European Medicines Agency

London, 3 March 2008
EMEA/325866/2008

# ASSESSMENT REPORT FOR NEOCLARITYN

**International Nonproprietary Name: Desloratadine**

**Procedure No. EMEA/H/C/314/II/36**

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

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

## 1. INTRODUCTION

Neoclarityn (desloratadine) is a non-sedating long acting histamine antagonist with selective peripheral $H_1$-receptor antagonist activity. Neoclarityn was first authorised in the European Union (EU) on 15 January 2001 with the indication: in adults and adolescents (12 years of age or over) for the relief of symptoms associated with allergic rhinitis (AR). On 6 August 2001, a Commission Decision extended the use of Neoclarityn in chronic idiopathic urticaria (CIU).

This variation refers to an extension of indication for Neoclarityn from *'chronic idiopathic urticaria'* to *'urticaria'*. Consequently sections 4.2 and 5.1 of the Summary of Product Characteristics (SPC) were updated. Sections 1 and 3 of the Package Leaflet (PL) were amended accordingly.

## 2. CLINICAL ASPECTS

### Introduction

Urticaria is a condition in which "wheal and flare" lesions develop on the skin as a result of mast cell degranulation, with liberation of several mediators, among which histamine is the most important. The causes of urticaria vary widely, but the end result is similar and is based on mast cell activation.
Causes are acute IgE mediated allergy (e.g to drugs or foods; in which case it is possible that the acute urticaria evolves to more generalised anaphylactic reactions), contact reactions (eg latex, water, certain chemicals), pseudo allergic reactions (foods, drugs), physical triggers (dermographism, pressure, vibration, heat, cold…), exercise, autoimmunity or unknown causes. The course can be hyper acute (from minutes to hours), acute (hours to six weeks) or chronic (more than six weeks).
The rationale for the antihistamine treatment (and of second generation antihistamines in particular) in urticaria patients is based upon the insights in the pathophysiology of urticaria, with the prominent role of histamine as a mediator.
The effectiveness of second generation oral antihistamines have however mainly been studied in the treatment of chronic urticaria, but the common patho-physiologic role of histamine supports their use in urticaria in general.
Urticaria can be mimicked by injection of histamine in the skin of normal volunteers, and second generation antihistamines effectively suppress this reaction[1].

### Treatment guidelines for urticaria

The 2006 guideline of the European Academy of Allergy and Clinical Immunology (EAACI), approved by the European Dermatology Forum (EDF)[2], states:
*"Considering their good safety profile, second generation antihistamines must be considered as first line symptomatic treatment for urticaria"*. Similarly, the position statements of the American Academy of Emergency Medicine[3] and other literature references[4] for treatment of acute urticaria in emergency departments uniformly recommend the use of second generation antihistamines as first line symptomatic treatment.

### Clinical Efficacy

Clinical studies with antihistaminics are generally performed in chronic idiopathic urticaria patients, because chronic patients can be prospectively recruited. Studies in other types of urticaria are limited.

---

[1] *Simons et al*; A double blind, single dose, crossover comparison of cetirizine, terfenadine, loratadine, astemisole and chlorpheniramine versus placebo: suppressive effects on histamine induced wheals and flares during 24 hours in normal subjects; *J Allergy Clin Immunol* 1990, 86: 540-7
[2] *Zuberbier et al*; EEACI/GA LEN/EDF guideline: management of urticaria; *Allergy* 2006; 61:321-331
[3] *Winters M*, Clinical practice guideline: initial evaluation and management of patients presenting with acute urticaria or angioedema, *Position statements of the American Academy of Emergency Medicine*, July 2006, http://www.aaem.org/positionstatements/clinical practice_guidelines.php,
[4] 1) *Simons FE*; Advances in H1 antihistamines ; *New Engl J Med* 2004, 351:2203-17; 2) Baxi and Dinakar, *Immunol Allergy Clin North America*, 2005;25: 353-67

One study has prospectively studied the prevention of acute urticaria in 510 atopic children with levocetirizine given for 18 months, and found it to be effective[5].
Studies on treatment in acute urticaria can only be done in emergency departments or in general practice, as the attacks are totally unexpected, and then last for hours to weeks.
For some types of chronic urticaria, different from the "*chronic idiopathic urticaria*", literature references (including studies with desloratadine) support the use of second generation antihistamines in cold urticaria[6], delayed pressure urticaria[7], dermographic urticaria[8], cholinergic urticaria[9].

**Clinical safety**

No new clinical safety data have been submitted in this application. From the safety database of desloratadine all the adverse reactions reported in clinical trials and post-marketing have already been included in the Summary of Product Characteristics.

**Overall conclusions and benefit-risk assessment**

Based on the limitation to recruit patients with urticarial conditions other than chronic urticaria and taking into account the common patho-physiologic role of histamine in the development of urticaria, the CHMP is of the opinion that the recommendation from EAACI guideline is justified and considers the use of the second generation antihistaminics as first line symptomatic treatment of urticaria to be acceptable. Furthermore, the safety profile in the proposed indication is expected to remain unchanged.
Thus, the CHMP concluded that the benefit-risk for Neoclarityn in the symptomatic treatment of urticaria was favourable and recommended the variation to the marketing authorisation.

## 3. CHANGES TO THE PRODUCT INFORMATION

The MAH proposed the following changes (new text= underlined, deleted text= strikethrough) :

**Summary of Product Characteristics**

- **Section 4.1**

Neoclarityn is indicated for the relief of symptoms associated with:
- allergic rhinitis (see section 5.1)
- ~~chronic idiopathic~~ urticaria

- **Section 4.2**

Reference to "chronic idiopathic urticaria" has been changed to "urticaria" in accordance to the change in section 4.1 of the SPC.

- **Section 5.1**

Chronic idiopathic urticaria was studied as a model for urticarial conditions. Since histamine release is a causal factor in urticarial diseases, desloratadine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria.

[5] *Simons et al*; H1-antihistamine treatment in young atopic children, *Ann Allergy Asthma Immunol* 2007;99: 261-66
[6] *Juhlin L*; inhibition of cold urticaria by desloratadine, *J Derm Treat* 2004; 15:51-54
[7] *Nettis et al*; Desloratadine in combination with montelukast suppresses the dermographometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: a randomized double-blind, placebo-controlled study, *Br J Dermatol* 2006; 155:1279-1282
[8] *Sharpe et al*; the effect of cetirizine on symptoms and wealing in dermographic urticaria, *Br J Dermatol* 1993; 129:580-583
[9] *Zuberbier et al*; double-blind crossover study of high-dose cetirizine in cholinergic urticaria. *Dermatology* 1996; 193:324-327

**Package Leaflet**

- **Sections 1 and 3**

Reference to “chronic idiopathic urticaria” has been changed to “urticaria” in accordance to the change in section 4.1 of the SPC.

Overall, the CHMP considered the proposed SPC and PL changes acceptable but required a cross-reference from section 4.1 to section 5.1 of the SPC to explain that it is hardly possible to perform clinical trials in the applied indication and thus the extension of indication from ‘*chronic idiopathic urticaria’* to ‘*urticaria’* is based on the use in patients with chronic urticaria as it is advised in clinical guidelines.
Further to the CHMP recommendations, the MAH amended the proposal for sections 4.1 and 5.1 of the SPC as follows (new text= underlined, deleted text= strikethrough):

- **Section 4.1**

Neoclarityn is indicated for the relief of symptoms associated with:
- allergic rhinitis (see section 5.1)
- ~~chronic idiopathic~~ urticaria (see section 5.1)

- **Section 5.1**

Chronic idiopathic urticaria was studied as a clinical model for urticarial conditions, since the underlying pathophysiology is similar, regardless of etiology, and because chronic patients can be more easily recruited prospectively. Since histamine release is a causal factor in all urticarial diseases, desloratadine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria, as advised in clinical guidelines.
~~Chronic idiopathic urticaria was studied as a model for urticarial conditions. Since histamine release is a causal factor in urticarial diseases, desloratadine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria.~~

The CHMP considered the final proposal for sections 4.1 and 5.1 of the SPC acceptable.