EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

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

Opatanol

olopatadine

Procedure no: EMEA/H/C/000407/P46/026

Note

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

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1. Introduction

On 28th June 2018, the MAH submitted an overview of a previously completed Phase IV study, involving paediatric patients, for Opatanol hydrochloride 0.6% intranasal spray, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has been provided.

2. Scientific discussion

2.1. Information on the development program

Study SMA-09-03 was a Phase IV, interventional, randomized, quadruple-masked (participant, care provider, investigator, and outcomes assessor), parallel-group study with a 2-week treatment period designed to examine the safety and efficacy of olopatadine hydrochloride 0.6% nasal spray (Patanase; 665 µg/spray) administered as 2 sprays per nostril twice daily and Azelastine 0.1% Nasal Spray (Astelin; 137 µg/spray) administered as 2 sprays per nostril twice daily for the treatment of symptoms of non-allergic vasomotor rhinitis (VMR) in subjects ≥ 12 years of age who had a diagnosis of VMR with at least 2 years of chronic non-allergic rhinitis.

Study SMA-09-03 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Olopatadine hydrochloride for nasal use was approved in the United States on 18-Apr-2008. It has not been registered in the EU or in any other country for intranasal use. The product is available as olopatadine hydrochloride 0.6% (i.e. 6.65 mg/mL) intranasal spray as a formulation which does not contain povidone. The nasal spray is registered for the relief of the symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older in the United States.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final overview/summary report for:

- Study SMA-09-03: a Phase IV, interventional, randomized, quadruple-masked (participant, care provider, investigator, and outcomes assessor), parallel-group study with a 2-week treatment period designed to examine the safety and efficacy of olopatadine hydrochloride 0.6% nasal spray (Patanase; 665 µg/spray) administered as 2 sprays per nostril twice daily and Azelastine 0.1% Nasal Spray (Astelin; 137 µg/spray) administered as 2 sprays per nostril twice daily for the treatment of symptoms of non-allergic vasomotor rhinitis (VMR) in subjects ≥ 12 years of age who had a diagnosis of VMR with at least 2 years of chronic non-allergic rhinitis.

It is important to highlight that this study was finalised in 2009 and only limited clinical data are available. The MAH has submitted a summary overview of this previously completed study as part of a commitment to provide information on paediatric clinical trial use of olopatadine in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

In the 2009 clinical study, records indicate that only 6 paediatric patients aged between 12-18 years were enrolled in this study, 2 of whom were randomised to the intranasal olopatadine hydrochloride treatment group.

2.3.2. Clinical study

Clinical study number and title

• **Study SMA-09-03:** a Phase IV, interventional, randomized, quadruple-masked (participant, care provider, investigator, and outcomes assessor), parallel-group study with a 2-week treatment period designed to examine the safety and efficacy of olopatadine hydrochloride 0.6% nasal spray (Patanase; 665 µg/spray) administered as 2 sprays per nostril twice daily and Azelastine 0.1% Nasal Spray (Astelin; 137 µg/spray) administered as 2 sprays per nostril twice daily for the treatment of symptoms of non-allergic vasomotor rhinitis (VMR) in subjects ≥ 12 years of age who had a diagnosis of VMR with at least 2 years of chronic non-allergic rhinitis.

Description

Olopatadine hydrochloride is a potent selective anti-allergic/anti-histaminic agent that exerts its effects through multiple distinct mechanisms of actions.

The purpose of this study was a comparison of Olopatadine hydrochloride 0.6% and Azelastine 0.1% nasal sprays in a Two Week non-allergic vasomotor rhinitis Trial in adults and paediatric patients over 12 years with chronic non-allergic rhinitis.

Methods

Objective(s)

The primary objectives of the study were to provide a comparison between Olopatadine 0.6% and Azelastine 0.1% nasal sprays in a Two Week non-allergic vasomotor rhinitis Trial in adults and paediatric patients over 12 years with chronic non-allergic rhinitis.

Study design

Phase IV, interventional, randomized, quadruple-masked (participant, care provider, investigator, and outcomes assessor), parallel-group study with a 2-week treatment period designed to examine the safety and efficacy of olopatadine hydrochloride 0.6% nasal spray (Patanase; 665 µg/spray) administered as 2 sprays per nostril twice daily and Azelastine 0.1% Nasal Spray (Astelin; 137 µg/spray) administered as 2 sprays per nostril twice daily for the treatment of symptoms of non-allergic vasomotor rhinitis (VMR) in subjects ≥ 12 years of age who had a diagnosis of VMR with at least 2 years of chronic non-allergic rhinitis.

The study started in September 2009 and was completed in November 2009. The study was conducted at 10 study centres in the United States and enrolled 129 subjects, including 6 subjects < 18 years of age. Available clinical data regarding study details and results are limited.

Study population /Sample size

129 subjects were randomized from 10 investigational sites in the United States, of whom 63 participants were randomized to the olopatadine hydrochloride 0.6% group (including 2 subjects < 18

years of age) and 66 participants were randomized to the azelastine 0.1% group (including 4 subjects < 18 years of age). A total of 115 participants completed the study.

Treatments

- Olopatadine hydrochloride 0.6% Nasal Spray
- Azelastine 0.1% Nasal Spray

Outcomes/endpoints

The primary endpoints were:

1) Mean Percent Change in Reflective Total Nasal Symptom Score (rTNSS) From Baseline.

Responses to patient-completed diaries for reflective Total Nasal Symptom Scores (rTNSS). TNSS is composed of 4 individual assessments, which included runny nose, itchy nose, stuffy nose, and sneezing; each of the 4 assessments were rated using a 4 point scale that ranged in whole units from 0 (none) to 3 (severe). All 4 assessments are then added together for a composite score (TNSS score), the maximum of which could be 12. Reflective scores were assessed from the hour since the last dose of study medication.

2) Assessment of the mean Percent Change in Instantaneous Total Nasal Symptom Score (iTNSS) From Baseline.

Responses to patient-completed diaries for instantaneous Total Nasal Symptom Scores (iTNSS). TNSS is composed of 4 individual assessments, which included runny nose, itchy nose, stuffy nose, and sneezing; each of the 4 assessments were rated using a 4 point scale that ranged in whole units from 0 (none) to 3 (severe). All 4 assessments are then added together for a composite score (TNSS score), the maximum of which could be 12. Instantaneous scores were assessed at the time of daily dosing.

3) Mean Percent Change in Reflective Total Ocular Symptom Scores (rTOSS) From Baseline

Responses to patient-completed diaries for reflective Total Ocular Symptom Scores (rTOSS). TOSS is composed of 3 individual assessments of ocular symptoms (itching/burning, tearing/watering, redness) each of the 3 assessments were rated using a 4 point scale that ranged in whole units from 0 (none) to 3 (severe). All 3 assessments are then added together for a composite score (TOSS score), the maximum of which could be 9. Reflective scores were assessed from the hour since the last dose of study medication.

4) Mean Percent Change in Instantaneous Total Ocular Symptom Scores (iTOSS) From Baseline

Responses to patient-completed diaries for instantaneous Total Ocular Symptom Scores (iTOSS). TOSS is composed of 3 individual assessments of ocular symptoms (itching/burning, tearing/watering, redness) each of the 3 assessments were rated using a 4 point scale that ranged in whole units from 0 (none) to 3 (severe). All 3 assessments are then added together for a composite score (TOSS score), the maximum of which could be 9. Instantaneous scores were assessed at the time of daily dosing.

Statistical Methods

Not applicable- no data available.

Results

Please note that only limited clinical data is available for this study.

Recruitment/ Number analysed/Baseline data

Baseline Measures

	Olopatadine HCL	Azelastine HCl	Total
Overall Participants Analyzed [Units: Participants]	57	58	115
Age [Units: Participants]			
<=18 years	2	4	6
Between 18 and 65 years	51	54	105
>=65 years	4	0	4
Gender [Units: Participants]			
Female	39	46	85
Male	18	12	30

Efficacy results

Limited data on the efficacy results arising from this study have been provided from the retrospective overview of the clinical study report dating from 2009.

The primary efficacy endpoint in this study was mean change from baseline to Visit 4 (Day 14) in reflective total nasal VMR symptom scores (rTVSS) based on responses to patient completed dairies. Reflective scores were assessed from the hour since the last dose of study medication.

TVSS were composed of 4 individual assessments, including nasal congestion, rhinorrhea, post nasal drip and sneezing. Each of the 4 assessments were rated using a 4-point scale that ranged in whole units from 0 (none) to 3 (severe). The TVSS was a composite score based on the sum of ratings from all 4 assessments; the maximum TVSS score could be 12.

The following results from values measured for each primary endpoint was provided but no additional discussion or statistical analysis is provided.

Measured Values

	Olopatadine HCL	Azelastine HCl
Participants Analyzed	**57**	**58**
Mean Change in 2-week rTNSS From Baseline [Units: Units on a scale] Mean (Standard Deviation)	**5.9 (3.0)**	**6.5 (2.3)**

No statistical analysis provided for Mean Change in 2-week rTNSS From Baseline

2. Secondary: Mean Change in Rhinorrhea Reflective Score [Time Frame: 2 week]

Measure Type	Secondary
Measure Title	Mean Change in Rhinorrhea Reflective Score
Measure Description	Change from baseline after 2 weeks in responses to patient-completed diaries for reflective Total Nasal VMR Symptom Scores (rTVSS). TVSS is composed of 4 individual assessments, which included nasal congestion, rhinorrhea, post nasal drip and sneezing; each of the 4 assessments were rated using a 4 point scale that ranged in whole units from 0 (none) to 3 (severe). All 4 assessments are totaled for a composite score (TVSS score), the maximum of which could be 12. Reflective scores were assessed from the hour since the last dose of study medication.

Measured Values

	Olopatadine HCL	Azelastine HCl
Participants Analyzed	**44**	**43**
Mean Change in Rhinorrhea Reflective Score [Units: Units on a scale] Mean (Standard Deviation)	**1.5 (1.1)**	**1.3 (1.0)**

No statistical analysis provided for Mean Change in Rhinorrhea Reflective Score

Measured Values

	Olopatadine HCL	Azelastine HCl
Participants Analyzed	**44**	**43**
Mean Change Postnasal Drip Reflective Score [Units: Units on a scale] Mean (Standard Deviation)	**1.5 (1.2)**	**1.8 (0.9)**

No statistical analysis provided for Mean Change Postnasal Drip Reflective Score

Measured Values

	Olopatadine HCL	Azelastine HCl
Participants Analyzed	**44**	**43**
Mean Change Nasal Congestion Reflective Score [Units: Units on a scale] Mean (Standard Deviation)	**1.4 (1.1)**	**1.7 (1.2)**

No statistical analysis provided for Mean Change Nasal Congestion Reflective Score

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Measured Values

	Olopatadine HCL	Azelastine HCl
Participants Analyzed	**44**	**43**
Mean Change in Sneezing Reflective Score [Units: Units on a scale] Mean (Standard Deviation)	**1.4 (0.9)**	**1.7 (0.8)**

No statistical analysis provided for Mean Change in Sneezing Reflective Score

Safety results

No serious adverse events or fatal cases were reported in the study. No new safety concerns were noted at the time of study conduct and posting of results.

2.3.3. Discussion on clinical aspects

Olopatadine hydrochloride nasal spray is not registered in the EU.

This study provides limited clinical data in respect of intranasal use of olopatadine hydrochloride when used over 2 weeks in a very small number of paediatric patients with chronic non-allergic rhinitis aged between 12-18 years (n=2).

No new safety concerns were identified with olopatadine hydrochloride 0.6% nasal spray when administered as 2 sprays per nostril twice daily for two weeks in a population of patients 12 years of age and older with chronic non allergic vasomotor rhinitis.

Based on the limited available data from this study, no changes are proposed to the paediatric information of the current olopatadine hydrochloride CCDS or the Summary of Product Characteristics of the approved ophthalmic olopatadine hydrochloride formulation in the EU.

This conclusion is endorsed.

3. Rapporteur's overall conclusion and recommendation

In summary, an overview of the clinical data available for this study, which was completed in 2009, provides limited information on the paediatric use of olopatadine hydrochloride 0.6% nasal spray, which is not authorised in the EU.

A total of 6 paediatric patients aged between 12-18 years were enrolled in this study and 2 patients were randomised to receive intranasal olopatadine hydrochloride.

No new safety or efficacy concerns relating to topical intranasal use of the active substance olopatadine hydrochloride arise from the limited data presented. It is acknowledged that only limited clinical data is provided.

Based on the data provided, it is considered that no changes to the paediatric information of the current olopatadine hydrochloride CCDS or the Summary of Product Characteristics of the approved ophthalmic olopatadine hydrochloride formulation in the EU are required as a result of the limited data available from this study.

This study does not impact on the current B/R balance of olopatadine hydrochloride, which remains positive.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

Not applicable.