Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carteolol hydrochloride Thea 20 mg/ml eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml eye drops solution contains 20 milligrams of carteolol hydrochloride. One vial of 5 ml eye drops solution contains 100 mg of carteolol hydrochloride.

One drop contains approximately 0.58 milligram of carteolol hydrochloride.

Excipients with known effect: 1 ml eye drops solution contains 0.51 mg of phosphates (disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.

It is a clear, colourless to slightly brown-yellow solution.
pH: 6.0 – 7.0
Osmolality: 270-340 mosmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ocular hypertension and primary open-angle glaucoma.

4.2 Posology and method of administration

Posology
One drop, twice daily.
The medical prescription should be complemented by an IOP check, especially at the start of treatment.
If appropriate, therapy with parasympathomimetic agents, prostaglandin-like carbonic anhydrase inhibitors or alpha agonists may be associated.

Replacement of other anti-glaucoma agents for topical use with Carteolol hydrochloride Thea
Discontinue treatment after a full day of therapy and initiate treatment with Carteolol hydrochloride Thea by instilling one drop twice daily.

Paediatric population
The safety and efficacy of Carteolol hydrochloride Thea in children aged 0 to 18 years have not been established, therefore, the use of these eye drops is not recommended for this patient group.

Method of administration
Ocular use.
Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.
If more than one topical ophthalmic medicine is being used, the medicinal products should be administered at least five minutes apart.

Patients should be instructed as follows:

1. Before each use, wash your hands thoroughly. Then unscrew the cap and remove it from the bottle tip. Avoid any contact of the bottle tip with the fingers.

2. To use, tilt your head back slightly and hold the bottle dropper vertically above your eye. With the index finger of the other hand, pull the lower eyelid down slightly. The created space is called the lower conjunctival sac. Avoid contact of the bottle tip with your eyes or eyelids.
To apply a drop in the lower conjunctival sac of the affected eye(s), **press firmly** on the bottle sides.

3. When using nasolacrimal occlusion or closing the eyelids for two minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4. Close the tip of the bottle with the cap immediately after use.

5. Remember to write the date of first opening of the bottle on the package.

4.3 Contraindications

- Hypersensitivity to the active substance (carteolol) or to any of the beta-blockers or any of the excipients listed in section 6.1.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease, bronchospasms, acute respiratory disorders.

- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker.
- Congestive heart failure,overt cardiac failure or cardiogenic shock.

4.4 Special warnings and precautions for use

Patients should be instructed to avoid allowing the tip of the bottle to come into contact with the eye or surrounding structures.
This medicinal product is a sterile solution that does not contain a preservative. Patients should be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.
Like other topically applied ophthalmic agents, carteolol is absorbed systemically. Due to beta-adrenergic component, carteolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur (including deteriorating Prinzmetal's angina, deteriorating peripheral circulatory disorders and hypotension).
Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders
In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be kept under observation for signs of deterioration of these diseases and of adverse reactions.
Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Vascular disorders
Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Bradycardia
Beta-blockers may induce bradycardia, therefore the heart rate should be monitored. In case of severe bradycardia (less than 50-55 bpm at rest), anti-glaucoma therapy with beta-blockers should be discontinued.

Pheochromocytoma
The use of beta-blockers in the treatment of pheochromocytoma-induced hypertension requires the close monitoring of arterial blood pressure.

Respiratory disorders
Respiratory reactions, including death due to bronchospasm, in patients with asthma have been reported following administration of some ophthalmic beta-blockers.
Carteolol hydrochloride Thea should be used with caution in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycaemia/diabetes
Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia (i.e. tachycardia, sweating, palpitations).

Hyperthyroidism
Beta-blockers may mask signs of hyperthyroidism, and specifically cardiovascular signs. The abrupt discontinuation of therapy with beta-blockers may result in the worsening of the symptoms.

Psoriasis
Deterioration of the disease has been reported with the administration of beta-blockers, and this needs to be considered when deterioration of psoriasis is observed when using of beta-blockers.

Corneal diseases
Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Other beta-blocking agents
The effects on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when carteolol is given to patients already receiving a systemic beta-blocking agent. The response of these patients should be closely monitored. The use of two topical beta-adrenergic blocking agents is not recommended (reference should be made to section 4.5).

Anaphylactic reactions
While taking beta-blockers, patients with history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenalin used to treat anaphylactic reactions.

Choroidal detachment
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Surgical anaesthesia
Beta-blocking ophtalmological preparations may block systemic beta-agonists effects, such as adrenalin. The anaesthetist should be informed if the patient is receiving carteolol.

Musculoskeletal and connective tissue disorders
Therapy with beta-blockers may worsen myasthenia gravis symptoms.

Elderly subjects, subjects with renal impairment and/or hepatic impairment
In these at-risk subjects, and when beta-blocker eye drops are co-administered with a systemic beta-blocker, an adjustment of the dosage regimen is often necessary.

Patients with a history of contact hypersensitivity to silver should not use this medicinal product as dispensed drops may contain traces of silver from the container.

Paediatric population
Due to the lack of clinical data, the paediatric use is not recommended.

4.5 Interaction with other medicinal products and other forms of interactions

No specific drug interaction studies have been performed with carteolol.

Although the quantities of beta-blockers entering the systemic circulation following ocular instillation are low, there is a risk of interactions with other medicinal products. It is therefore appropriate to consider the interactions observed with beta-blockers administered systemically.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

Mydriasis resulting from the concomitant use of ophthalmic beta-blockers and adrenalin (epinephrine) has been reported occasionally. In the event of concomitant treatment with eye drops containing epinephrine, monitoring by an ophthalmologist is required (risk of mydriasis).

1) Co-administration not recommended

Amiodarone
Automatism and conduction disorders (suppression of compensatory sympathetic mechanisms).

Calcium antagonists (bepridil, diltiazem and verapamil)
Automatism disorders (excessive bradycardia, sinus arrest), sinoatrial and atrioventricular conduction disorders, heart failure (synergy of effects).

Such an association must be carried out under strict clinical and ECG monitoring, particularly in elderly subjects or at the start of treatment.

Beta-blockers used in cardiac insufficiency
Risk of increased undesirable effects induced by beta-blockers, specifically, excessive risk of bradycardia.

Fingolimod
Potentiation of bradycardia that may prove fatal. In particular, beta-blockers are at risk in that they prevent the adrenergic compensatory mechanisms. This combination should be administered only under direct clinical supervision and continuous ECG monitoring for 24 hours after the first dose.

2) Co-administration requiring precautions for use

Volatile halogenated anaesthetics
Reduction of cardiovascular compensation reactions induced by beta-blockers (beta-adrenergic inhibition can be prevented during the surgical procedure via the use of beta stimulants). As a general rule, do not discontinue the beta-blocker treatment and, in all events, avoid sudden discontinuation. The anaesthetist should be advised of this treatment.

Anticholinesterases: donezepil, galantamine, rivastigmine, neostigmine, pyridostigmine, tacrine, ambenonium
Risk of excessive bradycardia (addition of bradycardiogenic effects).
Regular clinical monitoring is recommended.

Quinidine
A potentiation of the systemic beta-blocker effects of the eye drops solution and an increase in the plasma concentrations of the beta-blocker have been reported upon co-administration of a beta-blocker eye drops solution and quinidine, probably as a result of the inhibition of the metabolism of the beta-blocker by quinidine (as is the case for carteolol).

Lidocaine
If administered intravenously, an increase in lidocaine serum levels may cause cardiac risk and neurological adverse events (due to its reduced hepatic clearance) Clinical and ECG monitoring are recommended, possibly as complemented by the monitoring of the lidocaine serum levels during administration and after the interruption of beta-blockers. Proceed with the adjustment of the lidocaine dosage, as appropriate.

Baclofen
Increase in the antihypertensive effect.
Monitoring of arterial pressure and dosage regimen adjustment of the antihypertensive if necessary.

Clonidine and other central antihypertensives (alphamethyldopa, guanfacine, moxonidine, rilmenidine)
Significant increase in arterial pressure in the event of sudden discontinuation of treatment with a central antihypertensive.
Avoid the sudden discontinuation of the central antihypertensive.
Clinical supervision is recommended.

Insulin, hypoglycaemic sulfamides, glinides
All beta-blockers can mask certain symptoms of hypoglycaemia such as palpitations and tachycardia. Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycaemia.
Alert the patient and increase blood glucose self-monitoring, especially at the start of treatment.

Medicinal products causing torsade de pointes
Class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide) and class III antiarrhythmics (amiodarone, dofetilide, ibutilide, sotalol), certain neuroleptics: phenothiazine (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, tiapride, sultopride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide) and other medicinal products such as: bepridil, cisapride, diphenamil, erythromycin IV, vincamine IV, mizolastine, halofantrine, sparfloxacine, pentamidine, moxifloxacine.
Increased risk of ventricular rhythm disorders, specifically torsade de pointes. Clinical supervision and ECG monitoring are recommended.

Propafenone
Contractility, automatism and conduction disorders (suppression of compensatory sympathetic mechanisms).
Clinical supervision and ECG monitoring are recommended.

3) Co-administration to be considered

NSAIDs (systemic route) including Cox-2 inhibitors
Reduction of the antihypertensive effect (inhibition of vasodilatory prostaglandins by NSAIDs and fluid and salt retention with pyrazole NSAIDs).

Alpha-blockers: alfuzosine, doxazosine, prazosine, tamsulosine, terazosine
Increase in the hypotensive effect, risk of increased orthostatic hypotension.

Amifostine
Increase in the antihypertensive effect.

Dipyridamole
With dipyridamole IV, increase in the hypotensive effect.

Calcium antagonists (dihydropyridine)
Hypotension, heart failure in patients suffering from latent or uncontrolled cardiac insufficiency (*in vitro* negative inotropic effect of dihydropyridines, varying in degree with the medicinal products, and to be added to the negative inotropic effects of beta-blockers).
The presence of a beta-blocker can also minimise the sympathetic reflex reaction arising in the event of excessive haemodynamic repercussions.

Antidepressants of the imipramine family (tricyclics), antipsychotics
Antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

Mefloquine, pilocarpine
Risk of excessive bradycardia (accumulation of bradycardiogenic effects).

4.6 Fertility, pregnancy and lactation

The systemic absorption of beta-blockers administered by the ocular route is lower than by the systemic route, although it may occur nevertheless.

Pregnancy
There are no adequate data for the use of carteolol in pregnant women. Studies conducted in laboratory animals do not indicate any adverse effects on the foetus or on the embryo (see section 5.3), however, carteolol should not be used during pregnancy unless clearly necessary and under direct medical supervision. To reduce the systemic absorption, reference should be made to section 4.2.
Epidemiological studies have not revealed malformative effects, but show a risk for intra-uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonates when beta-blockers have been administered until delivery. If Carteolol hydrochloride Thea is administered until delivery, newborns should be carefully monitored during the first days of life.

Breastfeeding
Beta-blockers are excreted in breast milk. However, at therapeutic doses of carteololin eye drops, it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce systemic absorption, see section 4.2.

4.7 Effects on ability to drive and use machines

No studies on the effect of this medicinal product on the ability to drive and use machines have been conducted. While driving vehicles or operating different machines, it should be taken into account that occasionally visual disturbances may occur including refractive changes, diplopia, ptosis, frequent episodes of mild and transient blurred vision and occasional episodes of dizziness or fatigue.

4.8 Undesirable effects

Like other topically applied ophthalmic drugs, carteolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

Immune system disorders
Systemic allergic reactions including angio-oedema, urticaria, localised and generalised rash, pruritus, anaphylactic reaction, systemic lupus erythematosus.

Metabolism and nutrition disorders
Hypoglycaemia.

Psychiatric disorders
Insomnia, depression, nightmares, memory loss.

Nervous system disorders
Syncope, cerebrovascular accident, cerebral ischaemia, increases in signs and symptoms of myasthenia gravis, dizziness, paraesthesia and headache.

Eye disorders
Signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), blepharitis, keratitis, blurred vision and choroidal detachment following filtration surgery (see section 4.4), decreased corneal sensitivity, dry eyes, corneal erosion, ptosis, diplopia.

Cardiac disorders
Bradycardia, chest pain, palpitations, oedema, arrhythmia, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure.

Vascular disorders
Hypotension, Raynaud's phenomenon, cold hands and feet, intermittent claudication.

Respiratory, thoracic and mediastinal disorders
Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnoea, cough.

Gastroinstestinal disorders
Dysgeusia, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting.

Skin and subcutaneous tissue disorders
Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.

Musculoskeletal and connective tissue disorders
Myalgia, arthralgia, muscle cramps, increase in signs and symptoms of myasthenia gravis.

Reproductive system and breast disorders
Sexual dysfunction, decreased libido, impotence.

General disorders and administration site conditions
Asthenia/fatigue.

Investigations
Positive antinuclear antibody test.

There are insufficient data to establish the frequency of the effects outlined above.

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Although systemic absorption of beta-blockers after ocular instillation is low, the possible risk of overdosing should be borne in mind.
There is limited experience from ocular overdosing.
In the event of accidental overdose via the ocular route of administration, rinse the eyes with a sterile sodium chloride solution 9 mg/ml (0.9%).

In the event of accidental oral intake or misuse, the symptoms (that may include those listed in section 4.8) and the steps to be taken are identical to those for beta-blockers overdose via the general route.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: beta-blocking agents, ATC code: S01ED05
Carteolol hydrochloride is a powerful beta-adrenergic receptor antagonist characterised by a long-term pharmacological action, by the lack of beta receptor selectivity, by an intrinsic sympathomimetic activity (ISA), and a slight local anaesthetic activity (approximately 1/10 of that of propranolol).
Carteolol hydrochloride has a dose-dependent hypotensive effect and does not engender the onset of tachyphylaxis.
The pharmacological action consists in the decreased formation of aqueous humour, probably by acting at the level of the ciliary body presenting a wealth of $ß_2$ receptors.
The intrinsic sympathomimetic activity of carteolol is responsible for the low incidence of side effects and, thus, for maintaining the heart rate, pulse rate and arterial blood pressure within the normal physiological range.

5.2 Pharmacokinetic properties

The instillation of carteolol hydrochloride is followed by the rapid absorption by the ocular tissues.
Following the instillation of 10µl of ^{14}C-carteolol ophthalmic solution 20 mg/ml into rabbit eyes, the highest platelet and tissue concentrations were obtained between 30 minutes to 2 hours. The study shows that, following topical application, carteolol spreads rapidly into the ocular tissues, passing the corneal barrier.
The highest concentrations of ^{14}C-carteolol were found in the following ocular tissues: cornea, iris, anterior sclera, ciliary body and conjunctiva and extraocular muscle. Slightly lower concentrations were found in the retina, choroid, posterior sclera, optic nerve and aqueous humour.
The concentration was especially low in the lens, vitreous body and plasma.
In the various tissues of the contralateral eye, very low radioactivity levels were measured. After the instillation of one drop of carteolol ophthalmic solution 20 mg/ml in healthy volunteers, the plasma concentrations were negligible (1-2 ng/ml).
Approximately 16% of the dose is excreted in the urine as unchanged compound during the first 24 hours after the instillation of a single drop of carteolol hydrochloride 20 mg/ml. The urinary elimination half-life following topical application is about 5 hours.

5.3 Preclinical safety data

Acute and chronic toxicity studies conducted with different, and even high (4%) concentrations of carteolol hydrochloride administered as eye drops, show the absence of local and systemic alterations.
In rats, it is reported that carteolol hydrochloride is able to pass through the placental barrier and is excreted in small quantities in murine milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Disodium phosphate dodecahydrate,
Sodium dihydrogen phosphate dihydrate,
Water for injections.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening: 2 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

5 ml (at least 150 drops) in a 15 ml multidose bottle (PE) with a dropper applicator (PE) equipped with a 0.2 microns filtering membrane (polyethersulphone) and a PE cap.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA1107/016/001

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