

**Rapporteur's  
Public Assessment Report  
for paediatric studies submitted in accordance  
With Article 45 of Regulation (EC) No1901/2006, as  
amended**

**Clarityn (AT, IT, IE, DK, FI, SE, UK, MT, FR), Alorin (IT),  
Lisino (DE), Fristamin compresse rivestite (IT), Utel  
(EL), Alertrin (PT), Claritine (NL, CZ, SK, RO, BE, BG,  
EE, LV, LT, PL, PT, SL), Loratadine SP (BE),  
Clarityne (EL, ES)**

**INN: Loratadine**

**AT/W/0003/pdWS/001**

<b>Rapporteur:</b>	AT
<b>Start of the procedure (day 0):</b>	April 4, 2010
<b>Date of this report:</b>	August 02, 2010
<b>Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70):</b>	June 17, 2010
<b>Deadline for CMS's comments (day 85):</b>	July 02, 2010
<b>End of Procedure (day 120)</b>	August 06, 2010

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	Loratadine
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	R06AX13
Pharmaceutical form(s) and strength(s):	Syrup: 5 mg/5 ml Tablet: 10 mg
Rapporteur's contact person:	<b>Name: Sabine Polly</b> Tel: 0043 50555 36632 Email: sabine.polly@ages.at
Name of the assessor(s)	<b>Name: Dr. Johanna Wernsperger</b> Tel: 0043 50555 36558 Email: johanna.wernsperger@ages.at

## **I. EXECUTIVE SUMMARY**

No SmPC and PL changes are proposed.

## **II. RECOMMENDATION**

Based on the review of the paediatric data on safety and efficacy, the Rapporteur considers that the administration of loratadine in children 2 years or older in the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria can be recommended, provided an appropriate mode of administration.

## **III. INTRODUCTION**

The Marketing Authorization Holder of the originator Product, Schering Plough submitted 8 completed paediatric studies and six publications for loratadine, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Loratadine and that there is no consequential regulatory action.

All the submitted 8 studies and 3 of the assessable publications have been realized and/or sponsored by the MAH of the Originator-Product, Schering Plough Europe.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing
- A Statement of Schering-Plough that, according to the submitted data, an update of the Product Information is not required.
- A detailed Clinical Overview summarising the 8 submitted studies including an GCP compliance statement

## **IV. SCIENTIFIC DISCUSSION**

### **IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)**

Loratadine Tablets (10mg) and Syrup (5mg/5ml) were used in the submitted studies and publications. Different dosages were used.

### **IV.2 Non-clinical aspects**

No non-clinical data were submitted.

### **IV.3 Clinical aspects**

#### **Background**

Loratadine is a second-generation, non-sedating, oral, long-acting, selective receptor antagonist with demonstrated antihistaminic efficacy in the treatment of symptoms of allergic rhinitis (AR) and allergic skin disorders. Loratadine reduces nasal and non-nasal symptoms with reduced

undesirable central nervous system and anticholinergic effects compared to first-generation antihistamines.

Loratadine is marketed as 10-mg tablets, 5-mg chewable tablets and rapidly disintegrating tablets, and as 1 mg/mL syrup and oral solution.

Loratadine is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) and for the symptoms of chronic idiopathic urticaria (CIU) in patients aged 6 years and older, at a dose of 10 once daily. Loratadine syrup is being used to treat seasonal and perennial allergic rhinitis and chronic allergic skin conditions in children 2 years (most countries) or older. Products containing loratadine alone have been approved for use in 118 countries and are marketed in 115 countries worldwide (as of 01 FEB 2008).

Loratadine 10-mg Tablets have been marketed in countries of the EU since FEB 1988. Based on available data, total worldwide patient exposure to loratadine products is estimated to have been 13.1 billion patient days in the period from 01 JAN 1995 through 31 JUL 2009.

The eight studies described in this overview included a total of 1501 subjects. Six studies (Study Nos. C97-033, C98-566, P00241, P00256, P03428, and Q96-904) included 753 pediatric subjects between 6 months and  $\leq 11$  years of age and two studies (Study Nos. P00677 and P00687) included 95 adolescent subjects between 12 and  $\leq 17$  years of age and 653 subjects  $\geq 18$  years of age.

## 1. Introduction

### Studies

1. **C97033**: SCH 29851: Single dose bioavailability of Loratadine in healthy paediatric volunteers
2. **C98566**: Loratadine syrup for children 2 - 5 years old
3. **P03428**: Efficacy and safety of loratadine-betamethasone combination in the initial treatment of severe perennial allergic rhinitis in children
4. **P00256**: Safety of Loratadine Syrup in children 6 months - 2 Years Old.
5. **P00677**: Efficacy and Safety of SCH 29851 8 mg in Subjects with Allergic Rhinitis
6. **P00687**: Efficacy and Safety of SCH 29851 in 8 mg in Subjects with Allergic Rhinitis
7. **Q96-904-01**: Mometasone furoate 0,1% and Loratadine syrup vs Mometasone furoate 0,1% crema e sciroppo placebo nel trattamento della dermatite atopica infantile.
8. **P00241**: SCH 29851: Single-Dose Bioavailability of Loratadine Syrup in Pediatric Volunteers 6 Months to 2 Years of Age

The MAH submitted reports and extended synopsis for all 8 Studies.

### Publications

1. Children's school performance is not impaired by short-term administration of diphenhydramine or loratadine.

Bender BG, McCormick DR, Milgrom H.

J Pediatr. 2001 May; 138(5):656-60

*supported by Schering Plough*

Loratadine

AT/W/0003/pdWS/001

2. Double-blind comparison of cetirizine and loratadine in children ages 2 to 6 years with perennial allergic rhinitis.

Sienra-Monge JJ, Gazca-Aguilar A, Del Rio-Navarro B.  
Am J Ther. 1999 May; 6(3):149-55

3. A double-blind, placebo-controlled, and randomized study of loratadine (Clarityne) syrup for the treatment of allergic rhinitis in children aged 3 to 12 years.

Yang YH, Lin YT, Lu MY, Tsai MJ, Chiang BL.  
Asian Pac J Allergy Immunol. 2001 Sep; 19(3):171-5  
*supported by Schering Plough*

4. A comparative study of the efficacy and safety of loratadine syrup and terfenadine suspension in the treatment of 3- to 6-year-old children with seasonal allergic rhinitis.

Lutsky BN, Klose P, Melon J, Menardo JL, Molkhou P, Ponchetti R, Suonpaa J, Wahn U, Wessel F.  
Clin Ther. 1993 Sep-Oct; 15(5):855-65

5. The pharmacokinetics, electrocardiographic effects, and tolerability of loratadine syrup in children aged 2 to 5 years.

Salmun LM, Herron JM, Banfield C, Padhi D, Lorber R, Affrime MB.  
Clin Ther. 2000 May; 22(5):613-21.  
*supported by Schering Plough*

The following Publication was mentioned by PHARMEX S.A (Utel) in the line-listing, and submitted by Schering Plough. As the publication was submitted in Hungarian it could not be included in the assessment.

6. Effect of loratadine in children with allergic rhinitis

Kosa L, Kovacs N, Halasz A, Zsigmond G.  
Orv Hetil. 2001 Aug 26;142(34):1843-5

## 2. Clinical studies

### 2.1 Clinical pharmacology

#### 2.1.1 Study No. C97-033

Study No. C97-033 was an open-label, single-center, single-dose study conducted in the United States to characterize the pharmacokinetic profiles of loratadine and its major active metabolite, desloratadine, in healthy pediatric subjects 2 to 5 years of age administered a single 5-mg dose of loratadine. There were 18 subjects between the ages of 2 and 5 years of age enrolled in the study. Eleven subjects were male and 7 subjects were female. The majority of subjects were Black (12 subjects), 5 subjects were Caucasian, and one subject was identified as "Other." Loratadine was rapidly absorbed following oral administration (**Figure 1**). Maximum observed plasma concentrations (C<sub>max</sub>) ranging from 1.45 to 31.8 ng/mL (mean C<sub>max</sub>, 7.78 ng/mL) were observed within 1 to 2 hours after dosing (mean time to maximum observed plasma concentrations (T<sub>max</sub>), 1.17 hours) (**Table 3**). Thereafter, plasma concentrations of loratadine decreased rapidly. There were an insufficient number of quantifiable plasma concentrations of loratadine during the elimination phase to determine its elimination half-life.

**Table 3 Mean Pharmacokinetic Parameters for Loratadine and Desloratadine**

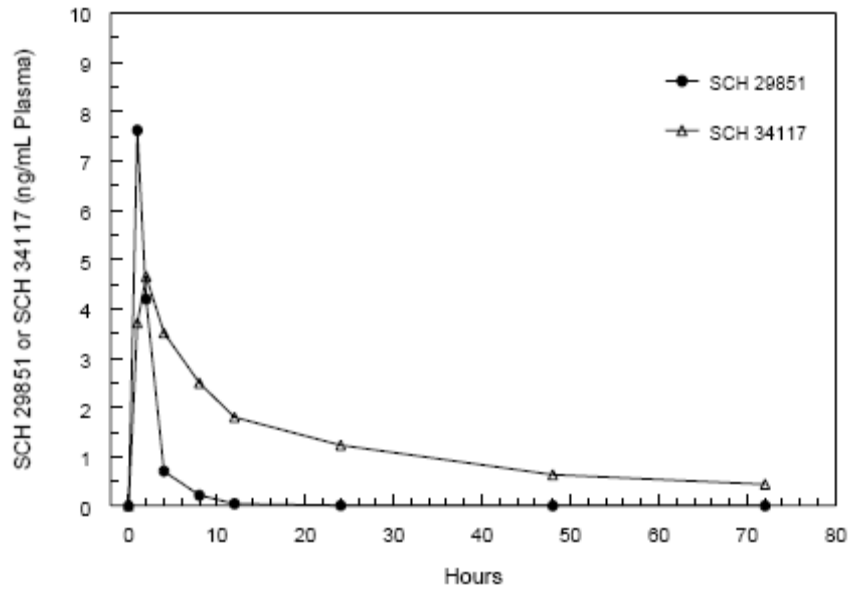
Study No. C97-033

Parameter	Unit	Loratadine		Desloratadine	
		Mean <sup>a</sup>	%CV	Mean <sup>a</sup>	%CV
C <sub>max</sub>	ng/mL	7.78	90	5.09	36
C <sub>max</sub> <sup>c</sup>	ng/mL	5.89	--	4.72	--
T <sub>max</sub>	hr	1.17	33	2.33	75
AUC(tf)	ng·hr/mL	16.7	80	87.2	88
AUC(tf) <sup>c</sup>	ng·hr/mL	13.1	--	67.6	--
AUC(l)	ng·hr/mL	---	---	61.4 <sup>b</sup>	41
t <sub>1/2</sub>	hr	---	---	14.4 <sup>b</sup>	20
tf	hr	9.11	49	60.0	25
AUC Ratio <sup>d</sup>		---	---	8.33	104

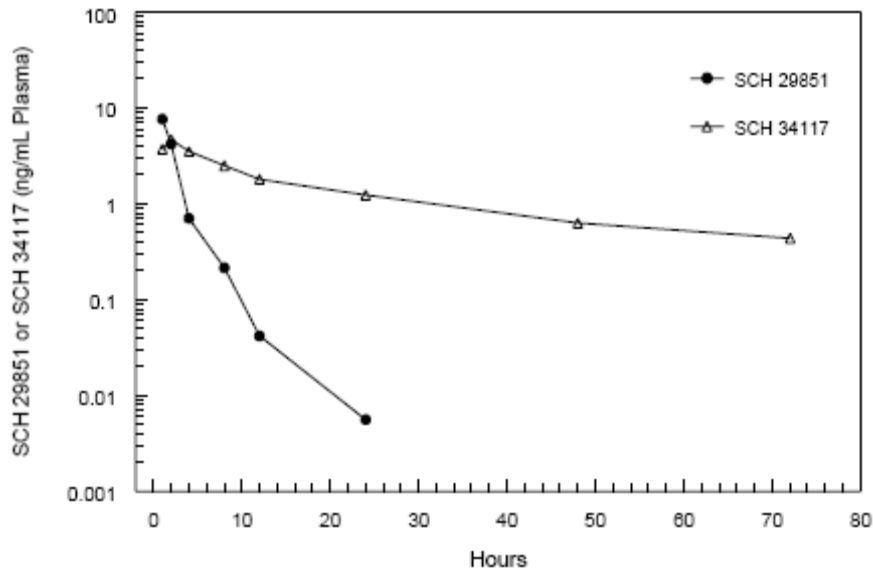
Abbreviations: AUC(l) – area under the concentration-time curve to infinity; AUC(tf) – area under the concentration-time curve to final time; C<sub>max</sub> – maximum observed plasma concentration; T<sub>max</sub> – time to maximum observed plasma concentration; t<sub>1/2</sub> – terminal elimination half-life; tf – final time.

- a: n=18 unless otherwise noted, arithmetic means.
- b: n=12, K was determinable for 12 subjects.
- c: Geometric means.
- d: Calculated as the ratio of AUC(tf) of desloratadine to loratadine.

Linear-Linear



Log-Linear



**Figure 1** Mean Plasma Concentrations of Loratadine and DL Following a Single 5 mg Dose of Loratadine Syrup to Pediatric Volunteers.

Loratadine was extensively metabolized to desloratadine (**Figure 1**). Maximal desloratadine plasma concentrations ranging from 1.78 to 8.12 ng/mL (mean  $C_{max}$ , 5.09 ng/mL) were observed within 1 to 2 hours after dosing for 14 subjects, at 4 hours after dosing for 3 subjects, and at 8 hours after dosing for one subject (mean  $T_{max}$ , 2.33 hours) (**Table 3**). The arithmetic

mean elimination half-life for desloratadine calculated from 12 of the 18 subjects was 14.4 hours (range 10.3- 19.2 hr).

A half-life could be determined for 3 other subjects (subjects 11, 12 and 15). The estimated values were longer (54-92 hr) compared with the other subjects (10.3-19.2 hr) and these subjects had substantial concentrations (1.3 - 3.0 ng/mL; limit of quantitation (LOQ) = 0.1 ng/mL) at 72 hours, the final sample time. These data suggest that blood samples were not collected for a long enough period ( $t_{1/2}$ ) to reliably estimate the terminal phase half life ( $t_{1/2}$ ) in these subjects. Therefore, the half-life values were not included in the estimate of the terminal phase  $t_{1/2}$  in this population. (Research with desloratadine subsequent to 1997 showed that approximately 17% of the Black population are poor metabolizers of desloratadine, and they have a terminal phase half-life of approximately 89 hours. The safety profile of these subjects is not different from that of the general population.) Based upon the area under the concentration-time curve to the final time (AUC[tf]) ratio for desloratadine to loratadine, the systemic exposure to desloratadine was approximately 8-fold greater than that to loratadine.

### 2.1.2 Study No. P00241

Study No. P00241 was an open-label, single-center, single-dose study conducted in the United States to characterize the pharmacokinetic profiles of loratadine and its active metabolite, desloratadine, in healthy pediatric subjects 6 months to <2 years of age administered a single 2.5-mg dose or 5-mg dose of loratadine. There were 50 subjects between the ages of 6 months and 2 years of age enrolled in the study. Twenty-six subjects were male and 24 subjects were female. The majority of subjects were Black (28 subjects), 18 subjects were Caucasian, 1 subject was Hispanic, and 3 subjects were identified as “Other.” The mean plasma concentration-time profiles for loratadine following administration of 2.5 mg or 5 mg of loratadine syrup to pediatric subjects with ages between 6 months to <1 year and  $\geq 1$  year to <2 years are illustrated in **Figure 2**. The associated mean plasma concentrations and pharmacokinetic parameters are provided in **Table 4**.

**Table 4** Mean Plasma Concentrations and Pharmacokinetic Parameters of Loratadine Following Single Dose Oral Administration of 2.5 mg or 5 mg Loratadine Syrup to Two Age Groups of Pediatric Subjects

Protocol No. P00241

Time (hr)	Age $\geq 6$ months to <1 year				Age $\geq 1$ year to <2 years			
	2.5 mg		5 mg		2.5 mg		5 mg	
	Mean (N=10)	%CV	Mean (N=10)	%CV	Mean (N=15)	%CV	Mean (N=15)	%CV
0	0	---	0	---	0.00746	361	0	---
1	5.64	92	10.4	100	3.13	91	7.73	82
6	0.542	74	1.02	76	0.278	75	1.09	225
12	0.307	73	1.10	192	0.154	68	0.618	234
24	0.0549	64	0.162	61	0.0382	112	0.154	164
AUC(tf) <sup>a,b</sup>	22.3 (16.9)	74 ---	52.2 (44.9)	67 ---	11.9 (7.79)	92 ---	35.4 (25.0)	128 ---
AUC Ratio <sup>c</sup>	4.09	60	3.52	86	7.60	151	4.21	57

a: Units: AUC(tf)-ng-hr/mL.

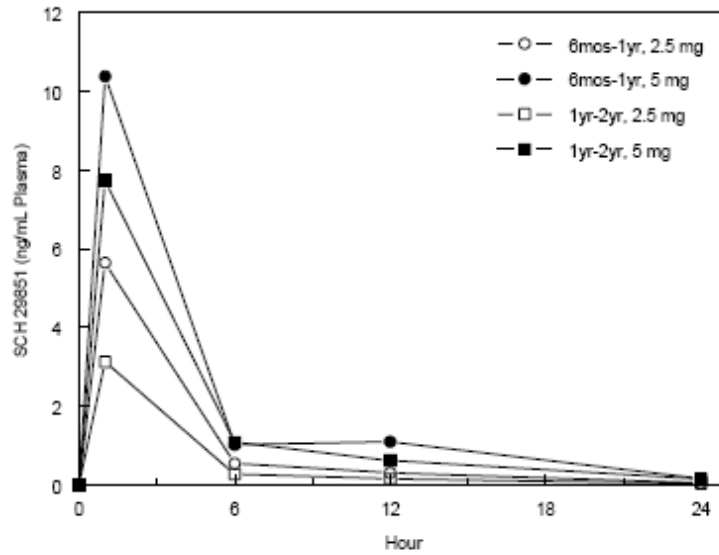
b: Median values in brackets.

c: Calculated as the ratio of AUC(tf) of SCH 34117 to SCH 29851.

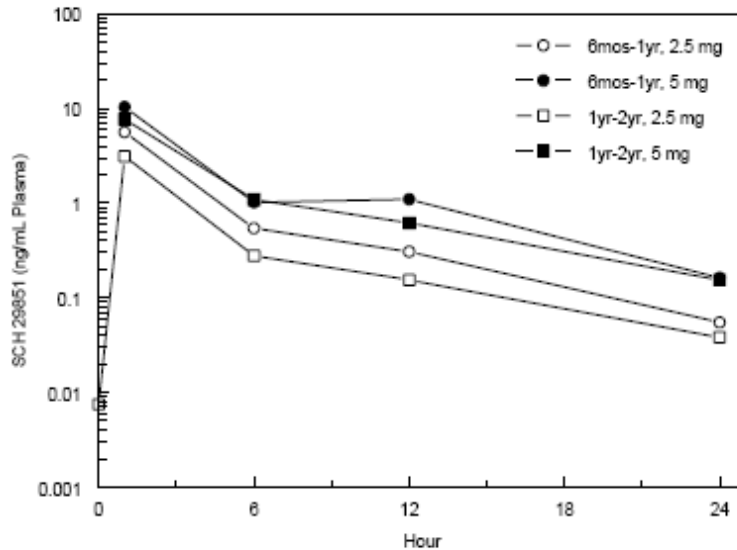
High intersubject variability in the plasma concentration-time data and derived pharmacokinetic parameters were observed, which was consistent with previously recorded data from studies conducted in adults. Subject No. 45 ( $\geq 1$  year to <2 years) in the 2.5 mg group had a predose (0

hour) loratadine concentration of 0.097 ng/mL, approximately 3-fold higher than the LOQ. This reason for this predose concentration is unknown. However, the contribution to AUC(tf) was negligible.

Linear:Linear



Log:Linear



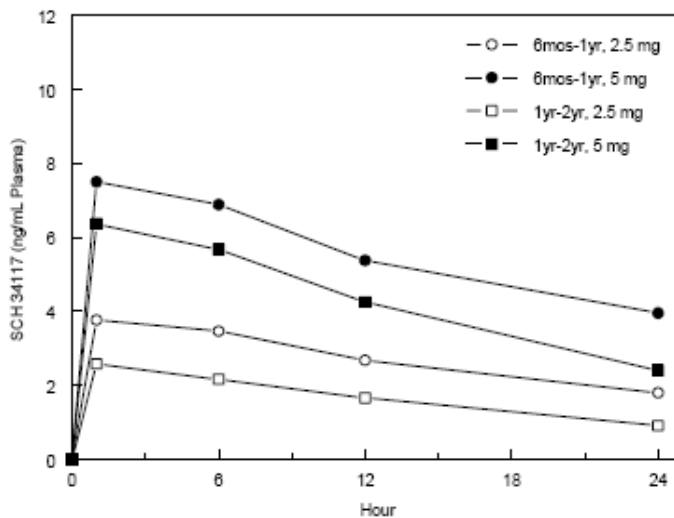
**Figure 2** Mean Plasma Loratadine Concentrations Following Single Dose Oral Administration of 2.5 mg or 5 mg Loratadine Syrup to Two Age Groups of Pediatric Subjects

### Desloratadine

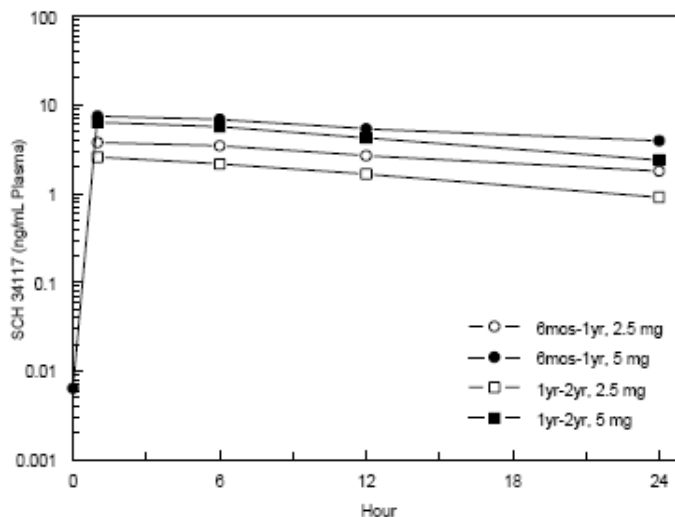
The mean plasma concentration-time profiles for desloratadine following administration of 2.5 mg or 5 mg of loratadine syrup to pediatric subjects with ages between 6 months to <1 year and

≥1 year to <2 years are illustrated in **Figure 3**. The associated mean plasma concentrations and pharmacokinetic parameters are provided in **Table 5**.

Linear:Linear



Log:Linear



**Figure 3** Mean Plasma Desloratadine Concentrations Following Single Dose Oral Administration of 2.5 mg or 5 mg Loratadine Syrup to Two Age Groups of Pediatric Subjects

**Table 5** Mean Plasma Concentrations and Pharmacokinetic Parameters of Desloratadine Following Single Dose Oral Administration of 2.5 mg or 5 mg Loratadine Syrup to Two Age Groups of Pediatric Subjects

Protocol No. P00241

Time (hr)	Age ≥6 months to <1 year				Age ≥1 year to <2 years			
	2.5 mg		5 mg		2.5 mg		5 mg	
	Mean (N=10)	%CV	Mean (N=10)	%CV	Mean (N=15)	%CV	Mean (N=15)	%CV
0	0	---	0.00644	300	0	---	0	---
1	3.77	71	7.50	45	2.58	58	6.36	84
6	3.47	58	6.89	45	2.16	43	5.67	66
12	2.68	56	5.38	47	1.66	49	4.25	64
24	1.80	81	3.95	97	0.911	94	2.40	71
AUC(tf) <sup>a,b</sup>	65.3 (57.2)	55 ---	132 (110)	49 ---	40.0 (35.4)	45 ---	103 (80.2)	63 ---

a: Units: AUC(tf)-ng.hr/mL.

b: Median values in brackets.

Plasma desloratadine concentrations declined slowly and at 24 hours, plasma concentrations of all subjects were above the LOQ (0.025 ng/mL). Subject No. 10 (≥6 months to <1 year) in the 5 mg group had a predose (0 hour) desloratadine concentration of 0.058 ng/mL (~2 fold the LOQ). The reason for this concentration is unknown. However, this value contributed negligibly to the AUC(tf).

## 2.2 Clinical efficacy

The results from four clinical studies (Study Nos. P00677, P00687, P03428, and Q96-904) summarized in this section cover efficacy objectives including treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and atopic dermatitis (AD) and include studies using both loratadine Tablet and Syrup formulations as well as a loratadine/betamethasone oral solution (1mg/0.05mg/mL). The study results are presented as in the clinical study reports without post-hoc analysis by age group.

### 2.2.1 Study No. P00677 Efficacy

Study No. P00677 was a randomized, multicenter, double-blind, placebo-controlled, parallel group study conducted in the United States to assess the efficacy and safety of loratadine 8 mg once daily (QD) for two weeks, compared to placebo, in subjects 12 to 67 years of age with SAR. Overall, there were 362 subjects between the ages of 12 and 67 years of age enrolled in the study. The mean age was 34.7 years of age. Most subjects were ≥18 years of age (309 subjects) and 53 subjects were between 12 to <18 years of age. The majority of subjects were female (232 subjects) and 130 subjects were male. The majority of subjects were Caucasian (275 subjects), 49 subjects were Black, 4 subjects were Asian, and 34 subjects were Hispanic. Treatment with loratadine resulted in a statistically significant mean change from Baseline compared to placebo for the primary efficacy variable, average AM and PM (prior 12 hours) reflective total symptom score, for the treatment period, Days 1 to 15 (p<0.01, see Table 6). Loratadine was statistically significantly better than placebo on Day 1 of treatment (p=0.05) and at all other secondary time points (p<0.01). The results in Table 6 show that treatment with loratadine resulted in a mean decrease in the total symptom score that ranged from -2.41 to -5.92 (-13.8% to -33.2%). This was in comparison to a mean decrease in total symptom score of -1.51 to -4.29 (-7.4% to -22.3%) in placebo treated subjects.

**Table 6** Total Symptom Score by Treatment Group Subject Evaluated Mean of AM and PM PRIOR 12 Hours (Intent-to-Treat Subset) (Reflective Scores)

Protocol No. P00677

AM/PM PRIOR 12 Hours	Loratadine 8 mg			Placebo		
	n	LS Mean <sup>a</sup>	(Mean % Change) <sup>b</sup>	n	LS Mean <sup>a</sup>	(Mean % Change) <sup>b</sup>
Baseline	179	16.41		179	16.90	
Change From Baseline						
Day 1	175	-2.41	(-13.8)	172	-1.51	(-7.4)
Day 2	179	-4.09	(-22.8)	178	-2.25	(-11.3)
Day 3	179	-4.54	(-25.9)	177	-2.70	(-14.5)
Day 4	179	-4.75	(-27.1)	178	-2.99	(-15.9)
Days 1-8	179	-4.79	(-26.7)	179	-3.05	(-15.9)
Days 9-15	173	-5.92	(-33.2)	169	-4.29	(-22.3)
Days 1-15	179	-5.20	(-29.3)	179	-3.53	(-18.8)
		Model p-Values				
Interval	Pstd <sup>a</sup>	Treatment	Center			
Change from Baseline						
Day 1	4.23	0.05	0.33			
Day 2	4.36	<0.01	0.56			
Day 3	4.67	<0.01	0.39			
Day 4	4.87	<0.01	0.30			
Days 1-8	4.19	<0.01	0.18			
Days 9-15	4.89	<0.01	0.55			
Days 1-15	4.28	<0.01	0.47			

Abbreviations: ANOVA – analysis of variance; LS – least squares.

a: LS means and pooled standard deviation (Pstd) are based on ANOVA model with treatment and center effects.

b: Mean percent changes are raw means.

*Assessor's Comment: The 8mg Dose does not comply with the 10mg Dose recommended in the SPC for patients > 30kg. As this is a study evaluated with regard to efficacy this is negligible.*

It was concluded that treatment with loratadine 8 mg tablet resulted in a statistically significant reduction from Baseline compared to the placebo treatment group in the mean AM and PM (prior 12 hours) reflective total symptom score for seasonal allergic rhinitis for the primary time interval, Days 1 to 15, and all secondary time points.

### 2.2.2 Study No. P00687 Efficacy

Study No. P00687 was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study conducted in the United States to assess the efficacy and safety of loratadine 8 mg QD for two weeks compared to placebo in subjects with SAR. Overall, there were 386 subjects between the ages of 12 and 75 years of age enrolled in the study. The mean age was 34.5 years of age. Most subjects were ≥18 years of age (344 subjects) and 42 subjects were between 12 to <18 years of age. The majority of subjects were female (251 subjects) and 135 subjects were male. The majority of subjects were Caucasian (305 subjects), 41 subjects were Black, 1 subject was American Indian, 9 subjects were Asian, and 30 subjects were Hispanic. Treatment with loratadine did not result in a statistically significant mean change from Baseline compared to Placebo for the primary efficacy variable, average AM and PM reflective total symptom score, for the treatment period, Days 1 to 15 (p=0.07). Loratadine was statistically significantly better than placebo at reducing the symptoms of seasonal allergic rhinitis on Days 1 to 8 (p<0.01) but not for Days 9-15 (p=0.53). The absence of a significant decrease in total symptom score compared

to placebo for Days 9 to 15 was not due to a loss of activity with loratadine. The mean change in total symptom score for the loratadine treatment group remained similar for Days 1 to 8 and Days 9 to 15 at -4.08 (-23.6%) and -4.83 (-28.3%), respectively. By comparison, the effect of placebo on the mean change from Baseline of the total symptom score improved from Days 1 to 8, -2.92 (-16.2%), to Days 9 to 15, -4.50 (-25.8%).

*Assessor's Comment: The 8mg Dose does not comply with the 10mg Dose recommended in the SPC for patients > 30kg. As this is a study evaluated with regard to efficacy this is negligible. The high effect of placebo is remarkable.*

**Table 7** Total Symptom Score by Treatment Group Subject Evaluated Mean of AM and PM PRIOR 12 Hours (Intent-to-Treat Subset) (Reflective Scores)

Protocol No. P00687

AM/PM PRIOR 12 Hours	Loratadine 8 mg			Placebo		
	n	LS Mean <sup>a</sup>	(Mean % Change) <sup>b</sup>	n	LS Mean <sup>a</sup>	(Mean % Change) <sup>b</sup>
Baseline	193	16.63		193	16.82	
Change From Baseline						
Day 1	191	-2.36	(-13.7)	189	-1.53	(-8.7)
Day 2	191	-3.50	(-20.2)	192	-2.20	(-12.0)
Day 3	192	-4.20	(-23.9)	193	-2.76	(-15.0)
Day 4	192	-4.08	(-23.1)	189	-3.00	(-16.4)
Days 1-8	193	-4.08	(-23.6)	193	-2.92	(-16.2)
Days 9-15	187	-4.83	(-28.3)	187	-4.50	(-25.8)
Days 1-15	193	-4.38	(-25.5)	193	-3.59	(-20.2)
Model p-Values						
Interval	Pstd <sup>a</sup>	Treatment	Center			
Change from Baseline						
Day 1	4.52	0.07	0.30			
Day 2	4.38	<0.01	0.05			
Day 3	4.56	<0.01	0.03			
Day 4	4.64	0.02	0.09			
Days 1-8	4.07	<0.01	0.11			
Days 9-15	5.03	0.53	0.73			
Days 1-15	4.27	0.07	0.26			

a: LS means and pooled standard deviation (Pstd) are based on analysis of variance (ANOVA) model with treatment and center effects.

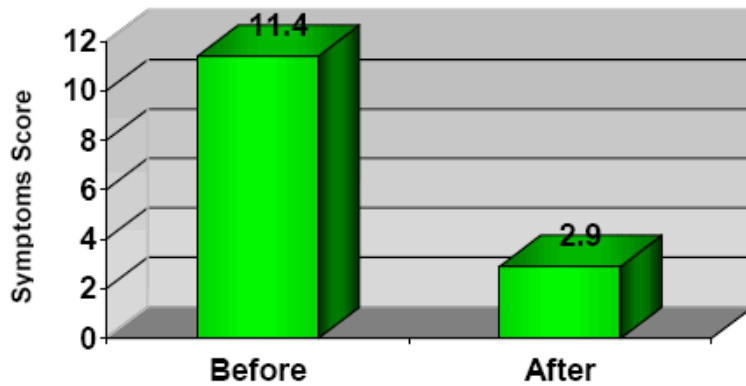
b: Mean percent changes are raw means.

It was concluded that there was no statistically significant difference in mean change from Baseline in the average AM and PM (prior 12 hours) total symptom score for seasonal allergic rhinitis between the two treatment groups; loratadine 8- mg tablet and placebo, for the primary time interval, Days 1 to 15 (p=0.07). Compared to placebo, treatment with the loratadine 8-mg tablet did result in a statistically significant mean change from Baseline in the average AM and PM reflective total symptom score for Days 1 to 8, but not Days 9 to 15 of the 2-week treatment period.

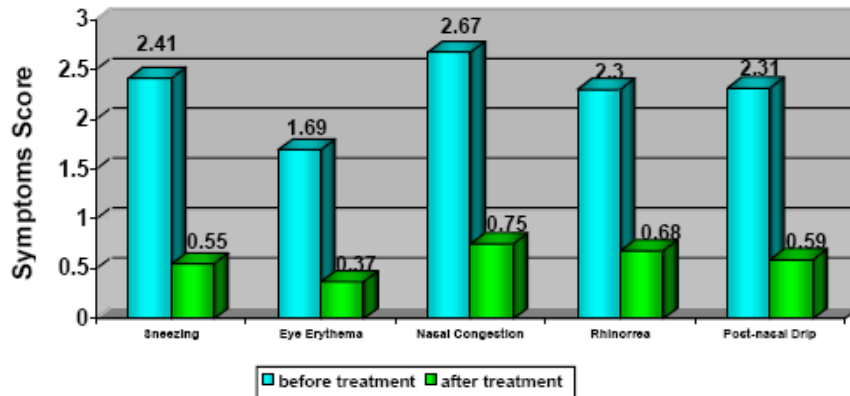
### 2.2.3 Study No. P03428 Efficacy

Study No. P03428 was an open-label, prospective, non-comparative, multicenter study conducted in Venezuela to evaluate the efficacy and safety of loratadine/betamethasone oral solution (1 mg/0.05 mg/1 mL), at a dose of 10 mg/0.5 mg, respectively, as an initial treatment for

severe perennial allergic rhinitis in school age children. There were **100** subjects between 6 and 12 years of age enrolled in the study. The average age of subjects was 9.73 years. Sixty-nine subjects were male and 31 subjects were female. The Primary efficacy parameter (nasal and eye symptoms total score) gave an average of  $11.4 \pm 2.1$  points before treatment. At Day 5 treatment, the mean score decreased to  $2.9 \pm 2.4$  (**Figure 4**). There was a significant difference between Baseline and Day-5 values ( $p < 0.01$ ). Individual analysis of nasal/eye symptoms (sneezing or nasal pruritus, eye reddening or eye pruritus, nasal congestion, nasal secretion, post-nasal drip) after treatment revealed a significant decrease ( $p < 0.01$ ) in all compared symptoms (**Figure 5**).



**Figure 4** Perennial Allergic Rhinitis Symptoms Total Score Before and After Five Days of Treatment



**Figure 5** Perennial Allergic Rhinitis Individual Symptoms Score Before and After Five Days of Treatment

It was concluded that the combination of loratadine and betamethasone in an oral solution (1 mg/0.05 mg/1 mL) was effective as an initial treatment for severe PAR in children of 6 to 12 years of age.

*Assessor's Comment: This study is only considered as supportive due to study-design*

## 2.2.4 Study No. Q96-904 Efficacy

Study No. Q96-904 was a randomized, multicenter, double-blind, placebo-controlled study conducted in Italy to evaluate the advantage of the oral supplementation with a non-sedating H1 antihistamine (loratadine) to the standard treatment with a topical steroid (mometasone furoate [MF]) for 14 days during flares of atopic dermatitis (AD) in children 2 to 12 years of age. Overall, there were **243** subjects between of 2 and 12 years of age enrolled in the study. There were 112 female subjects and 131 male subjects. Both treatments proved very effective in the reduction of signs and symptoms of AD. Statistically significantly better results, however, were obtained in the MF + loratadine (LO) group. At the end of the treatment, 89 (75.4%) subjects in the MF+LO group and 68 (56.7%) subjects in the MF+ placebo (PL) group were judged as healed ( $p < 0.05$ ); 23 (19.5%) subjects in the MF+LO group and 42 (35.0%) subjects in the MF+PL group as markedly improved ( $p < 0.05$ ); 6 (5.1%) subjects in the MF+LO group and 9 (7.5 subjects in the MF+PL group as moderately improved ( $p < 0.05$ ); and 1 (0.8%) subject in the MF+PL group as mildly improved ( $p < 0.05$ ): overall, at the end of the treatment 29 subjects in MF+LO group and 52 in the MF+PL group were judged as improved ( $p < 0.01$ ).

Both treatments induced a statistically significant reduction of the Scoring Atopic Dermatitis (SCORAD) index with respect to Visit 1 from the fourth day of treatment ( $p < 0.001$ ), and in both groups a reduction of the same index with respect to the preceding visit was maintained also during Visit 3 ( $p < 0.01$ ) and Visit 4 ( $p < 0.05$ ). The SCORAD index is a standardized tool for grading AD that evaluates three items: extent of the body area involved, objective symptoms (erythema, edema/population, oozing/crusts, excoriations, lichenification, and dryness), and subjective symptoms of itching and sleep loss. The analysis of the reduction of the SCORAD index during the treatment confirmed the finding of statistically significantly better results in the MF+LO group with respect to the MF+PL group. At Visit 1 the SCORAD index was  $44.5 \pm 15.19$  in MF+LO group and  $46 \pm 17.23$  in the MF+PL group; at Visit 2 it was  $20.2 \pm 11.34$  in MF+LO group and  $26.8 \pm 14.19$  in the MF+PL group ( $p < 0.001$ ); at Visit 3 it was  $8.9 \pm 0.61$  in MF+LO group and  $13.3 \pm 12.6$  in the MF+PL group ( $p < 0.01$ ), and at the end of treatment it was  $5.3 \pm 7.24$  in the MF+LO group and  $7.9 \pm 10.31$  in the MF+PL group ( $p < 0.001$ ). When taking into account the single parameters of the SCORAD index, a statistically significant reduction of each item with respect to Visit 1 was observed in both groups at every control visit ( $p < 0.001$ ). In the MF+LO group, edema/population showed a greater reduction at Visit 2 (0.5 vs 0.6;  $p < 0.05$ ), oozing/crusts at Visit 2 (0.4 vs 0.8;  $p < 0.001$ ) and at Visit 3 (0.1 vs 0.3;  $p < 0.001$ ), lichenification at Visit 2 (0.6 vs 0.9;  $p < 0.05$ ) and itching at Visit 2 (2.2 vs 2.9;  $p < 0.05$ ) and Visit 3 (0.9 vs 1.3;  $p < 0.001$ ) with respect to MF+PL group, confirming a superior efficacy of the treatment with MF+LO with respect to the treatment with MF+PL.

## 2.2.5 Supportive Data Safety: Publications

Double-blind comparison of cetirizine and loratadine in children ages 2 to 6 years with perennial allergic rhinitis.

Sierra-Monge JJ, Gazca-Aguilar A, Del Rio-Navarro B.  
Am J Ther. 1999 May; 6(3):149-55

The efficacy and safety of cetirizine and loratadine were compared in a prospective, randomized, double-blind, longitudinal, parallel-group study of 80 children, 2 to 6 years of age, with perennial allergic rhinitis. Patients received cetirizine or loratadine at 0,2mg/kg once daily in the morning for 28 days. Histamine skin tests and eosinophil counts from nasal smears were performed at baseline and at the end of treatment. Individual symptoms were assessed by the investigator at baseline and on day 28 and by parents at baseline and daily in symptom diaries. Global assessments were made by using a visual analog scale at baseline and at the end of treatment. Cetirizine produced significantly greater inhibition of the wheal response compared with loratadine ( $p < 0,0001$ ) Eosinophil counts were improved to a comparable degree with both agents. Cetirizine and loratadine produced comparable improvements in symptoms and according to a global evaluation as assessed by the investigator at the end of treatment. Both agents produced substantial symptomatic relief according to the patients' daily diary assessment; however cetirizine was more effective than loratadine in relieving the symptoms of rhinorrhea, sneezing, nasal obstruction and nasal pruritus ( $p < 0,0001$ ). Both treatments were well tolerated; two patients receiving cetirizine were dropped from the study because of adverse events.

*Assessor's Comment: This publication is considered as supportive due to study-design.*

A double-blind, placebo-controlled, and randomized study of loratadine (Clarityne) syrup for the treatment of allergic rhinitis in children aged 3 to 12 years.

Yang YH, Lin YT, Lu MY, Tsai MJ, Chiang BL.

Asian Pac J Allergy Immunol. 2001 Sep; 19(3):171-5

*supported by Schering Plough*

The aim of this double-blind, placebo-controlled, parallel, randomized study was to evaluate the effectiveness and safety of loratadine syrup for the treatment of children aged 3 to 12 years with allergic rhinitis. Sixty Chinese children with allergic rhinitis due to dust mites were enrolled. They were randomized into 2 parallel groups: one group received loratadine 5 mg or 10mg daily (<30kg body weight 5mg daily, >30kg body weight 10mg daily) for 3 weeks, and the other group received placebo. The patients returned to special clinics for symptoms evaluation at day 7 and day 21, and the parents were requested to record disease severity daily. Both evaluations, physicians' and parents' were recorded with a 4-point scale for 5 symptoms: sneezing, rhinorrhea, nasal congestion, nasal itching and ocular symptoms. Forty-six patients complete the study, 22 in the loratadine group and 24 in the placebo group. At the initial visit, the total symptom score (TSS) in both groups was not significantly different ( $p = 0.39$ ). The TSS of the loratadine syrup group at day 7 and day 21 was lower than those of the placebo group ( $p = 0.003$ ,  $p = 0.06$ ). The daily card scores in the experimental group were also significantly lower than those of the placebo group. No adverse reactions were recorded in both groups.

*Assessor's Comment: There is no information about the 14 patients who did not complete the study, it is only mentioned, that „only one of the 14 patients who did not complete the study complained about the unpleasant taste of the syrup.“*

A comparative study of the efficacy and safety of loratadine syrup and terfenadine suspension in the treatment of 3- to 6-year-old children with seasonal allergic rhinitis.

Lutsky BN, Klose P, Melon J, Menardo JL, Molkhou P, Ponchetti R, Suonpaa J, Wahn U, Wessel F.

Clin Ther. 1993 Sep-Oct; 15(5):855-65

The efficacy and safety of loratadine and terfenadine in the treatment of 3- to 6- year-old children with seasonal allergic rhinitis were compared in a third-party-blind, randomized, parallel-group study. A total of 96 children were included in the efficacy analysis: 49 children received 5 or 10 mg of loratadine once daily, and 47 received 25mg of terfenadine twice daily, for 14 days. The mean total score for both nasal and non-nasal symptoms was decreased significantly from baseline at days 3, 7 and 14 in both treatment groups. At endpoint, these scores had improved 73% in each group. There were no statistically significant differences between the two groups in the total symptom scores at any point during the study. Both treatments were effective in relieving individual nasal and non-nasal symptoms. Therapeutic response to treatment was good or excellent in 82% of loratadine-treated children and in 60% of terfenadine-treated children.

Few adverse events were reported during the study; all were mild or moderate and were not significantly different between the two treatment groups:

Blood pressure, temperature, pulse and respiratory rate were recorded at baseline and again on days 3, 7, and 14. Clinical laboratory tests (optional) and nasal examination were performed, and body weights were recorded, at baseline and at the end of the study. Parents or guardians of patients were questioned at each visit about adverse events that might have occurred since the previous visit. The results revealed no significant treatment-related changes. Treatment related adverse events (diarrhoea and nausea in the loratadine group) were reported in 4 % of the patients in each group. None of the patients discontinued the study because of adverse events.

*Assessor's Comment: Evaluation by the physician happened at baseline, day 3, 7, 14 and endpoint. The symptom scores were recorded daily for the patients by their parents or guardians. This publication is considered as supportive due to study-design.*

*Assessor's Comment on Efficacy: The submitted data gives some ambiguous information concerning efficacy in patients of all age groups, not especially in children. The CHMP considered in 2004 that loratadine has been shown to significantly reduce the symptoms of allergic rhinitis (AR) and chronic idiopathic urticaria. For each of this indications superiority to placebo was demonstrated in the change from baseline of total symptom scores or disease symptoms and signs.  
The questionable signs may occur due to publication bias.*

### **2.3 Clinical Safety**

The adverse event results summarized in this section are presented by age group. A summary of subject exposure by treatment duration across all studies is presented in **Table 8**.

**Table 8** Total Exposure in All Studies

Study No. (Study Duration) <sup>a</sup>	Number of Subjects							
	6 Months to 11 Years Old				12 to 17 Years Old		≥18 Years Old	
	LO	BM	MO	PL	LO	PL	LO	PL
1-Day Treatment								
C97-033 (1 day)	18	0	0	0	0	0	0	0
P00241 (1 day)	50	0	0	0	0	0	0	0
Subtotal <sup>b</sup>	68	0	0	0	0	0	0	0
5- to 15-Days Treatment								
C98-566 (15 days)	60	0	0	61	0	0	0	0
P00256 (7 days)	111	0	0	110	0	0	0	0
P00677 (15 days)	0	0	0	0	23	30	159	150
P00687 (15 days)	0	0	0	0	19	23	174	170
P03428 (5 days)	100	100	0	0	0	0	0	0
Q96-904 (14 days)	121	0	243	122	0	0	0	0
Subtotal <sup>b</sup>	392	100	243	293	42	53	333	320
Total	460	100	243	293	42	53	333	320

Abbreviations: BM – betamethasone; LO – loratadine; MO – mometasone furoate; PL - placebo.

a: Planned number of days of treatment.

b: Subtotal is the number of subjects within each treatment duration group.

### 2.3.1 Study No. C97-033 Safety

Study No. C97-033 was an open-label, single-center, single-dose study conducted in the United States to characterize the pharmacokinetic profiles of loratadine and its active metabolite, desloratadine in healthy pediatric subjects 2 to 5 years of age administered a single 5-mg dose of loratadine. There were 18 subjects between the ages of 2 and 5 years of age enrolled in the study. Eleven subjects were male and 7 subjects were female. The majority of subjects were Black (12 subjects), 5 subjects were Caucasian, and one subject was identified as “Other.” No adverse events were reported in any child in this study (**Table 9**).

**Table 9** Number (%) of Subjects with Adverse Events

Protocol No. C97-033	
	Number (%) of Subjects <sup>a</sup> 6 to 11 Years Old
	Loratadine (n=109)
Subjects Reporting Adverse Events <sup>b</sup>	0

a: Number of subjects reporting adverse events at least once during the study. Some subjects may have reported more than 1 adverse event.

b: Without regard to relationship to treatment.

In conclusion, loratadine was safe and well tolerated in pediatric subjects 2 to 5 years of age.

*Assessor's Comment: This study is only considered as supportive due to study-design*

### 2.3.2 Study No. C98-566 Safety

Study No. C98-566 was a randomized, double-blind, placebo-controlled, parallel group, single center, safety study conducted in the US to characterize the safety of loratadine syrup (5 mg QD), compared to placebo, administered for two weeks in children 2 to 6 years of age, with a documented history of allergic rhinitis or chronic idiopathic urticaria. Overall, there were 121 subjects between the ages of 2 and 6 years old. There were 67 female subjects and 54 male subjects. The majority of subjects were Caucasian (105 subjects), 15 subjects were Black, and 1 subject was Asian. The incidence of the most frequently reported adverse events, drowsiness, fever, headache, and vomiting, were comparable between the loratadine and placebo treatment groups: drowsiness (7% each), fever (loratadine 7% and placebo 8%), headache (loratadine 5% and placebo 7%), and vomiting (5% each). Dyspepsia was more common in the placebo group (7%) compared with the loratadine group (2%), although the actual number of subjects reporting this event was small. A summary of all treatment-emergent adverse events, by body system, reported by subjects in either treatment group is presented in **Table 10**.

**Table 10** Incidence of Treatment-Emergent Adverse Events by Body System/Organ Class (All Tre Subjects)

Study No. [C98-566](#)

Body System/Organ Class	Number <sup>a</sup> (%) of Subjects			
	Loratadine 5 mg (N = 60)		Placebo (N = 61)	
<b>Any Adverse Event<sup>b</sup></b>	<b>19</b>	<b>(32)</b>	<b>25</b>	<b>(41)</b>
<b>Autonomic Nervous System</b>	<b>0</b>		<b>1</b>	<b>(2)</b>
Lacrimation	0		1	(2)
<b>Body as a Whole – General Disorders</b>	<b>7</b>	<b>(12)</b>	<b>9</b>	<b>(15)</b>
Fatigue	1	(2)	0	
Fever	4	(7)	5	(8)
Headache	3	(5)	4	(7)
Influenza-like symptoms	1	(2)	0	
<b>Central and Peripheral Nervous System Disorders</b>	<b>0</b>		<b>2</b>	<b>(3)</b>
Hyperkinesia	0		2	(3)
<b>Gastro-Intestinal System Disorders</b>	<b>7</b>	<b>(12)</b>	<b>10</b>	<b>(16)</b>
Constipation	1	(2)	1	(2)
Diarrhea	2	(3)	0	
Dyspepsia	1	(2)	4	(7)
Loose stools	1	(2)	2	(3)
Nausea	0		2	(3)
Stomatitis	1	(2)	0	
Tooth disorder	1	(2)	0	
Vomiting	3	(5)	3	(5)
<b>Hearing and Vestibular Disorders</b>	<b>1</b>	<b>(2)</b>	<b>0</b>	
Earache	1	(2)	0	
<b>Musculoskeletal System Disorders</b>	<b>0</b>		<b>2</b>	<b>(3)</b>
Body aches	0		2	(3)
<b>Psychiatric Disorders</b>	<b>4</b>	<b>(7)</b>	<b>5</b>	<b>(8)</b>
Appetite increased	0		1	(2)
Drowsiness	4	(7)	4	(7)
<b>Resistance Mechanism Disorders</b>	<b>1</b>	<b>(2)</b>	<b>0</b>	
Infection, viral	1	(2)	0	
<b>Respiratory System Disorders</b>	<b>7</b>	<b>(12)</b>	<b>8</b>	<b>(13)</b>
Allergic rhinitis	1	(2)	2	(3)
Coughing	2	(3)	3	(5)
Epistaxis	2	(3)	0	
Nasal congestion	0		1	(2)
Pharyngitis	2	(3)	1	(2)
Sinus congestion	0		1	(2)
Sneezing	0		1	(2)
<b>Skin and Appendages Disorders</b>	<b>1</b>	<b>(2)</b>	<b>0</b>	
Rash	1	(2)	0	
<b>Urinary System Disorders</b>	<b>0</b>		<b>1</b>	<b>(2)</b>
Nocturia	0		1	(2)

a: Number of subjects reporting an adverse event at least once during the study. Some subjects may have reported more than one adverse event.

b: Without regard to relationship to treatment.

Body systems with the highest incidence of adverse events for both loratadine and placebo groups, respectively, were the body-as-a-whole (12% and 15%), gastrointestinal (12% and

16%), and respiratory (12% and 13%) systems. The overall incidence of adverse events was lower for the subjects treated with loratadine (32%) compared with placebo (41%). With the exception of dyspepsia (2% of loratadine-treated versus 7% of placebo-treated subjects), the incidence of individual adverse events was comparable ( $\leq 3\%$  difference) between the two groups. The majority of adverse events were considered by the Investigator to be unrelated to treatment. Overall, 20% of loratadine-treated subjects compared with 26% of placebo-treated subjects experienced adverse events considered possibly related to treatment. Drowsiness (7%) was the most commonly reported treatment related adverse event in the loratadine group. In the placebo group, drowsiness (7%), dyspepsia (7%), and vomiting (5%) were the most commonly reported treatment-related adverse events. All other treatment-related events had an incidence of  $\leq 3\%$  (one or two subjects) in either treatment group. All of the adverse events were of mild or moderate severity. None of the adverse events was considered severe. None of the subjects discontinued from the study because of adverse events.

In conclusion, loratadine was safe and well tolerated in the 121 pediatric subjects 2 to 6 years of age enrolled in this study.

### 2.3.3 Study No. P00241 Safety

Study No. P00241 was an open-label, single-center, single-dose study conducted in the United States to characterize the pharmacokinetic profiles of loratadine and its active metabolite, desloratadine, in healthy paediatric subjects 6 months to <2 years of age administered a single 2.5-mg dose or 5-mg dose of loratadine. There were 50 subjects between the ages of 6 months and 2 years of age enrolled in the study. Twenty-six subjects were male and 24 subjects were female. The majority of subjects were Black (28 subjects), 18 subjects were Caucasian, one subject was Hispanic, and three subjects were identified as "Other." Twelve (12) of the 50 subjects (24%) reported a treatment-emergent adverse event (**Table 11**). Of these 12 subjects, 7 subjects received the 2.5 mg (2.5 mL) loratadine syrup dose and 5 subjects received the 5 mg (5 mL) loratadine syrup dose reported treatment-emergent adverse events. All adverse events were mild in severity except for a single case of drowsiness ( $\geq 12$  to <24 months at 2.5 mg), which was reported as moderate. The most common adverse event reported was drowsiness (3/50, 6%). Three subjects required acetaminophen for adverse events. No subject discontinued from participation in the study due to an adverse event and there were no serious or unexpected adverse events reported. In subjects  $\geq 6$  months to <1 year of age a total of two subjects receiving a single 2.5 mg dose of loratadine syrup reported treatment emergent adverse events while there were no adverse events reported in subjects receiving 5 mg. In subjects  $\geq 1$  year to <2 years old a total of 5 subjects in both dose groups reported treatment emergent adverse events. Only one subject reported teething as an adverse event, which was considered unrelated to treatment. The follow-up physical examination and vital signs for all subjects were within ranges expected for healthy male and female pediatric subjects ages  $\geq 6$  months to <2 years. There were no clinically relevant changes in clinical laboratory safety test results reported for any subject.

*Assessor's Comment: There is some evidence that loratadine is safe in children from 6 months to <2 years. However, this alone is not sufficient for a recommendation for use in this age group.*

**Table 11** Incidence of Subjects Reporting All Treatment Emergent Adverse Events by Dose Group  
Protocol No. P00241

	Number (%) of Subjects Reporting Adverse Events by Dose Group	
	Loratadine Syrup 2.5 mg (N=25)	Loratadine Syrup 5 mg (N=25)
<b>No. of Subjects (%)<sup>a</sup> with Any Adverse Events<sup>b</sup></b>	<b>7 (28)</b>	<b>5 (20)</b>
<b>Body as a Whole-General Disorders</b>	<b>1 (4)</b>	<b>2 (8)</b>
Headache	0 (0)	1 (4)
Influenza-like Symptoms	1 (4)	0
Teething Pain	0 (0)	1 (4)
<b>Gastro-Intestinal System Disorders</b>	<b>3 (12)</b>	<b>0</b>
Anorexia	1 (4)	0
Dyspepsia	1 (4)	0
Flatulence	1 (4)	0
<b>Psychiatric Disorders</b>	<b>2 (8)</b>	<b>2 (8)</b>
Drowsiness	2 (8)	1 (4)
Emotional Lability	1 (4)	1 (4)
<b>Respiratory System Disorders</b>	<b>1 (4)</b>	<b>1 (4)</b>
Coughing	0	1 (4)
Nasal Congestion	1 (4)	0

a: Number of subjects reporting adverse events at least once. Subjects may have reported more than one adverse event.

b: All reported adverse events were mild in severity, with the exception of one moderate case of drowsiness and considered by the Investigator not to be related to study drug administration.

In conclusion, a single dose of loratadine was safe and well tolerated in the 50 pediatric subjects 6 months to 2 years of age enrolled in this study.

### 2.3.4 Study No. P00256 Safety

Study No. P00256 was a single-center, randomized, placebo-controlled, parallel-group, double-blind study conducted in the United States to characterize the safety of loratadine syrup (2.5 mL of 1 mg/mL syrup, orally QD) compared to placebo, for seven days, in children 6 months to 2 years of age with a personal or strong family history of allergies. Overall, there were **221** pediatric subjects between 6 and 24 months of age enrolled in the study. The mean age was 16.4 months. There were 110 female subjects and 111 male subjects. There were 111 Caucasian subjects, 108 Black subjects, and 2 subjects classified as "Other." No individual adverse events were reported by >3% of the subjects in either treatment group. The incidence of the most frequently reported adverse events, fever, loose stools, vomiting, and somnolence, were comparable between the loratadine and placebo treatment groups: fever (3% loratadine, 1% placebo), loose stools (2% loratadine, 3% placebo), vomiting (2% loratadine, 2% placebo), and somnolence (2% loratadine, 3% placebo). Hyperkinesia was reported in 3% of subjects from the placebo group while no subjects from the loratadine treatment group reported hyperkinesia (**Table 12**).

**Table 12** Incidence of Treatment-Emergent Adverse Events by Body System/Organ Class (All Treated Subjects)

Protocol No. P00256

Body System/Organ Class	Number <sup>a</sup> (%) of Subjects	
	Loratadine (n=111)	Placebo (n=110)
<b>Any Adverse Event<sup>b</sup></b>	<b>9 (8)</b>	<b>12 (11)</b>
<b>Body as a Whole – General Disorders</b>		
Fever	3 (3)	1 (1)
Headache	0	1 (1)
Teething Pain	1 (1)	0
<b>Central and Peripheral Nervous System Disorders</b>		
Hyperkinesia	0	3 (3)
<b>Gastrointestinal System Disorders</b>		
Anorexia	0	1 (1)
Loose Stools	2 (2)	3 (3)
Vomiting	2 (2)	2 (2)
<b>Metabolic and Nutritional Disorders</b>		
Thirst	0	1 (1)
<b>Psychiatric Disorders</b>		
Insomnia	0	1 (1)
Irritability	0	1 (1)
Somnolence	2 (2)	3 (3)
<b>Skin and Appendages Disorders</b>		
Rash	1 (1)	0

a: Number of subjects reporting an adverse event at least once during the study. Some subjects may have reported more than one adverse event.

b: Without regard to relationship to treatment.

Overall, 6% of loratadine-treated subjects reported treatment-related adverse events compared with 11% of placebo-treated subjects. All of the adverse events reported were mild or moderate severity. None of the adverse events was considered severe.

In conclusion, loratadine was safe and well tolerated in seven days of treatment in the 221 pediatric subjects 6 to 24 months old enrolled in this study.

### 2.3.5 Study No. P00677 Safety

Study No. P00677 was a randomized, multicenter, double-blind, placebo-controlled, parallel group study conducted in the United States to assess the efficacy and safety of loratadine 8 mg once daily (QD) for two weeks, compared to placebo, in subjects 12 to 67 years of age with SAR. Overall, there were 362 subjects between the ages of 12 and 67 years of age enrolled in the study. The mean age was 34.7 years of age. Most subjects were  $\geq 18$  years of age (309 subjects) and 53 subjects were between 12 to  $< 18$  years of age. The majority of subjects were female (232 subjects) and 130 subjects were male. The majority of subjects were Caucasian (275 subjects), 49 subjects were Black, 4 subjects were Asian, and 34 subjects were Hispanic. Overall, there were very few treatment-emergent adverse events. The most common adverse event was headache, reported in 11 (6.0%) subjects in the loratadine treatment group and 14 (7.8%) subjects treated with placebo. Other common adverse events included upper respiratory tract infections (loratadine: 7 subjects [3.8%]; placebo: 3 subjects [1.7%]), dry mouth (loratadine: 6 subjects [3.3%]; placebo: 5 subjects [2.8%]), fatigue (loratadine: 6 subjects [3.3%]; placebo: 2 subjects [1.1%]), and nausea (loratadine: 4 subjects [2.2%]; placebo: 6 subjects [3.3%]). The

incidence of adverse events was comparable in subjects 12 to 17 years of age and subjects  $\geq 18$  years of age in both the loratadine and placebo groups (Table 13). The only adverse events that were reported by more than one adolescent subject each were headache (loratadine: 1 subject [4.3%]; placebo: 2 subjects [6.7%]) and nausea (loratadine: 1 subject [4.3%]; placebo: 1 subject [3.3%]). There were too few subjects in the 12 to  $< 18$  (53 subjects, 14.6% of subjects overall) and  $\geq 65$  (2 subjects, 0.6% of subjects overall) age categories to provide a meaningful analysis by age.

**Table 13** Incidence of Treatment-Emergent Adverse Events ( $\geq 2\%$ ) by Age Group (Intent-to-Treat Subset)

Protocol No. P00677

	Number (%) of Subjects <sup>a</sup>					
	12 to $< 18$ Years Old		18 to $< 65$ Years Old		$\geq 65$ Years Old	
	LO (n=23)	PL (n=30)	LO (n=157)	PL (n=150)	LO (n=2)	PL (n=0)
<b>Any Adverse Event<sup>b</sup></b>	<b>5 (21.7)</b>	<b>8 (26.7)</b>	<b>52 (33.1)</b>	<b>48 (32.0)</b>	<b>2 (100.0)</b>	<b>0</b>
<b>Autonomic Nervous System Disorders</b>						
Mouth Dry	0	0	6 (3.8)	5 (3.3)	0	0
<b>Body as a Whole – General Disorders</b>						
Headache	1 (4.3)	2 (6.7)	8 (5.1)	12 (8.0)	2 (100)	0
Fatigue	0	0	6 (3.8)	2 (1.3)	0	0
Influenza-Like Symptoms	1 (4.3)	0	1 (0.6)	2 (1.3)	0	0
<b>Cardiovascular Disorders, General</b>						
Hypertension	0	1 (3.3)	0	0	0	0
<b>Central and Peripheral Nervous System Disorders</b>						
Dysphonia	0	1 (3.3)	0	0	0	0
<b>Gastrointestinal System Disorders</b>						
Nausea	1 (4.3)	1 (3.3)	3 (1.9)	5 (3.3)	0	0
Diarrhea	0	1 (3.3)	2 (1.3)	2 (1.3)	0	0
Dyspepsia	0	1 (3.3)	3 (1.9)	1 (0.7)	0	0
<b>Hearing and Vestibular Disorders</b>						
Ear Disorder NOS	0	1 (3.3)	0	1 (0.7)	0	0
<b>Musculoskeletal System Disorders</b>						
Fracture	0	1 (3.3)	0	0	0	0
Skeletal Pain	1 (4.3)	0	0	0	0	0
<b>Platelet, Bleeding, and Clotting Disorders</b>						
Bruise	0	1 (3.3)	0	1 (0.7)	0	0
<b>Respiratory Mechanism Disorders</b>						
Upper Respiratory Tract Infection	1 (4.3)	0	5 (3.2)	3 (2.0)	1 (50.0)	0
Pharyngitis	0	0	2 (1.3)	3 (2.0)	0	0
Epistaxis	0	0	1 (0.6)	3 (2.0)	0	0

Rhinitis	0	0	0	4 (2.7)	0	0
<b>Skin and Appendages Disorders</b>						
Urticaria	0	1 (3.3)	0	0	0	0
<b>Vascular (Extracardiac) Disorders</b>						
Migraine	0	0	0	3 (2.0)	0	0

Abbreviations: LO – loratadine; NOS – not otherwise specified; PL – placebo.

a: Number of subjects reporting an adverse event at least once during the study. Some subjects may have reported more than one adverse event.

b: Without regard to relationship to treatment.

Most adverse events reported in this study were assessed by the investigators as unrelated to study medication. Treatment-emergent adverse events considered as potentially related to study medication were reported in 13.7% (25/182) of the subjects in the loratadine treatment group and 11.1% (20/180) of the subjects treated with placebo. The only adverse events considered as potentially related to study medication in greater than or equal to 2% of the subjects in either treatment group were: dry mouth, headache, and fatigue. There were a similar number of subjects in both treatment groups that experienced dry mouth and headache as a potentially related treatment-emergent adverse event. However, 6 subjects (3.3%) in the loratadine treatment group compared to only 1 subject (0.6%) treated with placebo reported fatigue as an adverse event that was considered as potentially related to study medication. The majority of subjects experienced treatment-emergent adverse events that were rated as mild (loratadine: 20/182, 11.0%; placebo 13/180, 7.2%) or moderate (loratadine: 26/182, 14.3%; placebo 28/180, 15.6%) in severity. Treatment emergent adverse events that were rated as severe in intensity were reported in only 13 subjects (7.1%) in the loratadine treatment group and 15 subjects (8.3%) treated with placebo. The most common severe treatment-emergent adverse event was headache, which was reported in 4 subjects (2.2%) and 6 subjects (3.3%) in the loratadine and placebo treatment groups, respectively. Migraine was also reported in 2 subjects (1.1%) treated with placebo. Severe treatment-emergent adverse events that were considered to be potentially related to study medication were experienced by a similar number of subjects (loratadine: 6/182, 3.3%; placebo; 7/180, 3.9%) in both treatment groups. The most common potentially related severe treatment-emergent adverse event was headache, which was experienced by 2 subjects (1.1%) in the loratadine treatment group and 4 subjects (2.2%) treated with placebo. The migraine experienced by the 2 subjects (1.1%) in the placebo treatment group was also assessed as potentially related to study drug. A total of 8 subjects (loratadine: 3/182, 1.6%; placebo: 5/180, 2.8%) discontinued from the study because of an adverse event. The most frequently reported adverse events leading to discontinuation were adverse events that were coded to the Respiratory System, such as sinusitis and/or upper respiratory tract infection (loratadine, 2 subjects; placebo, 3 subjects) and cough (loratadine, 1 subject; placebo, 1 subject). The greatest number of subjects who discontinued due to adverse events was randomized to the placebo treatment group. The majority of adverse events that led to discontinuation were considered unrelated to study medication and were moderate in severity. One adolescent subject in the placebo group discontinued treatment due to elevated blood pressure. No other adolescent subjects discontinued treatment due to adverse events.

In conclusion, loratadine was safe and well tolerated in two weeks of treatment and no different treatment effect was noted in safety between the 53 adolescent subjects and the 309 adult subjects enrolled in this study.

### 2.3.6 Study No. P00687 Safety

Study No. P00687 was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study conducted in the United States to assess the efficacy and safety of loratadine 8 mg QD for two weeks compared to placebo in subjects with allergic rhinitis.

Overall, there were 386 subjects between the ages of 12 and 75 years of age enrolled in the study. The mean age was 34.5 years of age. Most subjects were  $\geq 18$  years of age (344 subjects) and 42 subjects were between 12 to  $< 18$  years of age. The majority of subjects were female (251 subjects) and 135 subjects were male. The majority of subjects were Caucasian (305 subjects), 41 subjects were Black, 1 subject was American Indian, 9 subjects were Asian, and 30 subjects were Hispanic. Overall, there were very few treatment-emergent adverse events. The most common adverse event was headache, reported in 19 (9.8%) subjects in the loratadine treatment group and 15 (7.8%) subjects treated with placebo. Other common adverse events included dizziness (loratadine: 5 (2.6%) subjects; placebo: 4 (2.1%) subjects), somnolence (loratadine: 8 (4.1%) subjects; placebo: 1 (0.5%) subjects), diarrhoea (loratadine: 2 (1.0%) subjects; placebo: 4 (2.1%) subjects), abdominal pain (loratadine: 0 (0.0%) subjects; placebo: 5 (2.6%) subjects), and epistaxis (loratadine: 4 (2.1%) subjects; placebo: 1 (0.5%) subjects).

The only adverse event that was reported by more than one adolescent subject was headache (loratadine: 2 subjects [10.5%]; placebo: 2 subjects [8.7%]). There were too few subjects in the 12 to  $\leq 18$  (42 subjects, 10.9% of subjects overall) and  $\geq 65$  (6 subjects, 1.6% of subjects overall) age categories to provide a meaningful analysis by age.

Table 14 Incidence of Treatment-Emergent Adverse Events (≥2%) by Age Group (Intent-to-Treat Subset)

Protocol No. P00687

	Number (%) of Subjects <sup>a</sup>					
	12 to <18 Years Old		18 to <65 Years Old		≥65 Years Old	
	LO (n=19)	PL (n=23)	LO (n=170)	PL (n=168)	LO (n=4)	PL (n=2)
<b>Any Adverse Event<sup>b</sup></b>	3 (15.8)	9 (39.1)	60 (35.3)	45 (26.8)	2 (50.0)	0
<b>Body as a Whole – General Disorders</b>						
Headache	2 (10.5)	2 (8.7)	16 (9.4)	13 (7.7)	1 (25.0)	0
Back Pain	0	0	1 (0.6)	4 (2.4)	0	0
Fatigue	0	1 (4.3)	2 (1.2)	0	0	0
<b>Central and Peripheral Nervous System Disorders</b>						
Dizziness	0	1 (4.3)	5 (2.9)	3 (1.8)	0	0
Tremor	1 (5.3)	0	0	0	0	0
<b>Gastrointestinal System Disorders</b>						
Diarrhea	0	1 (4.3)	2 (1.2)	3 (1.8)	0	0
Abdominal Pain	0	1 (4.3)	0	4 (2.4)	0	0
Dyspepsia	0	1 (4.3)	3 (1.8)	1 (0.6)	0	0
Nausea	0	1 (4.3)	1 (0.6)	0	0	0
Vomiting	0	1 (4.3)	0	0	0	0
<b>Musculoskeletal System Disorders</b>						
Arthralgia	1 (5.3)	0	1 (0.6)	0	0	0
<b>Myocardial, Endocardial, Pericardial and Valve Disorders</b>						
Coronary Artery Disorder	0	0	0	0	1 (25.0)	0
<b>Psychiatric Disorders</b>						
Somnolence	1 (5.3)	0	7 (4.1)	1 (0.6)	0	0
<b>Resistance Mechanism Disorders</b>						
Infection Viral	0	1 (4.3)	4 (2.4)	3 (1.8)	0	0
<b>Respiratory Mechanism Disorders</b>						
Pharyngitis	0	2 (8.7)	4 (2.4)	3 (1.8)	0	0
Epistaxis	0	0	4 (2.4)	1 (0.6)	0	0
Cough Nonproductive	0	1 (4.3)	0	0	0	0

Abbreviations: LO – loratadine; PL – placebo.

a: Number of subjects reporting an adverse event at least once during the study. Some subjects may have reported more than one adverse event.

b: Without regard to relationship to treatment.

Most adverse events reported in this study were assessed by the investigators as unrelated to study medication. Treatment-emergent adverse events considered as potentially related to study medication were reported in 13.5% (26/193) of the subjects in the loratadine treatment group and 7.8% (15/193) of the subjects treated with placebo. The only treatment-emergent adverse events considered as potentially related to study medication in greater than or equal to 2% of the subjects in either treatment group were: headache, dizziness, and somnolence. Approximately an equal number of subjects in both treatment groups reported headache as a potentially related treatment-emergent adverse event. However, dizziness and somnolence were experienced by 4 (2.1%) and 6 (3.1%) subjects in the loratadine treatment group compared to only 1 (0.5%) subject for both adverse events in the placebo treated subjects, respectively. The majority of subjects experienced treatment-emergent adverse events that were rated as mild (loratadine:

25/193, 13.0%; placebo 17/193, 8.8%) or moderate (loratadine: 28/193, 14.5%; placebo 31/193, 16.1%) in severity. Treatment emergent adverse events that were rated as severe in intensity were reported in 12(6.2%) subjects in the loratadine treatment group and 6 (3.1%) subjects treated with placebo. The only severe treatment-emergent adverse event that occurred in 2 or more subjects in either treatment group was headache (loratadine: 5/193, 2.6%; placebo: 2/193, 1.0%). Severe treatment-emergent adverse events that were considered to be potentially related to study medication only occurred in 3 (1.6%) subjects in the loratadine treatment group. One subject each in the loratadine treatment group experienced headache, constipation, and sinusitis that were rated as severe by the investigators. Two subjects in the loratadine treatment group experienced serious adverse events reported in this study. Neither of these events were considered related to study medication and neither subject was <18 years of age. A total of 6 subjects (loratadine: 3/193, 1.6%; placebo: 3/193, 1.6%) discontinued from the study because of an adverse event. Two subjects in the loratadine treatment group experienced treatment-emergent adverse events leading to discontinuation that were considered as possibly related to study medication. None of the treatment-emergent adverse events leading to study discontinuation that were reported by the placebo treated subjects were assessed as possibly related to study medication. One subject in the placebo group <18 years of age discontinued treatment due to an adverse event (pharyngitis) that was considered unlikely related to treatment.

In conclusion, loratadine was safe and well tolerated in two weeks of treatment and no different treatment effect was noted in safety between the 42 adolescent subjects and the 344 adult subjects enrolled in this study.

*Assessor's Comment: The 8mg dose is not in accordance to the common 10mg dose recommended in the current SPCs. Children >12 years of age usually weight 30kg or more.*

### 2.3.7 Study No. P03428 Safety

Study No. P03428 was an open-label, prospective, non-comparative, multicenter study conducted in Venezuela to evaluate the efficacy and safety of loratadine/betamethasone oral solution (1 mg/0.05 mg/1 mL), for five days, at a dose of 10 mg/0.5 mg, respectively, as an initial treatment for severe perennial allergic rhinitis in school age children. There were **100** subjects between the ages of 6 and 12 years of age enrolled in the study. The average age of subjects was 9.73 years. Sixty-nine subjects were male and 31 subjects were female. No adverse events were reported in any child or adult in this study (**Table 15**).

**Table 15** Number (%) of Subjects with Adverse Events

Protocol No. <b>P03428</b>	
	Number (%) of Subjects <sup>a</sup>
	Loratadine/Betamethasone (n=100)
<b>Subjects Reporting Adverse Events<sup>b</sup></b>	<b>0</b>

a: Number of subjects reporting adverse events at least once during the study. Some subjects may have reported more than 1 adverse event.

b: Without regard to relationship to treatment.

In conclusion, loratadine, in combination with betamethasone, was safe and well tolerated in pediatric subjects 6 to 12 years of age.

### **2.3.8 Study No. Q96-904 Safety**

Study No. Q96-904 was a randomized, multicenter, double-blind, placebo-controlled study conducted in Italy to evaluate the advantage of the oral supplementation with a non-sedating H1 antihistamine (loratadine) to the standard treatment with a topical steroid (mometasone furoate) for 14 days during the flares of AD in children 2 to 12 years of age. Overall, there were **243** subjects between of 2 and 12 years of age enrolled in the study. There were 112 female subjects and 131 male subjects. The tolerance of the treatment was judged excellent or good in both groups at every control visit, with no statistically significant difference between the two groups. The most frequently reported adverse event was sedation, which was reported by 8 subjects (6.6%) in the mometasone furoate (MF) + loratadine (LO) group and by 7 subjects (5.7%) in the MF + placebo (PL) group. Fatigue and headache were each reported by 3 subjects (2.5%) in the MF + LO group and 1 subject (0.8%) in the MF + PL group. Pruritus was reported by 1 subject (0.8%) in the MF + LO group and 3 subjects in the MF + PL group. Cough was reported by 2 subjects (1.7%) in the MF + LO group and not reported by any subjects in the MF + PL group, while skin irritation was not reported by any subject in the MF + LO group but by 2 subjects (1.6%) in the MF + PL group. All other adverse events were reported by one subject in either the MF + LO group, the MF + PL group, or both groups. In only one case, the occurrence of an adverse event possibly related to the administration of loratadine (ie, fatigue and difficulty in concentration) required the suspension of the treatment. In a second case the treatment was suspended by request of the subject's mother following an episode of mild sedation. As far as it concerns the adverse events of the topical treatment with MF+PL, pruritus was observed in four subjects, skin irritation in 2 subjects, and eczema in 2 subjects. Signs of atrophy due to the steroid use were accurately researched at every control visit, but were not observed in any subject.

Table 16 Type of Adverse Event Reported for Each Case

Protocol No. Q96-904

			Adverse Event		
	Case	Record	Visit 2	Visit 3	Visit 4
Mometasone Furoate + Loratadine (n=121)	021	052	-	-	Herpetic Gingivostomatitis
	025	128	-	Headache	-
	042	005	Sedation	Sedation	Sedation
	063	003	-	-	Eczema
	101	141	-	-	Flu Syndrome With Cough
	122	069	Fatigue	Sedation, Fatigue	-
	125	144	Sedation	Sedation	-
	176	218	-	Headache, Fatigue, Sedation	-
	223	148	Sedation	Sedation	Sedation
	241	077	-	-	Sedation
	251	208	Impetigo	-	-
	261	095	Headache	Headache	Headache
	265	242	Pruritus	-	-
	283	096	-	Fatigue, Impaired Concentration	-
	287	153	-	Sedation	-
	309	042	-	Sedation	-
	330	182	-	-	Cough
	332	184	-	Cough	-
426	188	-	Conjunctivitis Bacterial	-	
Mometasone Furoate + Placebo (n=122)	003	027	-	Gastrointestinal Disorder With Vomiting	-
	028	253	-	Asthmatic Attack	-
	048	054	-	Gastrointestinal Disorder	-
	049	232	Cold	-	-
	051	056	Pruritus	-	-
	061	001	Eczema	Pruritus, Eczema	-
	124	071	Sedation	-	-
	144	239	-	-	Rhinitis
	177	219	Headache, Fatigue, Sedation	-	-
	182	029	Skin Irritation	Skin Irritation	-
	284	150	Sedation	Sedation	-
	307	040	-	-	Sedation, Pruritus, Skin Irritation
	326	099	Impetigo	-	-
	329	181	-	Flu Syndrome	-
	334	197	-	Sedation	Nervousness
	430	190	Sedation	Sedation	Sedation
431	245	-	-	Sedation	

In conclusion, loratadine in combination with mometasone furoate was safe and well tolerated during two weeks of treatment in pediatric subjects 2 to 12 years of age, enrolled in this study.

### 2.3.9 Supportive Data Safety: Publications

Children's school performance is not impaired by short-term administration of diphenhydramine or loratadine.

Bender BG, McCormick DR, Milgrom H.  
J Pediatr. 2001 May; 138(5):656-60  
*supported by Schering Plough*

**Objective:** The purpose of this study was to determine whether a second generation H1 antihistamine produces less sedation in children and permits greater learning in a school setting than a classic antihistamine.

**Study design:** Sixty-three 8- to 10- year old children who had histories of seasonal allergic rhinitis but had no symptoms at the time of the study were randomly assigned to 1 of 3 treatment groups: placebo, diphenhydramin or loratadine (10 mg once daily). Medications were administered on 3 of 4 study days, twice 6 hours apart, while participants attended a laboratory school. Classroom testing at the end of each school day evaluated the children's retention of curriculum material. Potential sedative effects were additionally evaluated by self-report of somnolence and computerized reaction time testing.

**Results:** No treatment-related differences emerged on the verbal instruction score, reading test score, reaction time or somnolence scale.

**Conclusion:** Learning and response time in children attending a laboratory school were not significantly affected by either antihistamine.

*Assessor's Comment: Loratadine showed to be non-sedative in this study sample (about 20 children received loratadine).*

Salmun LM, Herron JM, Banfield C, Padhi D, Lorber R, Affrime MB.  
Clin Ther. 2000 May; 22(5):613-21.  
*supported by Schering Plough*

The results suggest that in a small, selected group of children aged 2 to 5 years at a dose providing exposure similar to that with the adult dose (ie, 10mg once daily), loratadine was well tolerated in both single and multiple doses with no adverse events occurring with greater frequency after multiple doses of loratadine than after placebo.

*Assessor's Comment: This publication seems to be extracted from the above mentioned studies C97-033 and C98 566.*

**The following Publications were summarized in section 2.2.5 but can also be considered with regard to safety evaluation:**

Double-blind comparison of cetirizine and loratadine in children ages 2 to 6 years with perennial allergic rhinitis.

Sienra-Monge JJ, Gazca-Aguilar A, Del Rio-Navarro B.  
Am J Ther. 1999 May; 6(3):149-55

A double-blind, placebo-controlled, and randomized study of loratadine (Clarityne) syrup for the treatment of allergic rhinitis in children aged 3 to 12 years.

Yang YH, Lin YT, Lu MY, Tsai MJ, Chiang BL.  
Asian Pac J Allergy Immunol. 2001 Sep; 19(3):171-5

*supported by Schering Plough*

A comparative study of the efficacy and safety of loratadine syrup and terfenadine suspension in the treatment of 3- to 6-year-old children with seasonal allergic rhinitis.

Lutsky BN, Klose P, Melon J, Menardo JL, Molkhou P, Ponchetti R, Suonpaa J, Wahn U, Wessel F.

Clin Ther. 1993 Sep-Oct; 15(5):855-65

*Assessor's overall Comment on Safety: The type and frequency of adverse events seem similar to those seen in the adult population.*

## **V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**

### **➤ Overall conclusion**

The eight studies described in this overview included a total of 1501 subjects of which 753 were pediatric subjects between 6 months and  $\leq 11$  years of age, 95 were adolescent subjects between 12 and  $\leq 17$  years of age, and 653 were adult subjects  $\geq 18$  years of age. The data from these studies revealed no concerns in the efficacy or safety of loratadine in any age group, when subjects are treated with age and weight-appropriate doses of loratadine, as determined by the Clinical Pharmacology studies included in this submission. Loratadine was consistently safe and well-tolerated in the subjects in the studies presented in this submission. The incidence and types of adverse events reported in pediatric and adolescent subjects in these studies were similar to those seen in previously reported studies with loratadine and indicative of common pediatric illnesses and the condition that the subjects were being treated for in the studies. Also, in general, the types and frequencies of the adverse events reported in pediatric and adolescent subjects were consistent with adverse events reported in adult subjects treated with loratadine.

Overall, the safety profile of loratadine observed in the studies summarized in this Overview is consistent with that in the existing Reference Safety Information for loratadine and does not indicate a need to make any changes to the current approved product information.

The efficacy and safety of Desloratadine have been well established through extensive clinical trial and post-marketing experience. Loratadine 10-mg Tablets have been marketed in the EU since FEB 1988. Based on available IMS data, total worldwide patient exposure to loratadine products is estimated to have been 13.1 billion patient days in the period from 01 JAN 1995 through 31 JUL 2009. Loratadine has not been withdrawn from any market worldwide for any reason related to safety or effectiveness.

After evaluating the presented data we conclude that the administration of Loratadine in children in Europe can be recommended according to the current SPC-recommendation (referral text (CPMP/1333/03 Annex III, Article 31)).

### **➤ Recommendation**

Schering Plough state that an update of the Product information is not required. The referral text (CPMP/1333/03 Annex III, Article 31) is recommended for all SmPCs.

In Austria Loratadine is only available on prescription for children < 12 years.

## VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable

## VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

<b>AESCA Pharma GmbH Traiskirchen</b>	Clarityn	5 mg/5 ml	SYRUP
<b>AESCA Pharma GmbH Traiskirchen</b>	Clarityn	10 mg	TABLETS
<b>Essex Italia S.p.A</b>	ALORIN	10 mg	TABLETS
<b>Essex Italia S.p.A</b>	ALORIN	5mg/5ml	SYRUP
<b>Essex pharma GmbH</b>	LISINO	10 mg	TABLETS
<b>F.I.R.M.A. S.p.A.</b>	FRISTAMIN 10 mg comprese rivestite	10mg	tbls
<b>PHARMEX S.A.</b>	UTEL	10mg/tab	Tablets
<b>PHARMEX S.A.</b>	UTEL	5mg/5ml	Syrup
<b>Plough-Farma, Lda.</b>	Alertrin	1mg/ml	SYRUP
<b>Plough-Farma, Lda.</b>	Alertrin	10 mg	TABLETS
<b>Schering-Plough S.p.A.</b>	CLARITYN	5mg/5ml	SYRUP
<b>Schering-Plough B.V.</b>	Claritine, stroop 1 mg/ml	1mg/ml	SYRUP
<b>Schering-Plough B.V.</b>	Claritine, tabletten 10 mg, Claritine, bruistabletten 10 mg	10 mg	TABLETS
<b>SP Europe, Bruxelles, Belgie</b>	Claritine	1mg/ml	SYRUP
<b>SP Europe, Bruxelles, Belgie</b>	Claritine	10mg	TABLETS
<b>SP Europe, Bruxelles, Belgie</b>	Claritine	1 mg/ml	SYRUP
<b>SP Europe, Bruxelles, Belgie</b>	Claritine	10 mg	TABLETS
<b>Schering-Plough Europe</b>	Claritine " SP Europe"	10 mg	tablets
<b>Schering-Plough Europe</b>	Claritine " SP Europe"	1mg/ ml	syrup

<b>Schering-Plough Europe</b>	Claritine	1,00 mg/ml	SYRUP
<b>Schering-Plough Europe</b>	Claritine	10,0 mg	TABLETS
<b>Schering-Plough Europe</b>	Loratadine SP Clarityn Syrup	10,0 mg 1mg/ml	SYRUP
<b>Schering-Plough Europe</b>	Clarityn Tablets	10mg	TABLETS
<b>Schering-Plough Europe</b>	CLARITINE	10mg	TABLETS
<b>Schering-Plough Europe</b>	CLARITINE	1mg/g	SYRUP
<b>Schering-Plough Europe</b>	Clarityn	1 mg/ml	SYRUP
<b>Schering-Plough Europe</b>	Clarityn	10 mg	TABLETS
<b>Schering-Plough Europe</b>	Clarityn	10 mg	Tablet
<b>Schering-Plough Europe</b>	Clarityn, MRP	1 mg/ml	SYRUP
<b>Schering-Plough Europe</b>	Clarityn, MRP	10 mg	TABLETS
<b>Schering-Plough Europe</b>	Clarityn Allergy Syrup	1mg/ml	SYRUP
<b>Schering-Plough Europe</b>	Clarityn Allergy Tablets	10mg	TABLETS
<b>Schering-Plough Europe</b>	Clarityn Allergy 1mg/ml Syrup	1mg/ml	SYRUP
<b>Schering-Plough Europe</b>	Clarityn Allergy Tablets	10mg	TABLETS
<b>Schering-Plough Europe</b>	CLARITINE	10 mg; 1mg/ml	TABLETS, SYRUP
<b>Schering-Plough Europe</b>	CLARITINE	10 mg; 1mg/ml	TABLETS, SYRUP
<b>Schering-Plough Europe</b>	CLARITINE	10 mg	TABLETS
<b>Schering-Plough Europe</b>	CLARITINE	1 mg/ml	SYRUP
<b>Schering-Plough Europe</b>	Alertrin	1mg/ml	SYRUP
<b>Schering-Plough Europe</b>	Alertrin	10 mg	TABLETS
<b>Schering-Plough Europe</b>	Claritine	1mg/ml	SYRUP
<b>Schering-Plough Europe</b>	Claritine	10 mg	TABLETS
<b>Schering-Plough Europe</b>	CLARITINE		TABLETS
<b>Schering-Plough Farma, Lda.</b>	Claritine	1mg/ml	SYRUP

<b>Schering-Plough Farma, Lda.</b>	Claritine	10 mg	TABLETS
<b>Schering-Plough France</b>	CLARITYN	10 mg	TABLETS
<b>Schering-Plough France</b>	CLARITYNE	0,1 g/ml	SYRUP
<b>Schering-Plough Ltd</b>	Clarityn Syrup	1mg/ml	SYRUP
<b>Schering-Plough Ltd</b>	Clarityn Tablets	10mg	TABLETS
<b>Schering-Plough S.A.</b>	CLARITYNE	5mg/5ml	SYRUP
<b>Schering-Plough S.A.</b>	CLARITYNE	10mg/TAB	TABLETS
<b>Schering-Plough S.A.</b>	CLARITYNE	10mg/tablet	TABLETS
<b>Schering-Plough S.A.</b>	CLARITYNE	5mg/5ml	SYRUP