PACKAGE INSERT FOR ATANA® OPHTHALMIC SOLUTION

SCHEDULING STATUS **S4**

PROPRIETARY NAME AND DOSAGE FORM

ATANA® Ophthalmic solution

COMPOSITION

Each ml of ATANA Ophthalmic Solution contains latanoprost 50 µg

Other ingredients are: Disodium phosphate anhydrous
Sodium chloride
Sodium dihydrogen phosphate monohydrate
Sodium Hydroxide / Hydrochloric acid
Water for injection
Preservative: Benzalkonium chloride 0,02 % *m/v*

PHARMACOLOGICAL CLASSIFICATION

A.15.4 Ophthalmic Preparations. Other

PHARMACOLOGICAL ACTION

Latanoprost is a prostanoid selective prostaglandin F_2 (FP) receptor agonist.

Pharmacodynamics:

Latanoprost is believed to reduce intraocular pressure by increasing the outflow of aqueous humor. Studies in man and animals indicate increased uveoscleral outflow as the main mechanism of action.

Pharmacokinetics:

Absorption:

Latanoprost is absorbed through the cornea following topical ocular administration. The peak concentration in the aqueous humor is reached about 2 hours after topical administration as indicated in studies conducted in man.

Biotransformation:

Latanoprost is an isopropyl ester prodrug and is hydrolysed by esterases in the cornea to the biologically active acid. The active acid of latanoprost that reaches the systemic circulation is primarily metabolised by the liver to the 1,2-dinor- and 1,2,3,4-tetranor-metabolites via fatty acid β-oxidation.

Elimination:

Following both intravenous and topical administration, the elimination of the latanoprost acid from human plasma is rapid (t½ = 17 minutes). The systemic clearance is approximately 7 ml/min/kg. Metabolites are

mainly eliminated via the kidneys, following hepatic β-oxidation. Approximately 88 % and 98 % of the administered dose is recovered in the urine following topical and intravenous dosing respectively.

INDICATIONS

ATANA ophthalmic solution is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma, ocular hypertension and chronic angle closure glaucoma.

CONTRA-INDICATIONS

- Known hypersensitivity to latanoprost, benzalkonium chloride or any other ingredient in the formulation of ATANA.
- Pregnancy and lactation (See **"Pregnancy and Lactation"**).
- ATANA contains a high concentration of the preservative, benzalkonium chloride, which may be absorbed by all contact lenses (See **"Dosage and directions for use"** and **"Warnings and special precautions"**).

WARNINGS AND SPECIAL PRECAUTIONS

- It is recommended that ATANA be used with caution in aphakic or pseudophakic patients with torn posterior capsules or in patients with known risk factors for cystoid macular oedema (See **"Side-effects"**).
- ATANA may result in a gradual change in eye colour, by increasing the amount of brown pigment in the iris (See **"Side effects"**). This colour change is not due to an increase in the number of melanocytes, but rather to the increased melanin content in the stromal melanocytes of the iris.
- The change in iris colour occurs gradually and may not be noticeable for several months to years. Patients should be made aware of the possibility of iris colour change, before treatment is instituted. It is necessary to inform patients who are expected to receive treatment in only one eye, about the potential for increased brown pigmentation in the treated eye and thus heterochromia between the eyes. The resultant pigmentation is irreversible.
- The change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e. grey-brown, green-brown, blue-brown and yellow-brown. The onset of the eye colour change is usually within the first 8 months of treatment but may occur at a later stage in a small number of patients. Based on evidence from consecutive photographs, this effect has been seen in 30 % of all patients during 4 years of treatment in clinical trials. The highest incidence was found in patients with yellow-brown and green-brown irides. The change has only rarely been seen in patients with homogenously green, blue, grey or brown eyes.
- The brown pigmentation around the pupil spreads concentrically towards the periphery of the affected eyes, but the entire iris or parts of it may also become more brownish. No further increase in brown iris pigmentation has been observed once treatment is discontinued.
- Changes in eyelashes may occur (See **"Side-effects"**).
- Neither freckles nor naevi of the iris has been affected by the treatment.

- Pigment accumulation in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical trials.
- As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.
- The safety and effectiveness of ATANA in children has not been established, therefore the use of ATANA in children is not recommended.
- ATANA has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in patients with these conditions.
- Latanoprost is known to be hydrolysed in the cornea. The effect that may occur as a result of continued administration of ATANA in the corneal epithelium has not been fully evaluated.
- There is limited experience of ATANA in patients with asthma, but cases of asthma, acute asthma attack, asthma aggravation, dyspnoea and coughing have been reported (See **"Side effects"**).
- There is limited experience in inflammatory ocular conditions, inflammatory, angle closure, neovascular, congenital or pigmentary glaucoma and also in pseudophakic patients with open angle glaucoma.
- ATANA has no or little effect on the pupil, however there is no experience in acute attacks of closed angle glaucoma. Until more experience is obtained, it is recommended that ATANA be used with caution in these conditions.
- ATANA contains a high concentration of the preservative, benzalkonium chloride, which may be absorbed by all contact lenses (See **"Contraindications"** and **"Dosage and directions for use"**).
- Bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products, has been reported.
- Patients should be instructed to prevent the tip of the dispensing container to make contact with the eye or surrounding structures, as this could cause the tip to become contaminated by common bacteria known to cause common ocular infections. The use of contaminated solutions may result in serious damage to the eye and subsequent loss of vision.
- It is also important to advise patients that should they develop an intercurrent ocular condition (e.g. infection or trauma) they should immediately seek their physician's advice concerning the continued use of the multidose container they have been using.
- In addition, patients should be advised that if they develop any ocular reactions, particularly lid reactions and conjunctivitis, they should seek their doctor's advice.

Effects on ability to drive and use machines:

Administration of eye drops may cause transient blurring of vision.

INTERACTIONS

In vitro studies have demonstrated the occurrence of precipitation when eye drops containing thiomersal are mixed with latanoprost. If such medicines are used, the eye drops should be administered with an interval of at least 5 minutes between applications.

Latanoprost is effective as monotherapy as demonstrated in pivotal studies.

Latanoprost's intraocular reducing effect has been shown to be additive to that of beta-adrenergic antagonists (timolol).

In short term studies (up to 2 weeks) the effect of latanoprost was additive in combination with oral carbonic anhydrase inhibitors (acetazolamide) and adrenergic agonists (dipivefrin) and at least partly additive with cholinergic agonists (pilocarpine).

In the case of combination therapy the eye drops should be administered with an interval of at least 5 minutes between applications (See **"Dosage and directions for use"**).

PREGNANCY AND LACTATION

The safety of ATANA for use in pregnancy has not been established. Since ATANA has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate, it should not be used in pregnancy (See **"Contraindications"**).

The safety of ATANA in lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

ATANA contains a high concentration of the preservative, benzalkonium chloride, which may be absorbed by all contact lenses (See **"Contraindications"** and **"Warnings and special precautions"**). Patients wearing contact lenses should be instructed to remove their lenses prior to ATANA administration and to wait at least 15 minutes to reinsert them.

Recommended dosage for adults (including the elderly):

- Recommended therapy is one drop in the affected eye(s) once daily. The optimal effect is obtained if ATANA is administered in the evening.
- Dosage should not exceed more than once daily administration, since more frequent administration may decrease the intraocular pressure lowering effect of ATANA.
- If a dose is missed treatment should continue with the next dose as planned.
- Reduction of the intraocular pressure in man is initiated about 3 to 4 hours after administration and maximum effect is reached after 8 to 12 hours. Intraocular pressure reduction is maintained for at least 24 hours.
- ATANA may be used concomitantly with other topical ophthalmic preparations to lower intraocular pressure. If more than one topical medicine is being used, the medicines should be administered at least 5 minutes apart (See **"Interactions"**).

SIDE EFFECTS

The most undesirable side effects relate to the ocular system.

Eye disorders:

Frequent:

An increase in brown pigmentation of the iris (See **"Warnings and special precautions"**); mild foreign body sensation; changes in the eyelashes (See **"Warnings and special precautions"**).

Transient punctate epithelial keratopathy, mostly without symptoms; mild to moderate conjunctival hyperaemia.

Less frequent:

Periorbital oedema; uveitis/iritis; symptomatic corneal oedema and erosions; darkening of the palpebral skin.

During treatment with ATANA eye drops, macular oedema including cystoid macular oedema was reported infrequently, mainly in patients with aphakia and pseudophakia with torn posterior lens capsule or anterior chamber lenses (See **"Warnings and special precautions"**).

Cardiac disorders:

Frequency unknown:

Chest pain and angina pectoris.

Respiratory, thoracic and mediastinal disorders:

Less frequent:

Dyspnoea; asthma and asthma aggravation (See **"Warnings and special precautions"**).

Frequency unknown:

Upper respiratory tract infection, colds and flu.

Skin and subcutaneous tissue disorders:

Less frequent:

Skin rash.

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown:

Muscle, joint and back pain.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Apart from conjunctival hyperaemia and ocular irritation, no other ocular side effects are known in the event of overdosage.

The following information may be useful if ATANA is accidentally ingested:

One bottle of ATANA contains 125 micrograms latanoprost. More than 90 % of this is metabolised during the first pass through the liver.

Intravenous infusion of 3 micrograms/kg in healthy volunteers induced no symptoms, however, a dose of 5,5 to 10 micrograms/kg resulted in nausea, abdominal pain, fatigue, dizziness, hot flushes and sweating.
Latanoprost has been intravenously infused in monkeys, in doses of up to 500 micrograms/kg without major effects on the cardiovascular system.
Latanoprost has been associated with transient bronchoconstriction when administered intravenously in monkeys. Bronchoconstriction, however, was not induced by latanoprost when applied topically to the eyes in a dose of seven times the clinical dose of ATANA, in patients with moderate bronchial asthma.
Treatment should be symptomatic, should overdosage with ATANA occur.

IDENTIFICATION

Clear, colourless aqueous solution.

PRESENTATION

ATANA solution is supplied in a low density polyethylene 5 ml sterile white bottle containing 2,5 ml solution, with a sterile white high density polyethylene screw cap and a sterile white low density polyethylene under-cap dropper. The dropper bottle is contained in an outer cardboard carton.

STORAGE INSTRUCTIONS

Store in a refrigerator at 2 ^{o}C – 8 ^{o}C. Avoid freezing. Protect from light.
Keep the bottle in the carton until required for use.
Keep well closed after initial opening.
Once the container is opened store at or below 25 ^{o}C. The contents must be used within 30 days.
KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

47/15.4/0116

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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