EMA/550989/2018
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

Opatanol

olopatadine

Procedure no: EMEA/H/C/000407/P46/019

Note

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

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1. Introduction

On the 13th April 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 Study C-07-01 a Phase III, multi-centre, randomized, double-masked, vehicle-controlled, parallel-group study to assess the safety and efficacy of olopatadine hydrochloride 0.6% nasal spray in pediatric patients aged 6 to 11 years with seasonal allergic rhinitis (SAR), when administered twice daily (BID) for 2 weeks is a stand - alone 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-07-01
- A Phase III, multi-centre randomized, double-masked, vehicle-controlled, parallel-group study to assess the safety and efficacy of olopatadine hydrochloride 0.6% nasal spray in paediatric patients aged 6 to 11 years with seasonal allergic rhinitis (SAR), when administered twice daily (BID) for 2 weeks.

Clinical study number and title

- Study C-07-01
  A Phase III, multi-centre, randomized, double-masked, vehicle-controlled, parallel-group study to assess the safety and efficacy of olopatadine hydrochloride 0.6% nasal spray in

paediatric patients aged 6 to 11 years with seasonal allergic rhinitis (SAR), when administered twice daily (BID) for 2 weeks.

Description

The purpose of study C-07-01 was to assess the safety and efficacy of olopatadine hydrochloride 0.6% nasal spray in pediatric patients aged 6 to 11 years. The estimated target sample size was 1000 patients. The study started on 28-Sep-2007 (first patient first visit) and completed on 24-Nov-2008 (last patient last visit). The study was conducted in 173 study centres in the United States.

Methods

Objective(s)

The primary objective of this study was to demonstrate the superiority of olopatadine hydrochloride 0.6% nasal spray compared to vehicle (i.e. placebo) in patients with SAR, when given as 1 or 2 sprays per nostril BID for 2 weeks.

Study design

The study consisted of a vehicle run-in period and a randomized treatment period. The vehicle run-in period was 4 to 16 days in duration and was single (patient) masked. During the vehicle run-in period, patients received 1 spray of vehicle per nostril daily, and assessments (including scoring of nasal symptoms) were completed in the same manner as during the treatment period. At the end of the run-in period, the patient's nasal symptoms scores were reviewed. Only those patients who achieved a reflective total nasal symptom score (rTNSS) score of ≥ 36 units (the sum of the rTNSS scores from 3 of the 4 calendar days immediately prior to randomization (Visit 2)) were eligible for randomization. Eligible patients were randomized to 1 of the following 4 treatment groups:

- Olopatadine hydrochloride 0.6% nasal spray 1 spray per nostril,
- Olopatadine hydrochloride 0.6% nasal spray 2 sprays per nostril,
- Olopatadine hydrochloride nasal spray vehicle 1 spray per nostril,
- Olopatadine hydrochloride nasal spray vehicle 2 sprays per nostril.

Study population /Sample size

Of the 1188 patients evaluable for the ITT data set, all patients were 6 to 11 years of age, with more patients in the 9 to 11 years age group than in the 6 to 8 years age group (59.2% vs. 40.8%). There were more males than females (57.8% vs. 42.2%) and the majority of patients were White (72.7%). There were no notable differences across the treatment groups with regard to demographic characteristics ,including age, sex, race, and ethnicity.

Treatments

- olopatadine hydrochloride 0.6% nasal spray
- olopatadine hydrochloride nasal spray vehicle

During the randomized double-masked treatment period, treatment was administered for ≥ 2 weeks, BID (morning (AM) and evening (PM)). The randomized treatment period was approximately 16 days in duration; however, only the first 14 consecutive days of treatment where patients had both AM and PM assessments were analysed for each patient. Parents/caregivers were instructed to complete the AM allergy symptom ratings prior to administration of the AM dose, and to complete the PM allergy symptom ratings prior to the PM dose, and to maintain a 12-hour dosing interval between the AM and PM doses. There were 2 scheduled post-randomization visits: a telephone contact (Visit 3; 7 ± 1 day from Visit 2) and an office visit (Visit 4; 16 + 7 days from Visit 2).

Outcomes/endpoints

The primary efficacy variable was the percent change from baseline in the rTNSS, calculated as the average of the AM and PM reflective (how the patient felt for the last 12 hours) severity scores for the sum of the assessments of the patient's runny nose, stuffy nose, itchy nose, and sneezing (averaged across 14 days). The reflective severity scores for runny nose, stuffy nose, itchy nose, and sneezing were evaluated twice daily while on study medication via a patient diary, using a 4-unit rating scale (i.e. 0 = none, 1 = mild, 2 = moderate, 3 = severe). Analysis of covariance was used to compare percent changes from baseline between olopatadine hydrochloride 0.6% nasal spray (1 spray per nostril or 2 sprays per nostril) and the corresponding dose of olopatadine hydrochloride nasal spray vehicle (1 or 2 sprays per nostril). Analyses were conducted on all data sets, but the primary inference was based on the ITT data set.

The key secondary efficacy variable was the percent change from baseline in the reflective total ocular symptom score (rTOSS), calculated as the average of the AM and PM reflective severity scores for the sum of the assessments of the patient's itchy eyes and watery eyes (averaged across 14 days).

The safety variables analysed included extent of exposure to study medication, nasal examination parameters (significant anatomic abnormalities, evidence of infection, and bleeding and ulcerations of the mucosa), general physical examination parameters (head, eyes, ears, nose, and throat (HEENT), neck, cardiovascular, pulmonary, abdomen, skin, and extremities, neurological, and lymph nodes), cardiovascular parameters (pulse, systolic blood pressure, and diastolic blood pressure), and adverse events (AEs).

Statistical Methods

The following datasets were used for the statistical analysis:

- All patients who received ≥ 1 dose of study drug were evaluable for the safety analyses.
- All patients who received study drug and had ≥ 1 on-therapy visit were evaluable for the intent-to-treat (ITT) analyses.
- All patients who received study drug, had ≥ 1 on-therapy visit, and met inclusion and exclusion criteria were evaluable for the per-protocol (PP) analyses.

Results

Recruitment / Number analysed

A total of 2388 patients were screened for possible study participation and were given olopatadine hydrochloride nasal spray vehicle to administer as run-in treatment. Of these, 1200 patients failed screening for the following reasons: insufficient diary score (836 patients), protocol violation (186 patients), lost to follow-up (63 patients), AEs (54 patients), patient decision unrelated to an AE (53 patients), and other reasons (8 patients), as presented.

The remaining 1188 patients were enrolled into the randomized treatment period as follows:

298 patients in the olopatadine hydrochloride 0.6% nasal spray 1 spray per nostril group,
297 patients in the olopatadine hydrochloride nasal spray vehicle 1 spray per nostril group
296 patients in the olopatadine hydrochloride 0.6% nasal spray 2 sprays per nostril group,
297 patients in the olopatadine hydrochloride nasal spray vehicle 2 sprays per nostril group.

Of the 1188 randomized patients, a total of 53 patients were discontinued prematurely for the following reasons: AEs (20 patients), treatment failure (17 patients), lost to follow-up (4 patients), decision unrelated to an AE (4 patients), protocol violation (4 patients), and other reasons (4 patients).

Baseline data

Efficacy results

Primary analysis – Percent change from baseline in reflective total nasal symptom score

The rTNSS was calculated as the average of the AM and PM reflective (how the patient felt since the last symptom assessment) severity scores for the sum of the assessments of the patient's runny nose, stuffy nose, itchy nose, and sneezing (averaged across 14 days).

Olopatadine hydrochloride 0.6% nasal spray, administered as 2 sprays per nostril, was superior to the corresponding dose of olopatadine hydrochloride nasal spray vehicle (p = 0.0120) for the percent change from baseline in the rTNSS for the ITT data set.

Comparison involving 1 spray per nostril was consistent with that involving 2 sprays per nostril, indicating that patients receiving the active treatment had notably greater percent change from baseline in the rTNSS compared to the corresponding dose of vehicle (p = 0.0007).

The results obtained for the PP data set were similar to those for the ITT data set.

Key secondary analysis – Percent change from baseline in reflective total ocular symptom score

The rTOSS was calculated as the average of the AM and PM reflective (how the patient felt for the last 12 hours) severity scores for the sum of the assessments of the patient's itchy eyes and watery eyes (averaged across 14 days).

Olopatadine hydrochloride 0.6% nasal spray, administered as 2 sprays per nostril, was superior to the corresponding dose of olopatadine hydrochloride nasal spray vehicle (p = 0.0010) for the percent change from baseline in the rTOSS for the ITT data set.

Comparison involving 1 spray per nostril was consistent with that involving 2 sprays per nostril, indicating that patients receiving the active treatment had notably greater percent change from baseline in the rTOSS compared to the corresponding dose of vehicle (p = 0.0084).

The other secondary analyses confirmed the results of the primary analysis.

Olopatadine hydrochloride 0.6% nasal spray, administered as 2 sprays per nostril, was notably different (i.e. greater improvement from baseline) compared to the 2 sprays per nostril vehicle.

Safety results

The safety evaluation was conducted on all patients who received ≥ 1 dose of olopatadine hydrochloride nasal spray vehicle during the run-in period of the study (overall safety population), and separately for all patients randomized to study medication (randomized safety population).

No notable differences were observed across the treatment groups with regard to mean duration of exposure to study drug. The majority of patients (i.e. 66.4% to 67.9%) in all treatment groups were exposed to the study drug for > 16 days.

Nasal examinations were performed at Visit 1 (screening/baseline), Visit 2, and Visit 4 (exit). The post-baseline nasal examinations consisted of 2 parts: an initial examination of the nasal cavity (Section A) and a follow-up examination of positive findings from the initial examination (Section B). Any clinically relevant change (absent to present) from Visit 1 in any nasal examination parameter was reported as an AE.

Overall, a review of the changes from baseline in the physical examination parameters revealed no safety issues and no clinically relevant differences were observed among the treatment groups.

The majority of patients in all treatment groups experienced some changes (increases or decreases) in cardiovascular parameters from baseline values to exit visit or to any visit; however, these fluctuations were attributed to normal inter-patient variability and were not considered to be clinically significant. Overall, based upon the analysis of the cardiovascular parameters (pulse rate, systolic blood pressure, and diastolic blood pressure), no safety issues were identified

Adverse event profile

Overall, 298 of 2388 patients (12.5%) had an AE during the vehicle run-in period and 292 of 1188 patients (24.6%) had an AE during the randomized treatment period. The frequency of AEs during the randomized treatment period was similar among patients treated with either olopatadine hydrochloride 0.6% nasal spray groups (1 spray group: 25.2%; 2 sprays group: 27.0%) and their corresponding vehicle groups (1 spray group: 21.9%; 2 sprays group: 24.2%)

During the vehicle run-in period, the most frequently reported adverse drug reactions (ADRs; i.e. AEs that were considered to be related to the study treatment) were epistaxis (13 patients; 0.5%) and headache (6 patients; 0.3%). The remaining ADRs, reported in ≤ 4 patients, included nasal discomfort, dysgeusia, dry throat, nasal ulcer, pharyngolaryngeal pain, and throat irritation.

During the randomized treatment period, epistaxis and dysgeusia were the most commonly reported ADRs. Epistaxis was reported in all treatment groups, occurring at an incidence rate of 1.7% to 3.0%. Dysgeusia was reported in all treatment groups except the olopatadine hydrochloride nasal spray

vehicle 1 spray group, occurring at an incidence rate of 0.3% to 1.4%. The remaining ADRs were reported in ≤ 1% of patients in any of the treatment groups.

No deaths were reported during the study. During the vehicle run-in period, 1 patient experienced a serious adverse event (SAE) of vasovagal syncope that was assessed as not related to study medication and the patient discontinued participation in the study due to this event prior to any exposure to randomized study medication. No other SAEs were reported during the course of the study.

2.3.2. Discussion on clinical aspects

Based upon a review of AEs and an assessment of nasal, general physical, and cardiovascular parameters, no safety issues were identified in the population of pediatric patients aged 6 to 11 years with SAR administered olopatadine hydrochloride 0.6% nasal spray 1 or 2 sprays per nostril BID or corresponding dose of olopatadine hydrochloride nasal spray vehicle for 2 weeks.

Olopatadine hydrochloride 0.6% nasal spray, administered as 2 sprays per nostril BID for 2 weeks, was found to be superior to the corresponding dose of olopatadine hydrochloride nasal spray vehicle for the treatment of SAR in pediatric patients 6 to 11 years of age.

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.

No changes to the paediatric information of the current olopatadine hydrochloride CCDS or the Summary of Product Characteristics of the approved Opatanol 1 mg/ml eye drops solution in the EU are proposed as a result of this study. Olopatadine hydrochloride nasal spray is not registered in the EU.

☒ Fulfilled:

No regulatory action required.

4. Additional clarification requested

N/A

MAH responses to Request for supplementary information

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report

Clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report