

Public Assessment Report Scientific discussion

Otrivin Comp (Xylometazoline hydrochloride 0.5 mg/ml+ Ipratropium bromide 0.6 mg/ml)

SE/H/848/01/MR

This module reflects the scientific discussion for the approval of Otrivin Comp, nasal spray solution 0.5 mg/ml+ 0.6 mg/ml. The procedure was finalised at October 2nd 2008. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Novartis has applied for a marketing authorisation for Otrivin Comp, nasal spray, solution, 0.5 mg/ml+ 0.6 mg/ml. The active substances are xylometazoline hydrochloride and ipratropium bromide. Xylometazoline hydrochloride is a sympathomimetic which acts on α -adrenergic receptors. Xylometazoline has a vasoconstrictive effect. Ipratropium bromide has anticholinergic effect through competitive inhibition of cholinergic receptors. The product is indicated for the symptomatic treatment of nasal congestion and rhinorrhea in connection with common colds for a maximum duration of 7 days.

The procedure was referred to the CMD(h) due to potential serious risk to public health concerns on grounds relating to quality and efficacy. The quality issues were related to concerns for the manufacturing process and priming of the dose prior to administration. With regard to efficacy, the claimed indication "Symptomatic treatment of nasal congestion and rhinorrhea in connection with common cold" and the proposed treatment duration was not considered sufficiently proven.

At the CMD(h) meeting, the RMS, referring CMS and the applicant presented their view on the outstanding issues. After the CMD(h) meeting, consensus was reached that the efficacy was sufficiently proven. Also the treatment duration of 7 days was accepted, however some CMS stated, although being a national issue, that the product is approvable with prescription status only at the present time. The quality issues were solved by the applicant's commitment to submit appropriate variations during 2009. Agreement reached.

II. QUALITY ASPECTS

II.1 Introduction

Otrivin Comp is presented in the form of nasal spray containing 0.5 mg/ml xylometazoline and 0.6 mg/ml ipratropium bromide. The excipients are disodium edetate, glycerol, water, and hydrochloric acid and sodium hydroxide which are used for pH adjustment. The solution is filled in a polyethylene bottle equipped with a spray pump.

II.2 Drug Substance

Both xylometazoline hydrochloride and ipratropium bromide have monographs in the Ph. Eur. Information on xylometazoline hydrochloride has been supplied in the form of an Active Substance Master File (ASMF). The manufacturers of ipratropium bromide hold Certificates of Suitability of the monograph (CEP).

Xylometazoline hydrochloride is a white to yellowish green, crystalline substance which is soluble in water. Ipratropium bromide is a white, crystalline substance which is soluble in water. The structures have been adequately proven and the physico-chemical properties sufficiently described. The routes of synthesis have been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Specifications of the drug substances include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Otrivin Comp 0.5 mg/ml + 0.6 mg/ml, nasal spray, solution, is formulated using excipients described in the current Ph. Eur. All raw materials used in the product are of chemical origin or has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the drug substances.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification. To further improve the microbiological quality of the product the applicant has committed to perform a drug product specific filter validation and establish a bioburden limit in routine production.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with the special storage precautions "Do not freeze".

III. NON-CLINICAL ASPECTS

III.1 Introduction

Both ipratropium bromide and xylometazoline hydrochloride are two well-established compounds and their respective pharmacology, pharmacokinetics and toxicology are considered well known. No unexpected undesired reactions or pharmacological interactions are expected from the combined use of ipratropium bromide and xylometazoline hydrochloride.

III.2 Toxicology

The principles recommended in the CPMP Guideline (CPMP/EWP/240/95) have been followed based on the established long use of the active substances. A nasal feasibility study (non-GLP) and a pivotal 28-day tolerance and intranasal toxicity study (GLP) in Beagle dogs have been performed in support of this application. The spray solution in the studies contained ipratropium bromide (0.6 mg/ml) and xylometazoline hydrochloride (1.0 mg/ml) in which the xylometazoline hydrochloride concentration was twice the concentration intended for the use in the clinical nasal dosing device spray. The clinical dosing device was used in both studies.

In the pivotal 28-day tolerance and intranasal toxicity study, Beagle dogs (3 animals/sex/group) were treated from 3 up to 6 times daily with doses ranging from 0.049 to 0.190 mg/kg/day for ipratropium bromide and from 0.082 to 0.316 mg/kg/day for xylometazoline hydrochloride. Groups dosed with Atrovent (0.050 mg/kg/day ipratropium bromide) and Zymelin (0.085 mg/kg/day xylometazoline hydrochloride) were included for comparison. The only observed treatment related clinical sign for the combination spray was loose or liquid faeces in males from the LD (0.049 mg/kg/day ipratropium bromide and 0.082

mg/kg/day xylometazoline hydrochloride) and in females from the HD (0.190 mg/kg/day ipratropium bromide and 0.316 mg/kg/day xylometazoline hydrochloride). However, loose or liquid faeces were also seen in the animals from the Atrovent group. In addition, increased blood urea was noted in males from the Atrovent group. Inflammatory cell infiltration was found in the nasal cavity of one control male dog, two male dogs in the MD and in all females but not in any male dog at the HD. There was no difference between the groups with respect to the incidence of total inflammatory responses in the nasal cavity or in the respiratory tract as a whole. Furthermore, no correlation of the incidence of the nasal findings across groups, sexes or in relation to the measured high plasma levels were observed and therefore, the finding of low level inflammatory cell infiltration of the nasal cavity noted was considered to be co-incident. Otherwise, no treatment related effects were observed.

The dogs at the highest tested dose in the pivotal study were exposed up to 4 times and 11 times the human exposure (in the PK study) for ipratropium bromide and xylometazoline hydrochloride, respectively. The pharmacokinetic data from the study also showed that when given together as in the combination spray, both compound seemed to be absorbed to a lesser extent in comparison to when they were administered individually. However, the reduction which was especially pronounced for ipratropium bromide was very large in dogs and smaller in humans (see respective AR).

Ipratropium bromide and xylometazoline hydrochloride were also detected in some control animals. A re-evaluation of the drug contamination in control blood samples was performed by the Applicant. The contamination was generally of a low level with no particular pattern of occurrence for either drug. As highlighted in the recent final EU guideline (CPMP/SWP/1094/04), issued after the submission of the Otrivin Comp dossier, the sources of contamination were investigated and possibly identified as *ex vivo*. The re-evaluation of the drug contamination in control blood samples confirmed that the result did not invalidate the 4-week local tolerance and toxicity intranasal, nor affected interpretation of the results or had an impact on the human risk assessment.

In conclusion, no apparent treatment related local or systemic effects were seen in dogs treated daily for 28 days by intranasal administration with the combination spray with doses up to 4 times the proposed clinical dosing regimen.

IV. CLINICAL ASPECTS

IV.1 Introduction

The common cold is the most frequently occurring acute illness in the industrialised world. More than 200 viruses are known to cause the symptoms of the common cold but 30 to 50% of all colds are caused by one of the numerous serotypes of rhinoviruses. The primary site of infection is the nasal epithelium, and the constellation of symptoms attending common cold virus infection appears to emanate from the inflammatory response mounted by the body's immune system rather from direct cellular necrosis or mucosal damage. The inflammatory response is characterised in part by the release of chemical mediators from inflammatory cells. These mediators (e.g. bradykinin and substance P) are capable of causing vascular engorgement of nasal capacitance vessels and increased vascular permeability, which leads to nasal congestion and rhinorrhea, two prominent symptoms of the common cold.

IV.2 Pharmacokinetics

The pharmacokinetics of ipratropium was investigated in ten healthy volunteers administered an i.v. dose, the terminal half-life was (mean $\pm$ SD) 98.4 $\pm$ 88.2 min; bioavailability after p.o. administration was approximately 1-5 %. The absorption of nasal ipratropium (as spray) in the

doses 84, 168 and 336 µg in healthy volunteers, 84 and 168 µg in patients with perennial rhinitis and 168 µg in subjects with induced common cold was studied based on renal excretion, which indicated a systemic availability of $\leq 10\%$ for all doses and in all groups including the patients with perennial rhinitis, who had used ipratropium for at least one year. Laurikainen *et al* found a $C_{\max}$ of 0.257 ng/ml after administration of 240 µg intranasal ipratropium to healthy volunteers. Pharmacokinetic variables for xylometazoline in man are not available but a slightly shorter half-life is expected based on preliminary results in dogs after nasal administration.

One pharmacokinetic study evaluated the absorption interaction between 0.6 mg/ml of ipratropium bromide and 1.0 mg/ml of xylometazoline hydrochloride of the actual product. The study was not able to derive values on total exposure and good approximations of the half-life because of too short blood sampling.

Overall, the pharmacokinetic documentation was considered sufficient. The slightly higher xylometazoline concentration in Otrivin Comp compared to xylometazoline alone, does not constitute a safety issue, since half the strength is used in the combination product (0.5 mg/ml versus 1.0 mg/ml).

IV.3 Pharmacodynamics

The pharmacodynamic profile of both active substances (Ipratropium bromide and Xylometazoline hydrochloride) included in Otrivin Comp have earlier been addressed in the RMS and found sufficient for the indications rhinorrhea and rhinitis respectively. Although the preclinical study data for Xylometazoline hydrochloride are limited, its extensive use for several decades has not linked it to any genotoxic potential.

The effects of Ipratropium bromide are mediated via the cholinergic nervous system in the nasal mucosa. The local anticholinergic effect causes a reduction in nasal discharge. Xylometazoline hydrochloride has a local alpha-adrenergic effect on the nasal mucosa reducing swelling and congestion by producing vasoconstriction of dilated blood vessels.

IV.4 Clinical efficacy

Data from two clinical studies, one dose finding study and one phase III study are submitted to support the claims of efficacy.

In the dose finding study 185 patients with early symptoms of common cold were randomised to treatment with a fixed dose of xylometazoline hydrochloride (280 mcg x3) combined with one of three doses of ipratropium bromide (84, 168 or 336 mcg x3) or placebo. Treatment period was 2x24 hours which could be extended up to 4x24 hours if needed. The primary endpoint was the number of paper tissues used during the first 24 hours. Statistically significant results for the primary endpoint but conflicting results for the secondary subjective symptoms endpoints were found for the combination 280/168 mcg x3 compared to 280/0 mcg x3. 280/168 mcg correspond to a concentration of the spray solution of 0.6/1.0 mg/ml of ipratropium bromide and xylometazoline hydrochloride respectively. The next higher dose of ipratropium bromide (336 mcg) did not increase the efficacy in this study.

Based on the data from the dose finding study the ipratropium bromide concentration of 0.6 mg/ml was combined with xylometazoline hydrochloride 0.5 mg/ml or 1.0 mg/ml chosen in two of the treatment arms in the phase III study. The other arms consisted of pure ipratropium bromide 0.6 mg/ml, pure xylometazoline hydrochloride 1.0 mg/ml or placebo. The 772 randomised patients had early symptoms of common cold. The primary endpoint was the subjective scores of rhinorrhea and congestive scores after 24 hours of treatment. The combination was favoured over each component with statistical significance. Rhinorrhea

suppression was more prominent than congestion suppression. The combined results from all centres in one of the five participating countries had considerably less favourable results. The well known drugs ipratropium bromide and xylometazoline hydrochloride in the combinations 0.6 mg/ml+0.5 mg/ml and 0.6 mg/ml/1.0 mg/ml have effect on both rhinorrhea and nasal congestion when used in the early phases of common cold. The results indicate that the “lower” strength has similar efficacy as the “higher” strength. The currently approved strength for pure xylometazoline hydrochloride when treating nasal congestion is 1.0 mg/ml. For nasal congestion the statistical significant difference for xylometazoline hydrochloride containing treatments versus ipratropium bromide and placebo treatments was present only at 24 hours, not afterwards.

The main effect is on the rhinorrhea. After the first 24 hours of treatment the xylometazoline component seems to add very little. The mean scores for rhinorrhea seem to be roughly similar between treatment arms including placebo after 4 days of treatment in patients still on trial (34-52%).

IV.5 Clinical safety

The IpraXylo treatment is associated with mostly local AEs (nasal mucosa). A mucosal bleeding is bothersome but hardly dangerous in the studied population.

The known adverse event spectrum for ipratropium bromide, with a relative high percentage of epistaxis (10-19%)/blood tinged mucus discharge (10-15%), nasal dryness, is also seen with the combination. However, most open published data concern ipratropium bromide as sole treatment and in these reports the frequency of epistaxis equals the frequency in the sole ipratropium bromide arms in the now submitted studies. The vasoconstrictive effect of xylometazoline hydrochloride seems not to have been able to counteract the nasal bleeding tendency. In the IpraXylo treatment arm 1/159 withdrew from the study due to epistaxis compared to 2/157 in the placebo arm.

The possibility for adverse events due to systemic exposure of the two drug components is not specifically investigated. The participating subjects had good “background” health. However, earlier studies indicate few systemic adverse effects if the recommendations in the SPC are followed. If local nasal adverse events are more common and/or severe in the elderly population with more fragile nasal mucosa is not investigated. To minimise the risk for developing rhinitis medicamentosa, the PL recommends maximum treatment duration of seven days.

IV.6 Risk Management Plan

The RMP was finalized after the national approval. Based on the assessment of this RMP minor adjustments to the interaction section of the SmPC were made. The MAH was also requested to present a synopsis of a Phase IV safety study and a plan for minimizing misuse/off-label use.

The results from the post-marketing non-interventional safety study (XY-005-IM) are submitted to all countries involved in the frame of a FUM and are presently evaluated.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

EMA’s Guideline for Fixed combinations of medicinal products demands an improvement of the benefit/risk assessment due to:

Addition or potentiation of therapeutic activities of their substances, which results in a level of efficacy similar to the one achievable by each active substance used alone at

higher doses than in combination, but associated with a better safety profile [applicable part of the Guideline].

Ipratropium bromide has a documented effect to decrease the amount of nasal discharge by its anticholinergic properties. Xylometazoline hydrochloride is less documented but has an established use to treat nasal congestion through its adrenergic effects.

These therapeutic effects, when mixing the two substances in a fixed combination and given to subjects in early phases of common cold, are explored in the two submitted studies.

The combined results of subjective rhinorrhea and nasal congestion scores in study XY-003-IN indicate that the effects of Ipratropium bromide and Xylometazoline hydrochloride, on rhinorrhea and nasal congestion respectively, when given separately are:

- a. Maintained when given concurrently in the combined product, with one component at a lower dose than earlier approved for the treated condition.
- b. Superior when given concurrently in the combined product compared to each component alone.

Both submitted clinical studies indicate that the benefit rapidly decreases. Obviously, the natural course of the symptoms has a great influence. The subject recruitment process may have delayed the start of the therapy in the submitted studies.

The main adverse effects are nasal bleeding and nasal irritation. A substantial part of the subjects had epistaxis (10.0% compared to 3.2% for placebo) and blood tinged nasal discharge (10.7% vs. 3.2%). however the withdrawal rate due to epistaxis was almost negligible. The post-approval Risk Management Plan included an additional safety study (XY-005-IM) and plan for minimizing misuse/off-label use. The results from the safety study are presently assessed.

User testing of the package leaflet has been performed.

The risk/benefit ratio is considered positive and Otrivin Comp was recommended for approval.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)