20 November 2014
EMA/205702/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

International non-proprietary name: desloratadine

Procedure No.

Aerius EMEA/H/C/000313/P46/064

Azomyr EMEA/H/C/000310/P46/064

Neoclarityn EMEA/H/C/000314/P46/064

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

It concerns a submission according to the P-46 article of the EU Paediatric Regulation (EC No 1901/2006) i.e. the results of two clinical studies (P201 – P202) conducted in Japan with desloratadine as these studies included subjects that were younger than 18 years old.

These studies are not being submitted in support of a new pediatric indication for desloratadine in the EU.

1.1. Steps taken for the assessment

Submission date:	10 September 2014
Start of procedure:	21 September 2014
CHMP Rapporteur's preliminary assessment report circulated on:	21 October 2014
CHMP outcome:	20 November 2014

2. Assessment of the post-authorisation measure P46-064

P201

Study design: multi-center, double-blind, parallel-group, randomized, placebo-controlled clinical trial to study the safety and efficacy of desloratadine (DL) tablets in Japanese subjects 12 years and older with chronic urticaria.

Participants: 239 randomized subjects, including 11 subjects 12-17 years of age

Study medication: after the screening period, subjects meeting all eligibility criteria received study treatment orally for 2 weeks in a double-blinded manner. They were randomized to one of 3 treatments:

- DL 10 mg once daily (10 mg group)
- DL 5 mg once daily (5 mg group)
- Placebo once daily (placebo group)

Primary efficacy endpoint: change from baseline in sum of pruritus/itch (either day- or nighttime whichever was higher than the other) and rash (overall assessment of rash) scores, as assessed by the (sub-) investigator at Week 2.

Efficacy Results: Primary endpoint:

Changes from Baseline in Sum Score of Pruritus/Itch (Either Daytime or Nighttime Whichever Was Higher Than the Other) and Rash (Overall Assessment of Rash) Assessed by (Sub-) Investigator at Week 2 (FAS) (P201)

Treatment	N	Baseline Mean(SD)	Week 2 Mean(SD)	Sum of Pruritus/itch (higher day or night) and Rash (overall) Change from Baseline at Week 2	
				Mean(SD)	LS Mean(95% CI) †
DL 10 mg	79	5.06(0.91)	1.85(1.58)	-3.21(1.72)	-3.16(-3.52,-2.79)
DL 5 mg	80	4.98(1.02)	1.79(1.52)	-3.19(1.68)	-3.19(-3.56,-2.83)
Placebo	80	4.91(0.75)	2.81(1.83)	-2.07(1.83)	-2.02(-2.40,-1.65)
Estimated Difference				Difference in LS Means (95% CI)	p-value
DL 10 mg vs. Placebo				-1.13(-1.66,-0.61)	<0.001
DL 5 mg vs. Placebo				-1.17(-1.69,-0.65)	<0.001

†Based on cLDA (constrained longitudinal data analysis) model with terms of visit, visit-by-treatment, visit-by-age strata, visit-by-severity interactions; visit is treated as a categorical variable.
N = Number of subjects with baseline or at least one post baseline observation.
CI = Confidence Interval; LS Mean = Least-Squares Mean; SD = Standard Deviation.
DL: Desloratadine

Conclusion on efficacy:
The change from baseline in the primary endpoint sum score of pruritus/itch (either day- or nighttime whichever was higher than the other) and rash was statistically significantly superior in the DL 10 mg group and the DL 5 mg group compared to the placebo group, demonstrating ***superiority of both DL groups over the placebo group***.

Safety Results

	DL 5 mg		DL 10 mg		Placebo	
	n	(%)	n	(%)	n	(%)
Subjects in population	80		79		79	
with one or more adverse events	24	(30.0)	18	(22.8)	16	(20.3)
with no adverse event	56	(70.0)	61	(77.2)	63	(79.7)
with drug-related† adverse events	7	(8.8)	11	(13.9)	2	(2.5)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	2	(2.5)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
ASaT: All-subjects-as-treated.
DL: Desloratadine.
Treatment period starts from the first dose day of study medication until 14 follow-up days after the last dose day of study medication.

The incidence of adverse events was 30.0% (24/80 subjects) for DL 5 mg group, 22.8% (18/79 subjects) for DL 10 mg group and 20.3% (16/79 subjects) for placebo group.
The incidence of drug-related adverse events was 8.8% (7/80 subjects) for DL 5 mg group, 13.9% (11/79 subjects) for DL 10 mg group and 2.5% (2/79 subjects) for placebo group.

The incidence of **drug-related somnolence was generally low**: 3.8% (3/80) in DL 5 mg, 6.3% (5/79) in DL 10 mg and 2.5% (2/79) in the placebo group. Recovery occurred during the study drug treatment period or within 2 days from the final dose.

No serious adverse events or deaths were reported.

The incidence of **treatment discontinuation due to adverse events** was 0.0% for the DL 5 mg group, 0.0% for DL 10 mg group and 2.5% (2/79 subjects) for placebo group i.e. because of dermatitis contact and seasonal allergy.

One of the subjects 12-17 years old experienced 2 non serious adverse events, that were mild in intensity and resolved after completion of treatment i.e. pyrexia and nasopharyngitis. The investigator considered these events to be unrelated to the study drug.

Conclusion on safety:
DL 10 mg and 5 mg administered once daily for 14 days were generally safe and well-tolerated.

P202

Study design: multi-center, open-label long-term Phase III trial to study the safety and efficacy of desloratadine (DL) tablets in Japanese subjects 12 years and older with eczema/dermatitis and dermal pruritus who were treated up to 8 to 12 weeks.

Participants: 94 enrolled and treated subjects, including 10 subjects 12-17 years of age in the eczema/dermatitis group and 4 in the dermal pruritus group.

Study medication: after the screening period, subjects meeting all eligibility criteria received open-label DL 5 mg once daily in an unblinded way.
After 4 weeks, an up-titration to DL up to 10 mg once daily was possible if the (sub-)investigator judged there was insufficient anti-pruritic efficacy and no safety concern. Only one dose increase was allowed from Week 4 (Visit 6) to Week 8 (Visit 8).
When DL was increased, the higher dose was maintained, but if the (sub-)investigator determined that there was a safety concern of the subject, dose reduction to DL 5 mg/day was allowed, depending on symptoms and the degree of severity of itching. After a dose reduction, no new increase of the dose was allowed.

Primary efficacy endpoint: change from baseline in the sum pruritus/itch scores (day- and nighttime), as assessed by the (sub-) investigator at Week 2.

Efficacy Results: Primary endpoint:

Change from Baseline in Sum Pruritus/Itch Score (Sum of Daytime and Nighttime) Assessed by (Sub-) Investigator at Week 2 (FAS) (P202)

Disease Group	N	Baseline Mean (SD)	At Week 2 Mean (SD)	Change from Baseline		
				Mean(SD)	LS Mean (95% CI)†	p-value
All Subjects	94	4.86 (1.23)	3.02 (1.44)	-1.83 (1.54)	-1.99 (-2.39, -1.59)	<0.001
Eczema/Dermatitis	65	4.75 (1.10)	3.06 (1.33)	-1.67 (1.32)	-1.63 (-2.01, -1.25)	<0.001
Dermal Pruritus	29	5.10 (1.47)	2.93 (1.69)	-2.17 (1.91)	-2.17 (-2.74, -1.61)	<0.001

†Based on the LDA (longitudinal data analysis) model with terms of visit, group, and group by visit interaction, a visit is treated as a categorical variable.
CI = Confidence Interval; LS Mean = Least-Squares Mean; SD = Standard Deviation.

Conclusion on efficacy:
A significant improvement from baseline in the primary endpoint sum score of pruritus/itch (sum of day- and nighttime) was observed both in the eczema/dermatitis group and the dermal pruritus group.

However, the significance of these data is limited as it concerned an open-label trial.

Safety Results

	Eczema/Dermatitis		Dermal Pruritus		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	65		29		94	
with one or more adverse events	35	(53.8)	14	(48.3)	49	(52.1)
with no adverse event	30	(46.2)	15	(51.7)	45	(47.9)
with drug-related[†] adverse events	7	(10.8)	1	(3.4)	8	(8.5)
with serious adverse events	1	(1.5)	0	(0.0)	1	(1.1)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	4	(6.2)	2	(6.9)	6	(6.4)
discontinued due to a drug-related adverse event	0	(0.0)	1	(3.4)	1	(1.1)
discontinued due to a serious adverse event	1	(1.5)	0	(0.0)	1	(1.1)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.
ASaT: All-subjects-as-treated.
Although a subject may have had 2 or more adverse experiences, a subject is counted only once within a category. The same subject may appear in different categories.
Treatment period starts from the first dose day of study medication until 14 follow-up days after the last dose day of study medication.

The incidence of adverse events was 53.8% (35/65 subjects) in the eczema/dermatitis group and 48.3% (14/29 subjects) in the dermal pruritus group.
The incidence of drug-related adverse events was 10.8% (7/65 subjects) in the eczema/dermatitis group and 3.4% (1/29 subjects) in the dermal pruritus group.

The most commonly reported drug-related adverse event was **somnolence**: 6.2% (4/65 subjects) in the eczema/dermatitis group, 0.0% (0/29 subjects) in the dermal pruritus group; all of them resolved during the study drug administration.

No serious drug-related adverse events or deaths were reported.

One serious adverse event of mild skin neoplasm requiring hospitalization was reported in 1 subject in the eczema/dermatitis group which was considered as unrelated to study drug. The subject was recovered after surgical removal of the neoplasm.
Other AEs leading to discontinuation included acarodermatitis, gastroenteritis, and headache (in one subject each) in the eczema/dermatitis group and asteatotic eczema and back pain (in one subject each) in the dermal pruritus group. Among them, only the asteatotic eczema was considered as a drug-related AE. The event was mild and resolved after the discontinuation of the study drug.

Dose increase
The dose of the study drug was increased to 10 mg once daily after Week 4 in 66 of 94 subjects (47 in the eczema/dermatitis group and 19 in the dermal pruritus group) in the trial. The incidence of an AE with and without dose up-titration in the groups was 51.5% (34/66 subjects) and 53.6% (15/28 subjects), respectively. Drug-related AEs developing after increased dose included laboratory adverse events in 3 subjects, one of whom was associated with dose reduction due to increased hepatic enzymes. All events were mild and resolved after completion of treatment.

In the eczema/dermatitis group, 6 of the subjects 12-17 years old experienced 9 non serious adverse events, most were mild in intensity and all resolved during study drug administration.
In the dermal pruritus group, 2 of the subjects 12-17 years old experienced 2 non serious adverse events, all were mild in intensity and most resolved during study drug administration.

The investigator considered all of these events to be unrelated to the study drug.

Conclusion on safety:
DL 10 mg (increased dose) and 5 mg administered once daily for up to 8 to 12 weeks days were generally safe and well-tolerated.

Assessment of the necessity for an update of the EU SmPC:
The 2 discussed studies (P201 and P202) have provided limited additional data on the efficacy and safety of desloratadine in a total of 25 subjects that were 12-17 years old.

The SmPC already contains the following information in this context:

- 4.2 “There is ***limited*** clinical trial efficacy experience with the use of desloratadine in adolescents 12 through 17 years of age”.
- 5.1 “The efficacy of Aerius/Azomyr/Neoclarityn ***has not been clearly demonstrated*** in trials with adolescent patients 12 through 17 years of age.”

The results of the study are covered by what is already mentioned in the SmPC about the efficacy of desloratadine in adolescent patients. Therefore, it is concluded that no update to the EU SmPC is necessary.

x PAM fulfilled (all commitments fulfilled) - No further action required

☐ PAM not fulfilled (not all commitments fulfilled) and further action required: