28 June 2018
EMA/504882/2018
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/P46/016

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 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 EXC458-C001/C-12-010 was a Phase III, multi-centre, parallel-group, active-controlled study that compared the safety and efficacy of olopatadine hydrochloride 0.2% ophthalmic solution once daily (QD) with olopatadine hydrochloride 0.1% ophthalmic solution twice daily (BID) in Chinese patients with allergic conjunctivitis and number **C-12-010** is a standalone study

2.2. Information on the pharmaceutical formulation used in the study

olopatadine hydrochloride 0.2% ophthalmic solution

olopatadine hydrochloride 0.1% ophthalmic solution

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study EXC458-C001/C-12-010
- A Phase III, multi-centre, parallel-group, active-controlled study that compared the safety and efficacy of olopatadine hydrochloride 0.2% ophthalmic solution once daily (QD) with olopatadine hydrochloride 0.1% ophthalmic solution twice daily (BID) in Chinese patients with allergic conjunctivitis.

2.3.2. Clinical study

Study EXC458-C001/C-12-010

A Phase III, multi-centre, parallel-group, active-controlled study that compared the safety and efficacy of olopatadine hydrochloride 0.2% ophthalmic solution once daily (QD) with olopatadine hydrochloride 0.1% ophthalmic solution twice daily (BID) in Chinese patients with allergic conjunctivitis.

Description

To support the registration of Olopatadine 0.2% in China, study EXC458-C001/C-12-010, a randomized, investigator-masked, multicentre, parallel-group, active-controlled study in Chinese patients with allergic conjunctivitis for 2 weeks treatment duration was conducted in Chinese male and female patients aged 10 years or older. The study was conducted in 10 study centres in China. The estimated target sample size was 250 patients.

Methods

Objective(s)

The primary objective of this study was to demonstrate that Olopatadine 0.2% QD is noninferior to Olopatadine 0.1% BID for the treatment of ocular itching associated with allergic conjunctivitis.

Study design

A Phase III, multi-centre parallel-group, active-controlled study. Patients were treated in both eyes for 14 days with topical ocular Olopatadine 0.2%/vehicle (i.e. placebo to mimic second daily dose in control group) or Olopatadine 0.1%. During the treatment period, patients were evaluated after 7 days and after 14 days.

Study population /Sample size

The patient disposition was similar in both treatment groups. A total of 253 patients from 10 sites in China were randomized in the study; 126 patients to the Olopatadine 0.2% group and 127 patients to the Olopatadine 0.1% group. Overall, 247 patients (97.6%) completed the study; 124 patients (98.4%) from the Olopatadine 0.2% group and 123 patients (96.9%) from the Olopatadine 0.1% group.

A summary of key demographic characteristics in the Per Protocol Set (PPS) was provided. Overall, the mean (standard deviation (SD)) age of patients was 32.2 (13.24) years (ranging from 10 to 77 years). Most patients were 18 to 64 years of age (211 patients; 86.1%). **A total of 28 patients (11.4%) were 10 to 17 years of age.** There were more female patients (167 patients; 68.2%) than male patients (78 patients; 31.8%). All patients were Chinese.

A summary of baseline characteristics for study eye in the PPS was provided.

All patients in the PPS (245 patients, 100%) were clinically diagnosed as having allergic conjunctivitis (primary diagnosis) with positive allergic skin test results. The mean (SD) itching score was 3.39 (0.376); 102 patients (41.6%) reported with an itching score of 3.0, 95 patients (38.8%) reported with an itching score of 3.5, and 48 patients (19.6%) reported with an itching score of 4.0. The distribution of baseline itching score was similar between the 2 treatment groups. The mean (S) eyelid swelling score was 0.8 (0.92), the mean (SD) bulbar conjunctival hyperemia score was 2.00 (0.799), and the mean (SD) chemosis score was 0.75 (0.761). No notable differences were observed between the 2 treatment groups with regard to eyelid swelling, bulbar conjunctival hyperemia, or chemosis.

Treatments

Olopatadine 0.2% ophthalmic solution

Olopatadine 0.1% ophthalmic solution

Patients were treated in both eyes for 14 days with topical ocular Olopatadine 0.2%/vehicle (i.e. placebo to mimic second daily dose in control group) or Olopatadine 0.1%. During the treatment period, patients were evaluated after 7 days and after 14 days.

An overall summary of exposure data was provided. The mean (SD) duration of study treatment exposure was similar between the treatment groups, with 14.0 (1.71) days in the Olopatadine 0.2% group (range: 2 to 18 days) and 14.1 (1.34) days in the Olopatadine 0.1% group (range: 7 to 18 days).

The extent of exposure to study treatment was also similar in the 2 treatment groups. The majority of patients were exposed to the study treatment for 8 to 14 days in both treatment groups: 91 patients (72.2%) in the Olopatadine 0.2% group and 88 patients (69.8%) in the Olopatadine 0.1% group

Outcomes/endpoints

The primary efficacy variable was the change from baseline for the worst ocular itching score during the 24 hours prior to the Day 14 visit. The supportive efficacy variables included:

- Worst ocular itching score during the 24 hours prior to the Day 7 and Day 14 visits;

Change from baseline for the worst ocular itching score during the 24 hours prior to the Day 7 visit

- Score and change from the baseline for the bulbar conjunctival hyperemia, chemosis, and eyelid swelling scores at Day 7 and Day 14
- Sum score and change from baseline for sum score of ocular itching, bulbar conjunctival hyperemia, chemosis, and eyelid swelling at Day 7 and Day 14

Safety was evaluated by adverse events (AEs), best corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp biomicroscopy (cornea, iris, anterior chamber, and lens), and undilated fundus assessments (vitreous, retina, macula, choroid, and optic nerve).

Statistical Methods

The full analysis set (FAS) comprised all patients who were randomized and had ≥ 1 on-therapy visit data. The per protocol set (PPS) consisted of all patients who were randomized, received study drug, had ≥ 1 on-therapy visit, satisfied inclusion/exclusion criteria, and had no major protocol deviations. The main efficacy analyses were performed using the FAS. Supportive efficacy analyses were performed using the PPS. The safety analysis set included all patients who received study treatment. All safety analyses were performed using the safety analysis set.

The hypothesis test for the primary comparison was based on a mixed model repeated measurement (MMRM) approach. The MMRM model included the following fixed effects:

treatment (Olopatadine 0.2% QD vs Olopatadine 0.1% BID), visit, treatment × visit interaction, and baseline itching score as a covariate. Investigator sites were considered as random effect. In the MMRM model, the variance-covariance matrix for the within-patient errors was modeled by an unstructured matrix. If the algorithm failed to converge, the Compound symmetry variance-covariance matrix was to be used. Noninferiority was deemed to have been established if the upper limit of the 95% confidence interval (CI) for the treatment difference between Olopatadine 0.2% QD and Olopatadine 0.1% BID in mean itching score (worst itching score during 24 hours) change from baseline at Day 14 was shown to be less than the predefined noninferiority margin +0.5. A similar MMRM model as mused in the primary efficacy analysis was used for the supportive efficacy analysis. The corresponding 95% CI of the treatment difference was constructed for each supportive efficacy variable with a solely descriptive summary purpose. No formal noninferiority testing was conducted for these analyses.

In the safety analysis set, all patients had a medical history of conjunctivitis allergic. The other reported ocular medical histories were cataract, pterygium, dry eye, and eye injury, each reported in no more than 2 patients (1.6%). Regarding surgical and medical procedures, 1 patient (0.8%) in the Olopatadine 0.2% group had eye laser surgery and 1 patient (0.8%) each in the Olopatadine 0.1% group had eye and retinal operations. There were no notable differences in ocular medical history between the 2 treatment groups

In the safety analysis set, the most frequently reported non-ocular medical history was rhinitis allergic (33 patients (26.2%) in the Olopatadine 0.2% group and 38 patients (30.2%) in the Olopatadine 0.1% group). Other non-ocular medical history was reported in no more than 3 patients (2.4%). Overall, the non-ocular medical history was similar between the 2 treatment groups

Protocol deviations leading to exclusion from analysis sets

Inclusion/exclusion criteria violations, which were considered to have an impact on the efficacy or safety evaluations, were regarded as major protocol deviations. The number of patients with major protocol deviations was similar in each treatment group. A total of 22 patients (8.7%) had major protocol deviations, including 8 patients (6.3%) in the Olopatadine 0.2% group and 14 patients (11.0%) in the Olopatadine 0.1% group.

The most frequently reported major protocol deviations were out of visit window (13 patients (5.1%), including 5 patients (4.0%) in the Olopatadine 0.2% group and 8 patients (6.3%) in the Olopatadine 0.1% group; among them 1 patient in the Olopatadine 0.1% group was excluded from the PPS) and drug administration compliance (12 patients (4.7%), including 5 patients (4.0%) in the Olopatadine 0.2% group and 7 patients (5.5%) in the Olopatadine 0.1% group; among them 2 patients in each group were excluded from the PPS).

Other major protocol deviations were no on-therapy assessment (only 1 patient (0.4%) in the Olopatadine 0.2% group; this patient was excluded from the PPS), prohibited drug administration (4 patients (1.6%), including 1 patient (0.8%) in the Olopatadine 0.2% group and 3 patients (2.4%) in the Olopatadine 0.1% group; these 4 patients were excluded from the PPS), missing visit (4 patients (1.6%), including 2 patients (1.6%) in each treatment groups; among them 1 patient in the Olopatadine 0.2% group was excluded from the PPS), and inclusion/exclusion criteria violation which were considered to have an impact on the efficacy or safety evaluation (2 patients (1.6%) in the Olopatadine 0.1% group; these 2 patients were excluded from the PPS).

Results

Recruitment/ Number analysed

Total number enrolled was 383. Number of screen failures was 130

The estimated target sample size was 250 patients. 253 patients from 10 sites were randomised

Baseline data

Efficacy results

Primary efficacy analysis

The primary efficacy analysis was performed. The difference in the mean change from baseline in worst itching score within preceding 24 hours at Day 14 between the 2 treatment groups (Olopatadine 0.2% - Olopatadine 0.1%) was 0.05 (95% CI: −0.17 to 0.26). The upper limit of 95% CI of treatment difference was 0.26, which was less than the pre-specified noninferiority margin of 0.5, demonstrating that Olopatadine 0.2% was noninferior to Olopatadine 0.1%.

The results from Full Analysis Set (FAS) analysis and the sensitivity analysis which incorporated missing data imputation as last-observation carry-forward were consistent with above Per Protocol Set (PPS) analysis.

Supportive efficacy analysis

Supportive efficacy analysis included worst ocular itching score during the 24 hours prior to the Day 7 and Day 14 visits, change from baseline for the worst ocular itching score during the 24 hours prior to the Day 7 visit score and change from the baseline for the bulbar conjunctival hyperemia chemosis and eyelid swelling scores at Day 7 and Day 14 sum score and change from baseline for sum score of ocular itching, bulbar conjunctival hyperemia, chemosis, and eyelid swelling at Day 7 and Day 14. These supportive efficacy analyses were performed on FAS.

Worst ocular itching score during the 24 hours prior to the Day 7 and Day 14 visits

At Day 7 visit, the least squares mean value (standard error (SE)) of worst itching score was 1.50 (0.115) in the Olopatadine 0.2% group and 1.48 (0.114) in the Olopatadine 0.1% group; the mean difference between the 2 treatment groups was 0.03 (95% CI: −0.22 to 0.27). At Day 14 visit, the least squares mean value (SE) of worst itching score was 0.86 (0.106) in the Olopatadine 0.2% group and 0.73 (0.107) in the Olopatadine 0.1% group; the mean difference between the 2 treatment groups was 0.13 (95% CI: −0.08 to 0.34). The above analysis results show that the Olopatadine 0.2% group was similar to Olopatadine 0.1% group at Day 7 and Day 14 visits for the treatment of ocular itching associated with allergic conjunctivitis, which was also consistent with the primary efficacy analysis result.

Change from baseline for the worst ocular itching score during the 24 hours prior to the Day 7 visit

The mean value of worst itching score at baseline was 3.4 in both treatment groups. The mean difference between the 2 treatment groups in mean itching score change from baseline at Day 7 was 0.03 (95% CI: −0.22 to 0.27). The upper limit of 95% CI of treatment difference was 0.27, which was less than the noninferiority margin of 0.5. The above analysis results show that the mean difference between the 2 treatment groups at Day 7 was consistent with that at Day 14, both upper limits of 95% CI of treatment difference at Days 7 and 14 were less than the pre-specified noninferiority margin of 0.5, supporting the conclusion that Olopatadine 0.2% was noninferior to Olopatadine 0.1% for the treatment of ocular itching associated with allergic conjunctivitis in Chinese patients.

Score and change from the baseline for the bulbar conjunctival hyperemia, chemosis, and eyelid swelling scores at Day 7 and Day 14

The mean change (SE) from baseline in bulbar conjunctival hyperemia at Day 7 was −1.03 (0.150) in the Olopatadine 0.2% group and −1.06 (0.149) in the Olopatadine 0.1% group; the mean difference between the 2 treatment groups was 0.03 (95% CI: −0.11 to 0.17). The mean change (SE) from baseline in bulbar conjunctival hyperemia at Day 14 was −1.29 (0.151) in the Olopatadine 0.2% group and −1.38 (0.151) in the Olopatadine 0.1% group; the mean difference between the 2 treatment groups was 0.09 (95% CI: −0.06 to 0.24). No notable difference was observed between the 2 treatment groups in the mean value and mean change from baseline of bulbar conjunctival hyperemia.

The mean change (SE) from baseline in chemosis at Day 7 was −0.54 (0.046) in the Olopatadine 0.2% group and −0.50 (0.045) in the Olopatadine 0.1% group; the mean difference between the 2 treatment groups was−0.04 (95% CI: −0.13 to 0.05). The mean change (SE) from baseline in chemosis at Day 14 was −0.64 (0.040) in the Olopatadine 0.2% group and −0.68 (0.040) in the Olopatadine 0.1% group; the mean difference between the 2 treatment groups was 0.04 (95% CI: −0.03 to 0.10). No notable difference was observed between the 2 treatment groups in the mean value and mean change from baseline of chemosis.

The mean change (SE) from baseline in eyelid swelling at Day 7 was −0.52 (0.049) in the Olopatadine 0.2% group and −0.46 (0.049) in the Olopatadine 0.1% group; the mean difference between the 2 groups was −0.05 (95% CI: −0.16 to 0.05). The mean change (SE) from baseline in eyelid swelling at Day 14 was −0.65 (0.045) in the Olopatadine 0.2% group and −0.59 (0.046) in the Olopatadine 0.1% group; the mean difference between the 2 treatment groups was −0.07 (95% CI: −0.16 to 0.03).No notable difference was observed between the 2 treatment groups in the mean value and mean change from baseline of eyelid swelling.

Safety results

Safety analysis was performed in the safety population.

The analysis of the AEs including the serious AE (SAE), included defining the total number of AEs, total number of subjects with AE, number of treatment-related AEs, number of AEs resulted in treatment discontinuation, number of withdrawals from the trial at the subject's initiative. Results were presented in a descriptive way.

In the safety analysis set, 17 patients (13.5%) in the Olopatadine 0.2% group and 6 patients (4.8%) in the Olopatadine 0.1% group reported ≥ 1 Treatment-Emergent Adverse Event (TEAE) during the study.

Among all TEAEs, 12 patients (9.5%) reported 29 ocular TEAEs and 6 patients (4.8%) reported 6 non-ocular TEAEs in the Olopatadine 0.2% group while 5 patients (4.0%) reported 12 ocular TEAEs and 2 patients (1.6%) reported 3 non-ocular TEAEs in the Olopatadine 0.1% group.

No notable difference was observed between the 2 treatment groups.

The most frequently reported ocular TEAEs, reported in ≥ 1% of patients, were eye pruritus (3 patients; 2.4%) and ocular hyperemia (2 patients; 1.6%) in the Olopatadine 0.2% group; and eye pain (3 patients; 2.4%) and foreign body sensation in eyes (2 patients; 1.6%) in the Olopatadine 0.1% group.

The only non-ocular TEAE, reported in ≥ 1% of patients, was urinary tract infection, reported by 2 patients (1.6%) in the Olopatadine 0.2% group.

Most TEAEs were mild in severity, of short duration, and with the outcome of recovered/resolved. A total of 20 ocular TEAEs in the Olopatadine 0.2% group and 12 ocular TEAEs in the Olopatadine 0.1% group were suspected to be related to the study treatment.

Although the occurrence of ocular TEAE related to study treatment was higher in Olopatadine 0.2% group, all these ocular events were also mild in severity, resolved without treatment, and did not lead to treatment discontinuation. None of non-ocular TEAEs was suspected to be related to the study treatment.

There were no deaths or serious TEAEs reported during the study. Only 1 patient (an adult) experienced a non-ocular TEAE (VIIth nerve paralysis) that led to study discontinuation in the Olopatadine 0.2% group which was considered by the investigator as not related to study treatment.

Ocular

The overall incidence of ocular TEAEs that were reported as related to study treatment was 8 patients (6.3%) in the Olopatadine 0.2% group compared with 5 patients (4.0%) in the Olopatadine 0.1% group. No notable difference was observed between the treatment groups. In general, most TEAEs were reported by the patients in the 18-64 years age group, including 15 patients (11.9%) in the Olopatadine 0.2% group and 5 patients (4.0%) in the Olopatadine 0.1% group.

TEAEs were reported in only 3 patients in the 10 to 17 years age group,including 2 patients (1.6%) in the Olopatadine 0.2% group and 1 patient (0.8%) in the Olopatadine 0.1% group.

The most frequently reported ocular TEAEs were eye pruritus (1 patients (7.1%) in the 10 to 17 years age group, and 2 patients (1.8%) in the 18 to 64 years age group in the Olopatadine 0.2% group); eye pain (3 patients (2.8%) in the 18 to 64 years age group in the Olopatadine 0.1% group); ocular hyperemia (2 patients (1.8%) in the 18 to 64 years age group in the Olopatadine 0.2% group), and foreign body sensation in eyes (2 patients (1.8%) in the 18 to 64 years age group in the Olopatadine 0.1% group). Other ocular TEAEs were reported no in more than 1 patient in any subgroup.

Non Ocular

In general, most non-ocular TEAEs were reported in patients in the 18 to 64 years age group, Only 1 patient (7.1%) in the Olopatadine 0.2% group in the 10 to 17 years age group was reported with 1 non-ocular TEAEs (enteritis).

Other safety data

Best corrected visual acuity

Best-corrected visual acuity was measured at baseline, Day 7, Day 14, or early exit visit and unscheduled visit using a numerical early treatment diabetic retinopathy study visual acuity chart at 4 meters. In general, the mean BCVA and mean BCVA change from baseline were similar between the 2 treatment groups.

There were no notable imbalances in the distribution of BCVA letter changes between the Olopatadine 0.2% and Olopatadine 0.1% groups, with the exception of 3 (2.4%) patients in the Olopatadine 0.2% group (1 [0.8%] patients at Day 7 visit; 1 [0.8%] patients at Day 14 visit; and 1 [0.8%] patient at Day 7 and 14 visits) who experienced a BCVA decrease of more than 15 letters compared to no patients in the Olopatadine 0.1% group. Two of the 3 patients' BCVA decrease was assessed as not clinical relevant, the other one was reported as an AE which was assessed as not related to the study drug by the investigator.

Slit-lamp biomicroscopy

Slit-lamp biomicroscopy was performed at all 3 study visits. Results of corneal examination iris score anterior chamber score and lens score were similar in the 2 treatment groups.

Intraocular pressure

An assessment of IOP was performed at the baseline and Day 14 visit.

For most patients, IOP remained stable and there was no notable difference between the 2 treatment groups.

Undilated fundus examination

Undilated fundus examination was performed at the baseline and Day 14 visit. There were no increase in severity grade from baseline in undilated fundus examination in either treatment group during the study.

2.3.3 Discussion on clinical aspects

Based on a review of AEs and an assessment of ocular safety parameters (BCVA, IOP, slit-lamp biomicroscopy and undilated fundus assessments), olopatadine hydrochloride 0.2% ophthamic solution

QD was safe and well-tolerated in both paediatric and adult Chinese patients with allergic conjunctivitis, which is comparable with the safety profile of olopatadine hydrochloride 0.1% ophthalmic solution BID. The safety findings observed in this study reveal no new safety concerns for paediatric or adult Chinese patients treated with olopatadine hydrochloride 0.2% ophthalmic solution QD.

Regarding efficacy, olopatadine hydrochloride 0.2% ophthalmic solution QD was demonstrated to be noninferior to olopatadine hydrochloride 0.1% ophthalmic solution BID for the treatment of ocular itching associated with allergic conjunctivitis.

In addition, olopatadine hydrochloride 0.2% ophthalmic solution QD was shown to be similar to olopatadine hydrochloride 0.1% ophthalmic solution BID for the treatment of bulbar conjunctival hyperemia, chemosis, and eyelid swelling associated with allergic conjunctivitis.

3. Rapporteur's CHMP overall conclusion and recommendation

In conclusion, the benefit-risk assessment for olopatadine hydrochloride remains positive for the currently approved indications 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 Company Core Data Sheet or the Summary of Product Characteristics are proposed as a result of this study.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

None.

MAH responses to Request for supplementary information