratadine and 120% for DCL compared with normal subjects. The mean $T_{1/2}$ for loratadine (7.6 hours) and DCL (23.9 hours) were similar to values in normal subjects. The sponsor's current prescription labeling recommends a dose of one tablet every other day in patients with renal insufficiency (GFR <30 mL/min) [Volume 3, 8.H., pages 36, 77, 81, 90].

The sponsor's proposed OTC labeling instructs consumers with liver or kidney disease to ask a doctor before use of loratadine single ingredient products or loratadine/PSE combination products and indicates that a different dose may be needed [Volume 1, Section 2., pages 1-40, NDA 19-658, SE6-018 BL, 8/9/02].

Reviewer comment:
The sponsor's application notes that loratadine/PSE products should generally be avoided in consumers with hepatic insufficiency. However, it appears that this recommendation is because the fixed dose combination products could result in a lack of

[8] Abernethy DR, Barbey JT, Franc J, et. al. Clin Pharmcol Ther. 2001 69(3):96-103.
[9] Barbey JT. Clin Pharmacol Ther 2002; 71:403.

efficacy of the PSE component in consumers with hepatic disease if the dose was titrated based on the recommended dose of loratadine, and not because of possible safety concerns. The sponsor's proposed recommendations for the single ingredient loratadine products and loratadine/PSE combination products for consumers with liver or kidney disease are appropriate and acceptable for the OTC setting.

7.15. Overdose and abuse potential

The sponsor notes that there were 417 cases in their postmarketing safety database listed as overdoses of loratadine and 92 for the loratadine/PSE combinations. Approximately 40% of overdoses resulted in no adverse reaction (loratadine 38%, D-12 36%, D-24 42%). The most frequently reported AEs for overdoses were similar to the types of AEs noted in clinical trials and in the overall postmarketing database. The sponsor also examined overdoses in the pediatric population. Most pediatric patients had no adverse reaction associated with the overdose. Somnolence was noted in a higher proportion of patients <6 years of age for loratadine (15%) and D-12 (17%) with overdose than noted in overall postmarketing database (loratadine 5%, D-12 6%). There were proportionally more AEs for tachycardia in patients <6 years of age with overdose of loratadine (17%) than with the overall postmarketing database (3%) [Volume 3, 8.H., pages 58-61].

The sponsor states that there is no pharmacological basis or clinical evidence of abuse or dependency with loratadine, nor were there any cases of drug abuse or addiction in the sponsor's postmarketing database. There were also no cases of abuse, addiction, or misuse of the loratadine/PSE drug products. The current prescription labeling notes that PSE, like other CNS stimulants, has been abused, that tolerance develops with clinical use, and that depression may follow rapid withdrawal [Volume 3, 8.H., pages 67-68].

Reviewer comments:
Sedation has been noted in some patients with higher than recommended dose of loratadine. The increased rate of somnolence in pediatric patients with overdose is likely to reflect their increased systemic levels. This reviewer concurs with the sponsor that the increased proportion of AEs for tachycardia in pediatric patients with overdose may represent cholinergic activity from larger than recommended clinical doses, and perhaps an increased sensitivity to this effect in young children.

The regulation for OTC nasal decongestant products that specifies labeling for PSE does not require a warning regarding abuse potential [21 CFR 314.80]. There is no warning regarding abuse potential in the sponsor's proposed OTC labeling for the loratadine/PSE products. The proposed OTC labeling for the loratadine/PSE products is consistent with the sponsor's data and the OTC monograph.

7.16. Safety update

The sponsor submitted an update of safety information received since the applications have been filed [NDA 19-658, SE-6-018 S4, 9/16/02, pages 2-3]. The update provided summaries of spontaneous AEs reported from 12/17/01 until 9/6/02. There were no new clinical trials completed since this time.

There was an increase in AEs for drug exposure during pregnancy for single ingredient loratadine formulations, likely due to publicity surrounding the reports a possible link of hypospadias with loratadine use during pregnancy and reporting bias. There were 9 cases of hypospadias reported over this period. Hypospadias is discussed in detail in an earlier section of this Integrated Review of Safety. There have been no AEs reported for esophageal obstruction or dysphagia for the loratadine D-24 product over this period of time, as expected due to the reformulation of the product. Otherwise, the pattern of AEs is similar to that reported in the NDA and discussed in an earlier section of this review, "Worldwide Postmarketing Safety Data." The sponsor concludes that these safety data are consistent with those previously reported in the applications.

Reviewer comment:
The safety update data reveal no new safety signal.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

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 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 D 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 D 12-hour product is not for use in children under 12 years of age.

The proposed OTC dose of the loratadine/PSE D 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 D 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. The daily PSE dose is the same as that specified by the monograph for these ages. This dose of PSE is not acceptable for consumers less than 12 years of age.

Current prescription label for the D 24-hour product states that patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis should not use the product. This is not reflected in the proposed OTC label for the D 24-hour product. The D 24-hour product was reformulated because of these events. There have been no reports of esophageal obstruction associated with the revised formulation. It is acceptable for the sponsor to not include this precaution in the OTC label.

Dosing for consumers with liver or kidney diseases is discussed in the following section of this review, "Use in Special Populations."

9. USE IN SPECIAL POPULATIONS

Use in special populations is discussed below.

9.1. Elderly

The sponsor performed uncontrolled studies of loratadine in the treatment of 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 [NDA 19-658, SE6-018 BM, 9/16/02 pages 1-2]. The sponsor notes that clinical experience has not revealed differences in safety between the elderly and younger patients [Volume 3, 8.H., page 33]. . The sponsor conducted a clinical pharmacology study that included 12 healthy subjects 66 to 78 years of age. AUC and C_{max} of loratadine and desloratadine (DCL) 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 3, 8.H., pages 33, 77].

Reviewer comment:
This reviewer concurs with the sponsor that one would expect the RediTabs and the regular tablets to be similarly effective for the AR, CIU, and hives diagnoses in consumers ≥65 years of age.

The sponsor conducted a two-week multicenter trial of loratadine in the treatment of SAR that examined AEs and laboratory values for patients stratified by age, <65 years versus ≥65 years. There were 2877 patients <65 years of age and 242 patients ≥65 years of age in this trial. In general, the types and incidences of AEs were similar in patients ≥65 years (3%) than in patients <65 years. Somnolence was slightly less frequent in patients ≥65 years (3%) than in patients <65 years (5%).[10] *These data would indicate that geriatric consumers might not experience somnolence even though they experience higher systemic exposures. There is no dose adjustment in this group recommended in the current prescription labeling for loratadine products. The sponsor's proposed OTC*

[10] Lorber RR, Danzig MR, Ludwig G, et. al. J Allergy Clin Immunol 1994; 93(1 Part 2):163.

labeling appropriately makes no special recommendations for dosing for healthy geriatric consumers.

9.2. Pediatric population

The approval of loratadine syrup 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]. Adverse events in placebo controlled trials of loratadine in children were similar in character and frequency to those noted in the adult population, and were similar to those noted in the placebo group [Volume 3, 8.H., pages 29-32]. Worldwide postmarketing data showed that the types and relative frequencies of AEs for loratadine and the loratadine/PSE combinations in the pediatric population were also similar to those noted for all spontaneous AEs [Volume 3, 8.H., pages 44-45].

The sponsor has already satisfied the pediatric study requirement. The sponsor has completed pediatric studies for loratadine in children down to [redacted]. The studies of children age 2 to <6 years of age supported the approval of loratadine as a prescription product in children down to the age of 2 years. [redacted] The amount of PSE in the combination products is not appropriate for children under the age of 12 years.

Reviewer comment:
It is likely that loratadine is similarly safe and effective in children under from 6 to 12 years of age as it is in consumers 12 years of age and older. The sponsor changed the proposed ages for use of Claritin syrup to include children 2 to 6 years of age since the original submission of these applications [NDA 19-658 SE06-018, Volume 1, 2.B., page 16 and 3.A. page 26, 1/25/02]. Claritin syrup was approved on 12/4/00 as a prescription product in the US for use in children from 2 to 6 years for the SAR and CIU indications. The product has been approved in the US for this population for almost two years. The safety database for the allergic rhinitis indication does not reveal evidence for a safety signal in this population. An allergic rhinitis indication for children ages ≥2 to < 6 years at the currently approved Claritin syrup dose of 5 mg once daily is acceptable. [redacted] *Use of the product in children under 2 years of age is not appropriate.*

9.3. Gender

There were no consistent differences in the changes from baseline in symptom scores 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]. In clinical trials for AR, for loratadine tablets and RediTabs, the overall frequency of adverse events in females receiving both active drug and placebo were more common than in males. There were no clinically important differences

between the active and placebo groups within subgroups. The types and frequencies of AEs were similar in males and females in the loratadine syrup clinical program for AR. In clinical trials for CIU, for loratadine tablets, the overall frequency of adverse events in females receiving both active drug and placebo were more common than in males. There were no clinically important differences between the active and placebo groups within subgroups. There were no clinical trials with the RediTabs or controlled trials of the syrup for the CIU indication. It would be expected that a similar pattern of AEs in males and females would be noted for the for the CIU indications with the RediTabs and syrup [NDA 19-658 SE06-018 BM, 9/16/02, page 4].

Reviewer comment:
There appear to be no gender-related efficacy or safety issues with these products.

9.4. Race

The AUC and C_{max} for 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 [Volume 1, 3.F., pages 5-6]. There have been no differences in safety profiles noted between normal and fast metabolizers [Volume 1, 3.F., pages 3-4]

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

The sponsor provided a subgroup summary of safety by race. In the AR clinical trials of the tablet, RediTab, and syrup formulations of loratadine, 82-93% of patients were of Caucasian race, making meaningful comparisons difficult. The types of AEs in patients of Caucasian and non-Caucasian races were similar. In the CIU clinical trials of the tablet formulation of loratadine, 87% of patients were of Caucasian race. The types of AEs in patients of Caucasian and non-Caucasian races were similar. There were no clinical trials with the RediTabs or controlled trials of the syrup for the CIU indication. It would be expected that a similar pattern of AEs in consumers of Caucasian and non-Caucasian races would be noted for the for the CIU indications with the RediTabs and syrup [NDA 19-658 SE06-018 BM, 9/16/02, page 5].

Reviewer comment:
There appear to be no efficacy or safety issues related to race with these products.

9.5. Hepatic disease

The sponsor's study of seven patients with chronic alcoholic liver disease demonstrated an increase in AUC and C_{max} of loratadine were twice that of normal subjects. No substantial change in DCL levels was noted. The mean $T_{1/2}$ for 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 current prescription label recommends a dose of one tablet (10 mg) once daily for the single ingredient products. The sponsor recommends that the loratadine/PSE products be avoided in consumers with hepatic insufficiency because hepatic insufficiency results in a greater decrease in loratadine clearance than for PSE [Volume 3, 8.H., pages 36, 77, 81, 90]. However, it appears that this recommendation is because the fixed dose combination products could result in a lack of efficacy of the PSE component in consumers with hepatic disease if the dose was titrated based on the recommended dose of loratadine, and not because of possible safety concerns. The sponsor's proposed OTC labeling instructs consumers with liver to ask a doctor before use of loratadine single ingredient products or loratadine/PSE combination products and indicates that a different dose may be needed [Volume 1, Section 2., pages 1-40, NDA 19-658, SE6-018 BL, 8/9/02].

Reviewer comment:
The sponsor's recommendation for the single ingredient loratadine products for consumers with liver disease is appropriate and acceptable for the OTC setting.

9.6. Kidney disease

The sponsor conducted a clinical pharmacology study in 12 patients with chronic renal impairment and creatinine clearances of ≤30 mL/min. The AUC and C_{max} increased 73% for loratadine and 120% for DCL compared with normal subjects. The mean $T_{1/2}$ for loratadine (7.6 hours) and DCL (23.9 hours) were similar to values in normal subjects. The sponsor's current prescription labeling recommends a dose of one tablet every other day in patients with renal insufficiency (GFR <30 mL/min) [Volume 3, 8.H., pages 36, 77, 81, 90].

The sponsor's proposed labeling instructs consumers with liver or kidney disease to ask a doctor before use of loratadine single ingredient products or loratadine/PSE combination products and indicates that a different dose may be needed [Volume 1, Section 2., pages 1-40, NDA 19-658, SE6-018 BL, 8/9/02].

Reviewer comment:
The sponsor's recommendation for the single ingredient loratadine and the loratadine/PSE combination products for consumers with kidney disease is appropriate and acceptable for the OTC setting.

9.7. Pregnancy

The sponsor's current package insert notes that there was no evidence of teratogenicity in studies performed in rats and rabbits. The sponsor reports that studies of the loratadine/PSE combination product at the same ratio (1:24) revealed no evidence of teratogenicity in reproduction studies. Loratadine-containing products are currently labeled as Pregnancy Category [Volume 3, 8.H., pages 33-34].

There was a cluster of 15 cases of hypospadias associated with loratadine use during pregnancy in Sweden. These are discussed in depth in a previous section of this review, "Hypospadias." 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. Other reports of birth defects appear to be similar to the expected background rate for such events [Volume 3, pages 62-63].

Reviewer comment:
The association of hypospadias with loratadine use has been noted only in Sweden. Most of the cases in the SMBR 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. 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 [Volume 1, Section 2., pages 1-40, NDA 19-658, SE6-018 BL, 8/6/02]. The sponsor's recommendation to pregnant consumers is appropriate.

Loratadine and DCL are excreted into breast milk and achieve concentrations in breast milk similar to those of plasma. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4% to 0.7%. The authors estimate that 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. [11] The sponsor's proposed OTC labeling instructs consumers who are breast feeding to ask a health professional before using the product [Volume 1, Section 2., pages 1-40, NDA 19-658, SE6-018 BL, 8/6/02].

Reviewer comment:
The sponsor's recommendation for use of the single ingredient loratadine and the loratadine/PSE combination products in breast feeding consumers is appropriate.

10. CONCLUSIONS AND RECOMMENDATIONS

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
-

[11] Hilbert J, Radwanski E, Affrime E, et. al. J. Clin Pharmacol 1988; 28(3):234-9.

•
•

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 allergic rhinitis and 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.

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. The Joint Advisory Committees on Nonprescription and Pulmonary-Allergy Drug Products has 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.

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 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 some additional support for, and no evidence against, the efficacy of loratadine in the treatment of urticaria.

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.

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 consumers 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 periodic 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 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 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.

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 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.

11. APPENDIX 1, BRIEF LABEL REVIEW

Brief comments on proposed labeling follow. Detailed and final comments on proposed labeling will be incorporated in the final labeling.

11.1. Label for allergic rhinitis indication

The updated labeling in this submission includes directions for use of Claritin syrup in children with allergic rhinitis from 2 to up to 6 years of age at the dose of 1 teaspoonful daily (5 mg once daily). The labeling in the original application did not include an indication for children under 6 years of age. The labeling in the original application stated that the consumer is to ask a doctor before using the product in children less than 6 years of age [NDA 19-658 SE06-018, Volume 1, 2.B., page 16 and 3.A. page 26, 1/25/02]. In the sponsor's opinion, this change is appropriate because of the excellent history of prescription use of this product in this age group, and because the product represents the first non-sedating antihistamine for use in this age group OTC. The sponsor also notes that the product has a wide margin of safety and limited contraindications and warnings for this age group.

Reviewer comment:
The sponsor changed the proposed ages for use of Claritin syrup for allergic rhinitis from what was proposed in the original submission. Claritin syrup was approved on 12/4/00 as a prescription product in the US for use in children from 2 to 6 years for the SAR and CIU indications. The product has been approved in the US for this population for almost two years. The safety database for the allergic rhinitis indication does not reveal evidence for a safety signal in this population. The sponsor's submission and argument supports the change in the ages for use of Claritin syrup for the allergic rhinitis indication. however. An allergic rhinitis indication for children ages ≥2 to < 6 years at the currently approved Claritin syrup dose of 5 mg once daily is acceptable.

The sponsor's labeling for Claritin RediTabs and Junior Claritin RediTabs includes the phrase Disintegrating Tablets" on various locations in labeling, including the principal display panel.

Reviewer comment:
The correct name for the dosage form is "Orally Disintegrating Tablets." Labeling should be changed to reflect the appropriate dosage form.

The sponsor's current labeling for the prescription products recommends that the Claritin D 12-hour and D 24-hour products be avoided in patients with hepatic insufficiency because hepatic insufficiency results in a greater decrease in loratadine clearance than for PSE, and because the fixed dose combination products cannot be individually titrated [NDA 19-658 SE6-018, 1/25/02, Volume 1, 3.C., pages 98, 108]. However, it appears that this recommendation is because the fixed dose combination products could result in a lack of efficacy of the PSE component in consumers with hepatic disease if the dose was

titrated based on the recommended dose of loratadine, not because of possible safety concerns. The sponsor's proposed OTC labeling for the Claritin D 12-hour and Claritin D 24-hour products instructs consumers with liver or kidney disease to contact a doctor before using the product because a different dose may needed.

Reviewer comment:
The sponsor's proposed labeling regarding consumers with liver or kidney disease is appropriate and acceptable.

The sponsor's current labeling for Claritin D 24-hour notes that patients who have a history of difficulty swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis should not use this product [NDA 19-658 SE6-018, 1/25/02, Volume 1, 3.C., page 108].

Reviewer comment:
This reviewer checked the AERS database for reports of esophageal obstruction and dysphagia occurring after the reformulation of the product in December 1998. There was a single report of esophageal obstruction reported on 5/3/99 that occurred on 4/7/00 (— #325692). It was not known if the tablet was the initial or revised formulation. There were no other reports in the AERS of similar events occurring since January 1999. It is acceptable for the sponsor to not include this precaution in the OTC label.

11.2. Label for "hives" indication

Comments on proposed labeling and package insert for the hives indication follow below. Final comments on proposed labeling will be incorporated in the final labeling.

11.2.1. Proposed Package labeling

Comments on the proposed package labeling follows. No package insert was included in this submission [NDA 19-658 SE6-018 MR, 9/6/02].

1. "Non-Drowsy" claim

   Division comment:
   *As with the allergic rhinitis labeling, the sponsor must place an asterisk immediately after the statement "Non-Drowsy". The asterisk refers consumers to the following statement: "*When taken as directed. See Drug Facts Panel." This statement must appear at the bottom of the PDP in conspicuous print.*

2. The "Uses" section includes the following text: [redacted]

3. The "Warnings, Do Not Use" section includes the following text: Do not use "to prevent [redacted] known to be caused by:

- Foods
- Insect stings
- [redacted]
- Latex or rubber gloves

[redacted]

Division comment:

[redacted]

The proposed indication is hives, [redacted] *Because the indication is hives, this section should be worded:*

"Do not use to prevent hives [redacted] *known to be caused by:*

- *Foods*
- *Insect stings*
- [redacted]
- *Latex or rubber gloves*

[redacted]

4. The "Warnings, Do Not Use" section advises the consumer or parent/guardian not to use Claritin as a replacement for epinephrine or for an allergic reaction if a doctor has prescribed an epinephrine injection for allergic reactions.

Division comment:
The label should recommend that consumers with a history of anaphylaxis should have self-injectable epinephrine and carry it with them. The text appropriately emphasizes use of epinephrine in consumers who already have such a prescription.

5. The "Warnings, Do Not Use" section advises the consumer or parent to seek emergency medical attention [redacted] if hives or rash are associated with trouble swallowing, dizziness [redacted] wheezing or problems breathing, [redacted] swelling in or around mouth, [redacted] trouble speaking, or drooling, and advises the consumer that these symptoms could appear up to a few hours after onset of hives.

Division comment:
The label should instruct the consumer to seek emergency medical attention "immediately" [redacted]

[redacted]

6. The principal display panel includes a statement "New! [redacted] Prescription Strength."

Division comment:
The sponsor has previously been advised by DOTCDP that the [redacted] prescription strength" claim is not acceptable and that the statement "New!" must be removed after the product has been on the market for 6 months. DOTCDP advised the sponsor that "Original Prescription Strength" is acceptable.

7. The labeling does not include directions for consumers with liver or kidney disease.

Division comment:
The sponsor must include directions for use for consumers with liver or kidney disease similar to that in the allergic rhinitis label. The allergic rhinitis label instructs consumers with liver or kidney disease to ask a doctor before using the product.

11.2.2. Package insert

The sponsor included a package insert with an older version of labeling that was tested in a label comprehension study [NDA 19-658 SE6-018 BL, 9/25/02]. The sponsor did not include a package insert with the most recent labeling that was submitted and which is to be tested in a future label comprehension study [NDA 19-658 SE6-018 MR, 9/6/02]. In general, the points included in the package insert are similar to those emphasized in the labeling reviewed above. Points for comment follow below.

1. "What are Claritin Hives Relief tablets?" "non-drowsy" claim

Division comment:
*The sponsor must place an asterisk immediately after the statement "Non-Drowsy". The asterisk refers consumers to the following statement: "*When taken as directed. See Drug Facts Panel." This statement must appear at the bottom of the package insert in conspicuous print.*

2. "What are Claritin Hives Relief tablets?" "... [redacted]

Division comment:

[redacted]

3. [redacted]

Division comment:

[redacted]

4. "What can cause hives"

Division comment:
This section states that "certain foods" may cause hives. Although certain foods are more frequent as causes of hives, any food has the potential of causing hives. The sponsor should delete the word "certain."

[redacted]

5. [redacted]

Division comment:

[redacted]

6. [redacted]

Division comment:

[redacted]

8. [redacted]

Division comment:

9.

Division comment:

11.2.3. Additional comments, hives indication

12. APPENDIX 2, DR. ANTHONY SCIALLI'S REVIEW: LORATADINE AND HYPOSPADIAS

The Agency consulted Dr. Anthony Scialli, of Georgetown University Medical Center, to evaluate the potential association of hypospadias with loratadine use in pregnancy. Dr Scialli is an expert in teratology and evaluation of pregnancy outcome data. Dr. Anthony Scialli's review is appended below:

Loratadine and Hypospadias

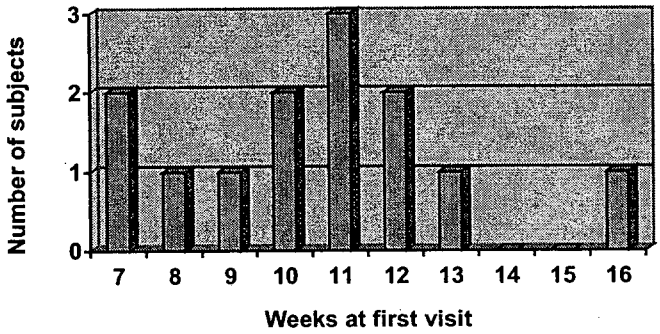
1. Statement of task and documents reviewed

I was asked to comment on a reported association between the use of loratadine in pregnancy and hypospadias among male offspring, specifically with regard to the likelihood that there is a nonchance relationship of the association. I was provided a copy of an evaluation dated November 15, 2001, submitted by Doctor Bengt Källén, an epidemiologist from the Tornblad Institute in Lund, Sweden. I was provided with a prior report from Doctor Källén dated April 16, 1999. I was provided with a report from Doctor Carolyn A. McCloskey, an epidemiologist from the US Food and Drug Administration. I was provided with Adverse Events Reports including some of the Swedish cases covered by Doctor Källén, some reports from after the consultation was completed, and some reports of congenital anomalies associated with other antihistamines. I independently retrieved and reviewed the FDA pharmacology reviews on desloratadine (Clarinex®), the active metabolite of loratadine. These pharmacology reviews are available on the FDA web site.

2. The Swedish cases

The reports of Doctor Källén summarize the operation of the Swedish computerized registers that permit identification of associations between congenital malformations and self-reported medication use in pregnancy. The information on pregnancy exposure to medication is obtained from pregnant women at the time of the first prenatal visit. The first prenatal visit is usually in the first trimester of pregnancy, according to Dr. Källén.

The association between loratadine use in pregnancy and hypospadias in the offspring is based on 15 cases (including two cotwins) of hypospadias among 2780 loratadine exposed pregnancies. An inspection of the Adverse Event Reports for the Swedish cases shows that of 13 reports, covering 14 of the 15 pregnancies, the timing of the first prenatal visit was at or before 13 weeks in 12. The distribution of first prenatal visits is as follows:



For three of the pregnancies, the timing of loratadine exposure was not specified and for an additional three it was specified only as "first trimester." For three pregnancies, exposure appears to have occurred by week 5, and for two other pregnancies, exposure occurred by week 7. In one pregnancy, exposure was reported to have occurred prior to conception.

Doctor Källén presents an analysis that assumes that any of these exposures may have produced hypospadias through a recognized mechanism on genital development or through an as-yet unrecognized early pregnancy effect on the gonad. Based solely on the epidemiologic analysis, he recommends regarding the putative association between hypospadias and loratadine exposure as nonrandom. I agree with his recommendation, based on his analysis plus the pharmacology review, but I believe that additional data may exist that would clarify the biologic plausibility of the association.

Here are my observations:

2.1. The proportion of exposed children with hypospadias is significantly different from an appropriate comparison proportion

Doctor Källén indicates that the expected proportion would be 7 or 8 cases of hypospadias among 2780 births. Using a Fisher exact test to compare the observed proportion (15 of 2780 births) with the expected proportion (7 of 2780 births) yields an odds ratio of 2.15 with a 95% confidence interval of 0.82-6.24, one-tailed $P < 0.07$, two-tailed $P < 0.09$. Given the fact that the association originated using a multiple-comparison surveillance methods, the lack of formal statistical significance can be important. A better comparison, however, is the proportion of children with hypospadias born to women who used other antihistamines. This comparison yielded an odds ratio of 4.00 (95% confidence interval 1.42-12.9), which is significant at a P value well under 0.001. This comparison is more appropriate than the unadjusted Fisher test using expected general population numbers. Even excluding the case with preconception exposure and excluding the twins (because twinning is an independent risk for hypospadias) yields a significantly elevated odds ratio.

2.2. The timing is not appropriate for a direct effect of loratadine on the production of hypospadias in at least seven of these cases