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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/P46/018

Note

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

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1. Introduction

On 23rd March 2018 the MAH submitted a completed paediatric study for Opatanol 1 Mg/Ml. Eye Drops Solution in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that this was a Phase IV, multi-centre, randomized, double-masked, vehicle-controlled, parallel-group study designed to assess local nasal adverse effects and systemic effects of olopatadine hydrochloride 0.6% nasal spray (PATANASE) relative to its acidic (pH 3.7) vehicle (PATANASE Veh 3.7) and a neutral (pH 7.0) vehicle (PATANASE Veh 7.0) in patients with perennial allergic rhinitis (PAR), when given as 2 sprays per nostril, twice daily (BID) for up to 12 months. Study C-08-32 is a stand - alone study.

A total of 146 patients (11.6%) were 12 to < 18 years of age (i.e. adolescents), no patients under 12y were enrolled in the study.

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical form used in the study was olopatadine hydrochloride 0.6% nasal spray Olopatadine hydrochloride for nasal use was approved in the US on 18-Apr-2008. It has not been registered in any other country for nasal use. The product is available as olopatadine hydrochloride 0.6% (i.e. 6.65 mg/mL) intranasal spray and is registered for the relief of the symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study C-08-32

A Phase IV, multi-center, randomized, double-masked, vehicle-controlled, parallel-group study designed to assess local nasal adverse effects and systemic effects of olopatadine hydrochloride 0.6% nasal spray (PATANASE) relative to its acidic (pH 3.7) vehicle (PATANASE Veh 3.7) and a neutral (pH 7.0) vehicle (PATANASE Veh 7.0) in patients with perennial allergic rhinitis (PAR), when given as 2 sprays per nostril, twice daily (BID) for up to 12 months.

Clinical study number and title

Study C-08-32 was a Phase IV, multi-center, randomized, double-masked, vehicle-controlled, parallel-group study designed to assess local nasal adverse effects and systemic effects of olopatadine hydrochloride 0.6% nasal spray (PATANASE) relative to its acidic (pH 3.7) vehicle (PATANASE Veh 3.7) and a neutral (pH 7.0) vehicle (PATANASE Veh 7.0) in patients with perennial allergic rhinitis (PAR), when given as 2 sprays per nostril, twice daily (BID) for up to 12 months.

Description

The purpose of study C-08-32 was to examine the safety of the nasal spray with respect to nasal septal perforation, local nasal adverse effects, including epistaxis and nasal ulceration, and systemic effects.

The original protocol for the study was amended following comments received from the US Food and Drug Administration. At the time of the amendment, 231 patients were enrolled in the study, and an additional 3 patients were enrolled prior to implementation of the amendment. As the amendment substantially revised the study plan, the analysis variables, and the entry criteria, all active enrolled patients (i.e. 234 patients) were discontinued and an entirely new cohort of patients was subsequently enrolled on implementation of the amendment. The study overview described herein pertains to the amended protocol; a description of the changes from the original protocol was presented.

Methods

Objective(s)

Primary objective

The primary objective of the study was to assess local nasal adverse effects (including epistaxis, nasal ulceration and nasal septal perforation), as well as systemic effects, of PATANASE when compared with PATANASE Veh 3.7 and PATANASE Veh 7.0 in patients with PAR, when given as 2 sprays per nostril BID for up to 12 months.

Secondary Objective

The evaluation of the responses to patient-rated efficacy assessment question

Study design

A Phase IV, multi-center, randomized, double-masked, vehicle-controlled, parallel-group study. This study consisted of 13 visits conducted at monthly intervals over a 12-month period. Enrolled patients were randomized (1:1:1) to 1 of the 3 study treatment groups. Patients administered their assigned study medication as 2 sprays in each nostril, BID (morning and evening) for the entire study duration.

At all study visits, patients underwent routine nasal and cardiovascular examinations (pulse and blood pressure), reported their concomitant medication uses along with any adverse events (AEs) that occurred since the previous visit, and answered an efficacy assessment question. At entry and exit, physical examinations were performed. Additionally, for a subset of patients in the PATANASE group (approximately 40%), a single blood draw was performed at a randomized study visit to verify dosing compliance; the selected patients were not told in advance which visit would include the blood draw.

Study population /Sample size

Overall, 1260 patients were enrolled, including 421 in the PATANASE group, 417 in the PATANASE Veh pH 3.7 group, and 422 in the PATANASE Veh pH 7.0 group. Of these, a total of 803 patients completed the study including 262 patients (62.2%) in the PATANASE group, 278 patients (66.7%) in the PATANASE Veh pH 3.7 group, and 263 patients (62.3%) in the PATANASE Veh pH 7.0 group.

The patient disposition was similar across all treatment groups.

The 1260 randomized patients (i.e. the safety analysis set, which included patients enrolled under Version 1.0 and Version 2.0 of the protocol, combined) had a mean age of 37.1 (± 14.4) years. The

majority of patients (1086 patients; 86.2%) were 18 to < 65 years of age (i.e. adults), while a **total of 146 patients (11.6%) were 12 to < 18 years of age (i.e. adolescents),** and 28 patients (2.2%) were ≥ 65 years of age (i.e. elderly). Overall, patients were primarily female (789 patients; 62.6%), not Hispanic/Latino/Spanish (1102 patients; 87.5%), and White (1054 patients; 83.7%).

Of the 1260 patients enrolled and included in the safety population, 457 patients (36.3%) discontinued early; this was largely due to the discontinuation of all active patients at the time

Version 2.0 of the protocol was implemented (234 patients 18.6%). Separate from these patients, 34 patients (2.7%) discontinued because of an AE and 189 patients (15.0%) discontinued for reasons other than an AE (lost to follow-up, patient decision, treatment failure, and protocol violation). Overall, similar percentages of patients in each treatment group discontinued for similar reasons.

Treatments

- PATANASE Olopatadine hydrochloride 0.6% nasal spray (PATANASE®)
- PATANASE Veh 3.7 Olopatadine nasal spray vehicle acidic pH
- PATANASE Veh 7.0 Olopatadine nasal spray vehicle neutral pH

Outcomes/endpoints

Safety variables

The primary safety variables included AEs and nasal examination parameters. The AEs were presented descriptively by treatment group. The number and percentage of patients with abnormal nasal examination findings was tabulated.

The secondary safety variables included physical examination parameters and cardiovascular Parameters.

Clinical efficacy variable

The clinical efficacy variable was the mean response at Visit 2 (Day 30) to the patient-rated efficacy assessment question.

Statistical Methods

Analyses of safety were performed for all patients enrolled under both Version 1.0 and Version 2.0 of the protocol and separately for patients enrolled exclusively under Version 2.0 of the protocol. All safety results were presented overall and by age category, i.e. adolescents (12 to 17 years of age, inclusive), adults (18 to 64 years of age, inclusive), and elderly (≥ 65 years of age). The efficacy and dosing compliance analyses were conducted using both the intent-to-treat (ITT) and per-protocol (PP) analysis sets. Olopatadine plasma concentrations were evaluated using the pharmacokinetic (PK) analysis set.

Of the 1260 enrolled patients, 1014 were included in the ITT analysis set and 998 were included in the PP analysis set.

234 patients were discontinued on implementation of the protocol amendment and excluded from both the ITT and PP analysis sets. There were no notable differences across the treatment groups with regard to other reasons for discontinuation from the ITT and PP analysis sets.

Of the 1260 enrolled patients, 234 were discontinued when Version 2.0 of the protocol was implemented; 12 other patients had no on-therapy study visits and 16 other patients had

inclusion/exclusion violations. Thus, 246 patients were excluded from the ITT analysis set due to protocol deviations and 262 patients were excluded from the PP analysis set due to protocol deviations. A Chi-square test (or Fisher's exact test if ≥ 1 expected cell counts were < 5) was used to compare PATANASE with each of the vehicle groups for each of the nasal examination parameters.

Changes in physical examination parameters were presented and a Chi-square test (or Fisher's exact test if ≥ 1 expected cell counts were < 5) was used to compare PATANASE with each of the vehicle groups for each of the physical examination parameters. Additionally, changes in cardiovascular parameters were presented and repeated measures analysis of variance was used to assess differences between PATANASE and each of the vehicle groups.

A 2-sample t-test was used to compare treatment differences between PATANASE and PATANASE Veh pH 3.7 in the mean response to the efficacy assessment question at this visit. Primary inferences were based on the ITT analysis set.

Results

Recruitment / Number analysed

The estimated target sample size was 1200 patients (total enrolled under Version 1.0 and Version 2.0 of the protocol).

Of the 1260 enrolled patients, 234 were discontinued when Version 2.0 of the protocol was implemented; 12 other patients had no on-therapy study visits and 16 other patients had inclusion/exclusion violations. Thus, 246 patients were excluded from the ITT analysis set due to protocol deviations and 262 patients were excluded from the PP analysis set due to protocol deviations.

Baseline data

Efficacy results

Overview of efficacy

Evaluation of response at Day 30 to the patient-rated efficacy assessment question

The patients recorded their answers to an efficacy assessment question at each study visit from Visit 2 through Visit 13. The question posed to the patients was as follows:

"I would rate the study medication's effectiveness for relieving my allergy symptoms since my last visit as:

1. Complete relief
2. Moderate relief
3. Mild relief
1. 4.No relief

The analysis of efficacy was limited to an evaluation of the response to the efficacy assessment question at 1 month (Day 30).

Overall, the mean response in the PATANASE group was significantly lower (better) than the mean response in the PATANASE Veh 3.7 group (p = 0.0008) and in the PATANASE Veh 7.0 group (p=0.0017)

Safety results

Adverse events profile

In general, similar numbers of patients in each treatment group experienced AEs regardless of seriousness, intensity, or relationship to treatment, including 305 patients (72.4%), 307 patients (73.6%), and 314 patients (74.4%) in the PATANASE, PATANASE Veh 3.7, and PATANASE Veh 7.0 groups, respectively

Adverse drug reactions (ADRs), i.e. AEs that were assessed by the investigator as being related to the study treatment, were reported for 92 patients (21.9%) in the PATANESE group, 65 patients (15.6%) in the PATANASE Veh 3.7, and 77 patients (18.2%) in the PATANASE Veh 7.0 group.

The most common nasal ADRs (i.e. nasal ADRs that occurred in > 1% of the patients in any treatment group) reported in the PATANASE, PATANASE Veh 3.7, and PATANASE Veh 7.0 group, respectively, were as follows

- Epistaxis in 55 patients (13.1%), 37 patients (8.9%), and 55 patients (13.0%)
- Rhinitis in 27 patients (6.4%), 34 patients (8.2%), and 43 patients (10.2%)
- Nasal ulcer in 19 patients (4.5%), 22 patients (5.3%), and 26 patients (6.2%)
- Nasal discomfort in 5 patients (1.2%), 6 patients (1.4%), and 3 patients (0.7%)

One patient (50-year-old female patient) in the PATANASE Veh 3.7 group had an ADR of nasal septum perforation that led to study discontinuation. This event was assessed by the Investigator as not serious, moderate in intensity, related to test article, and resolved with treatment (septal button)

The only non-nasal ADR that occurred in > 1% of the patients was dysgeusia (reported for 18 patients (4.3%) in the PATANASE group).

No deaths were reported during the study. Overall, 29 patients experienced ≥ serious AEs (SAEs) during the study. Of these, only 1 SAE of periorbital cellulitis, which was experienced by 1 patient (50-year-old female patient) in the PATANASE Veh 3.7 group, was assessed as treatment-related; this event also resulted in patient discontinuation from the study.

The remaining SAEs were not related to treatment, did not result in patient discontinuation from the study, and with 2 exceptions (1 patient with an injury that required continuing treatment and 1 patient with an injury of unknown outcome), resolved with or without additional treatment.

Physical examinations

With the exception of changes from Baseline (Visit 1) in nasal parameters or PAR symptoms (recorded under the body system/organ class of head, eyes, ears, nose and throat), no meaningful differences in physical examination findings from Baseline (Visit 1) to the Exit Visit were observed across treatment groups. Furthermore, there were no notable differences between treatment groups in regard to the number of patients for whom clinically relevant changes in physical examination findings were reported.

Similar results were obtained for the population of patients who participated in the study under Version 2.0 of the protocol.

2.3.2. Discussion on clinical aspects

No previously unknown safety issues were identified in a population of patients 12 years of

age and older with PAR who administered PATANASE as 2 sprays per nostril BID for up to 12 months, based on a review of AEs, cardiovascular parameters, and outcomes of nasal and physical examinations (safety data).

Based on an overall review of the types and characteristics of nasal AEs, it is considered unlikely that pH contributes to an increased risk of AEs in patients exposed to PATANASE. PATANASE was found to be superior to PATANASE Veh pH 3.7 and PATANASE Veh pH 7.0 with regard to the patient-rated efficacy assessment question at 1 month (Day 30) (ITT data).

3. Rapporteur's CHMP overall conclusion and recommendation

In conclusion, the benefit-risk assessment for olopatadine hydrochloride 0.6% nasal spray remains positive for the currently approved indications outlined in the CCDS and justifies the continued use of the product in the approved paediatric patient populations.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

N/A