LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Timosan 1 mg/ml, Eye Drops, Prolonged release, Single dose units
(Timolol maleate)

Asp. no: 2005-0323

This module reflects the scientific discussion for the approval of Timosan. The procedure was finalised at 2007-09-07. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Santen Oy has applied for a marketing authorisation for Timosan 1 mg/ml, Eye Drops, Prolonged release, Single dose units (SDU). The active substance timolol maleate is the same as in Timosan 1 mg/ml, Eye Drops, Prolonged release, marketed by Santen Oy since 2000. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Timosan is presented in the form of Eye drops, prolonged release, single dose units containing 1 mg/ml of timolol. The excipients are carbomer, lysine monohydrate, poly(vinylalcohol), sodium acetate trihydrate, sorbitol and water. The eye drops are filled in single dose containers.

II.2 Drug Substance

Timolol maleate has a monograph in the Ph Eur.

Timolol maleate is a white or almost white, crystalline powder or colourless crystals. The structure of timolol maleate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on e.g. polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes 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

Timosan 1 mg/ml, Eye Drops, Prolonged release, Single dose units is formulated using excipients described in the current Ph Eur, except for lysine monohydrate which is controlled according to current Deutsches Arzneibuch and polyvinyl alcohol which is controlled according to internal monograph. All raw materials used in the product of animal origin 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 (EMEA/410/01). No raw material is of animal origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

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.

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 no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Timolol maleate is a well characterised compound and besides ocular absorption and local tolerance studies with the new, preservative-free formulation reference is made to bibliographical data regarding the pharmacological, pharmacokinetic and toxicological properties of timolol. This is appropriate.

III.2 Pharmacology

Timolol is a non-selective, β-adrenergic receptor blocking agent that lowers IOP by decreasing aqueous humour formation in the ciliary epithelium. Despite the long experience of the compound, the precise mechanism of action has not yet been clearly established.

III.3 Pharmacokinetics

Removal of bensalkonium chloride (BAC) may decrease the penetration through the cornea. This was investigated in a study comparing AQH concentration of timolol after topical, ocular application of preserved and non-preserved formulations of Timosan to pigmented rabbits. There were no major or statistical differences between the two formulations even though, numerically, the BAC-containing formulation gave a somewhat higher average AQH concentration of timolol. Nevertheless, non-inferiority between the two formulations was established in a phase III study (clinical assessment below) and the borderline inferior anterior chamber penetration of timolol in the BAC-free solution was found to be of no clinical relevance.

III.4 Toxicology

Ocular tolerance of the non-preserved formulation was assessed in one single dose study and compared with the preserved formulation in one 28-day study in albino rabbits. In the single dose study, a transient minimal ocular irritation was observed. In the repeat dose study, there were no clinical signs, or effects on body weights/gain. Slit lamp examinations, corneal staining, Draize test (ocular irritation) or histopathology of eyes and adnexa showed no relevant difference between the two formulations of Timosan. Removal of BAC may be expected to result in a better ocular tolerance, but the submitted studies were relatively short and as expected, there were no signs of a decreased ocular tolerance with the non-preserved formulation. The new formulation of Timosan had no corneal anaesthetic effect.

III.5 Ecotoxicity/environmental risk assessment

Removal of BAC does not call for an updated environmental risk assessment.

IV. CLINICAL ASPECTS

IV.1 Introduction

It is established that the preservative BAC may adversely affect corneal and conjunctival tissues, especially during chronic treatment. BAC has also been reported to reduce tear secretion and to induce alterations of the lachrymal film. Therefore, the introduction of a timolol formulation without BAC is appropriate.

IV.2 Pharmacokinetics

There is a potential that removal of the preservative may reduce the efficacy of the eye drop by decreasing corneal transfer of the drug. However, paracentesis of the anterior chamber is an invasive procedure which is not justified to an intact eye, due to the inherent risks, for e.g. intraocular bacterial contamination, unless it is performed in conjunction with ocular surgery. Measurements of plasma drug levels after topical, ocular application are also not a reliable, since only a small amount of the drop is absorbed through the cornea and the major part is lost through the lacrimal drainage system resulting in very low, often highly variable, systemic exposure levels. Therefore, a conventional pharmacokinetic bioequivalence study was considered of low value.

Systemic exposure data was nevertheless generated from a sub-population of patients (n=26) in conjunction with the phase III study discussed below (No. LTG1030-PIII-01/02). The systemic exposure after once daily administration of the non-preserved formulation of Timosan was compared with that of preserved formulation of Timosan in multidose (MD) containers. Blood samples collected before (time 0) and 2 hours after instillation of study medication the last (week 12) visit reviled plasma timolol levels detectable. but below the limit of quantification in the majority of patients and no conclusions can be drawn from these data.

IV.3 Pharmacodynamics

No new studies have been performed. Considering the well established profile of timolol, this is adequate.

IV.4 Clinical efficacy

Two new studies were presented.
In a single-masked, randomised (1:1), 28-day phase I study (n= 40), the ocular and systemic tolerance of two preservative-free timolol-based formulations: T-Gel 0.1% eye gel SDU and timolol 0.5% SDU eye drops, were compared to assess the safety and tolerability in healthy volunteers. As expected, the removal of BAC did not alter the tolerability of Timosan. Both formulations lowered IOP significantly, without any differences between treatments but with a numerically superior effect (~ 1 mmHg) for the 0.5% formulation.

In the second study, a 12 week, multicentre, open-label, randomised (1:1) study, the IOP-lowering effect and safety of the non-preserved formulation was compared with that of the preserved formulation of Timosan in patients (n = 175) with ocular hypertension or primary open angle glaucoma. The primary objective of the study was to demonstrate the non-inferiority of the IOP-lowering effect of the test product without BAC versus the reference product with preservative following once daily (QD) treatment for 12 weeks. The 12-week treatment duration is considered to be adequate in order to obtain the optimum IOP-lowering effect of timolol. The non-inferiority limit of 1.5 mmHg was chosen in accordance with published data. With today’s knowledge, a limit of 1 mmHg might have been chosen, since in the Early Manifest Glaucoma Trial, it was reported that each mmHg of decrease in IOP may be of clinical relevance (Hejl et al., 2002 Arch. Ophthalmol. 120;1268-1279). The two-sided 95%

confidence interval on mean difference between the groups at the primary, final 12-week visit was however well within this limit [-0.66; +0.66 mmHg]. The non-inferiority analysis is in accordance with ICH E9, NfG on Statistical Principles for Clinical Trials. In the ITT population, 84 and 81 patients in the test and reference groups, respectively, were treated during 12 full weeks. In the PP population the corresponding numbers were 73 and 71.

Discontinuations were few and balanced between treatment arms. Seven patients discontinued due to AEs, while no subjects withdrew from the study due to treatment failure. The analysis was primarily performed in the PP population. Reasons for excluded patients have been explained and the approach is acceptable.

The primary efficacy variable, the change in IOP (worse eye evaluated) between baseline and before instillation at the last visit was justified as it was at the end of the validated duration of action of one drop of the preserved formulation.

At the time point selected for the primary analysis, the reduction in IOP was 24% in each treatment group (IOP reduction of 5.6 mmHg in both groups) and within the pre-defined equivalence limit of 1.5 mm Hg. Even though the 1.5 mmHg non-inferiority limit may be discussed, the results from this study were consistent, well within the limits, and there were no numerical differences suggestive that one of the tested compounds should be in favour over the other. Therefore, it is considered that there is no clinically meaningful difference between the formulations. Similar results were observed in the ITT population, where the mean reduction in IOP was 5.3 and 5.2 mmHg in the reference and test-group, respectively. Secondary efficacy variables at week 4 (pre-instillation) and week 12 (peak effect at 2 hours post instillation) confirmed the non-inferiority between the two formulations in both the ITT and PP populations. In conclusion, it is considered non-inferiority between the formulations has been shown.

IV.5 Clinical safety

The removal of BAC is not expected to decrease the tolerability of Timosan or to change the adverse event profile. This was confirmed. The frequency of ocular adverse events and symptoms is in accordance with what is previously reported for timolol and reflects the wording of the SPC.
Overall, there are no new safety concerns with this formulation.

IV.6 Discussion on the clinical aspects

The non-preserved formulation of Timosan eye drops was demonstrated to be non-inferior to the equivalent BAC-containing formulation of Timosan eye drops, both with regards to efficacy and safety. Since the long-term use of BAC-containing eye drops have been reported to induce eye irritation or even punctuate keratopathy and/or toxic ulcerative keratopathy in certain conditions like in patients with dry eyes, or in conditions where the cornea is compromised, a formulation without BAC is valuable. Since the present formulation is also of a low strength, this formulation could be of importance for the use in children with primary congenital or aphakic glaucoma. However, there are not yet any studies addressing the efficacy and safety of Timosan in single dose units and such studies would be welcomed.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed. The justification for absence of user testing is acceptable.

The risk/benefit ratio is considered positive and Timosan 1 mg/ml, Eye Drops, Prolonged release, Single dose units is recommended for approval.

VI. APPROVAL

Timosan 1 mg/ml, Eye Drops, Prolonged release, Single dose units was approved in the national procedure on 2007-09-07.

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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)

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