IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0118/048/002
Case No: 2043927

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Chauvin Pharmaceuticals Limited

106 London Road, **Kingston-upon-Thames**, **Surrey**, **KT2 6TN**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Fortinol LA 2 %w/v Eye Drops Prolonged Rel.

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/11/2007**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fortinol LA 2%, Eye drops, prolonged-release.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Carteolol hydrochloride: 2 g per 100 ml (1 ml eye drops, prolonged release contains Carteolol hydrochloride 20 mg).

Excipient: benzalkonium chloride solution (10 mg/100 ml).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, prolonged-release.

Clear and light brown yellow solution.

The pH is between 6 and 7, compatible with the pH of the tears.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Intraocular hypertension.
- Chronic open-angle glaucoma.

4.2 Posology and method of administration

Ocular use

Two strengths of eye drops are available: 1% and 2%.

Instill one drop of Carteol L.P. into the affected eye, once a day, in the morning.

- To administer the treatment, gently pull down the lid of the eye and apply one drop while looking upwards, close the eye a few seconds.
- Eye closed, clean properly the surplus.
- Reclose the bottle after each use.

It is recommended that the treatment be started by the instillation into the affected eye of one drop of Carteol L.P. at the lowest dose.

However, the normalization of intraocular pressure by carteolol eye drops sometimes takes several weeks, and consequently the evaluation of the treatment must include a measurement of the intraocular pressure and a corneal examination at the beginning of therapy and consequently regularly after a period of treatment of approximately 4 weeks.

The ophthalmologist may, if deemed necessary, co-administer carteolol eye drops with one or more other glaucoma therapies (by the local and/or general route).

The concomitant eye drops must be administered at least 15 minutes prior to Carteol L.P.

Replacement of a former treatment

When carteolol eye drops L.P. must replace another type of glaucoma eye drops, the latter eye drops must be discontinued at the end of a complete day of treatment, and carteolol eye drops LA must be administered the following day at the dosage regimen of one drop in the affected eye once a day.

If carteolol eye drops is to be used as a replacement for several associated glaucoma medicinal products, only one medicinal product may be discontinued at a time.

In the event of the replacement of miotic eye drops by carteolol eye drops, an examination of the refraction may prove to be necessary when the effects of the miotics have disappeared.

The medical prescription will be accompanied by a check of the intraocular pressure, especially at the time of the initiation of treatment.

Use in children and adolescents (< 18 years)

No clinical trials have been conducted with these eye drops in children and adolescents. Consequently, the use of these eye drops is not recommended for this patient group.

4.3 Contraindications

It is appropriate to keep in mind the contraindications of beta-blockers administered by the general route, although the systemic effects of beta-blockers are only observed in exceptional cases after ocular instillation.

- Asthma and chronic obstructive bronchopneumopathies.
- Cardiac insufficiency.
- Cardiogenic shock.
- Second-degree and third-degree atrioventricular blocks not controlled with a pacemaker.
- Prinzmetal's angina.
- Sick sinus syndrome (including sino-atrial block).
- Bradycardia (< 45-50 beats per minute).
- Raynaud’s disease and peripheral circulatory disorders.
- Untreated pheochromocytoma.
- Arterial hypotension.
- Hypersensitivity to carteolol, or to any of the excipients.
- Combination with floctafenine (see Section 4.5 Interactions with other medicinal products and other forms of interactions).
- Combination with sultopride (see Section 4.5 Interactions with other medicinal products and other forms of interactions).

4.4 Special warnings and precautions for use

Ocular
The co-administration of two beta-blocker eye drops is not recommended (see Section 4.2 Dosage regimen and mode of administration).

In the event that these eye drops are administered to reduce intraocular pressure in patients suffering from acute closed-angle glaucoma, a miotic must be co-administered. Indeed, in these patients, the immediate objective of the treatment is the reopening of the angle, which requires the use of a miotic to cause papillary constriction, since carteolol has little or no effect on the pupil.

Choroidal detachments contemporaneous with ocular hypotony have been reported with administration of aqueous suppressant therapy, after surgical treatment of glaucoma (described with timolol and acetazolamide).

Contact lens wearers
There is a risk of intolerance to contact lenses by the reduction of lacrimal secretions, generally associated with beta-blockers.

The preservative used in these eye drops, benzalkonium chloride, may cause eye irritation; it may be deposited on and discolour soft contact lenses.

Consequently, these eye drops must not be used simultaneously with the wearing of soft contact lenses. Lenses must be removed before the application of the drops and may not be reinserted until at least 15 minutes after the use of these eye drops.

Reduced sensitivity to carteolol may arise after prolonged treatment. The absence of tachyphylaxis should therefore be checked annually to ensure that long-term therapy remains effective.

General
It is appropriate to keep in mind the contraindications of beta-blockers administered by the general route, although the systemic effects of beta-blockers are only observed in exceptional cases after ocular instillation.

This medicinal product must generally not be combined with amiodarone, certain calcium antagonists (bepridil, verapamil, diltiazem) and the beta-blockers used to treat cardiac insufficiency (see Section 4.5 Interactions with other medicinal products and other forms of interactions).

Sportsmen
Sportsmen should be warned that this medicinal product contains an active substance which may induce positive analytical results in anti-doping controls.

Discontinuation of treatment
A beta-blocker treatment administered by the general route must never be interrupted suddenly, especially in patients with angina: sudden discontinuation may lead to serious cardiac rhythm disorders, myocardial infarction or sudden death.

The dosage regimen must be reduced progressively, i.e. over one or two weeks.

Bradycardia
If the heart rate drops below 50-55 beats per minute at rest and the patient presents symptoms associated with bradycardia, the dosage regimen must be reduced.

First-degree atrioventricular block
In view of the negative dromotropic effect of beta-blockers, they must be administered with caution to patients presenting a first-degree atrioventricular block.

Pheochromocytoma
The use of beta-blockers in the treatment of hypertension due to treated pheochromocytoma requires strict monitoring of arterial pressure.

Elderly subjects, subjects with renal insufficiency and/or hepatic insufficiency
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.

Diabetic subjects
Pre-emptively screen out diabetes sufferers and strengthen glycemic index self-monitoring at the start of the treatment. The indicatory signs of hypoglycemia may be masked, in particular tachycardia, palpitations and sweating.

Psoriasis
Aggravation of the disease has been reported under administration of beta-blockers, and the indication deserves to be given due consideration.

Allergic reactions
In patients susceptible to suffer a severe anaphylactic reaction, whatever its origin, in particular iodized contrast mediums or floctafenine (see Section 4.5 Interactions with other medicinal products and other forms of interactions) or during desensitizing treatments, the beta-blocker treatment may lead to an aggravation of the reaction and resistance to its treatment with epinephrine at the normal doses.

General Anaesthesia
Beta-blockers lead to an attenuation of the sympathetic reflex phenomena. The administration of a beta-blocker treatment reduces the risk of arrhythmia, myocardial ischemia and perioperative hypertensive attacks. It is appropriate to advise the anaesthesiologist that the patient is receiving a beta-blocker treatment.

If the discontinuation of the treatment is deemed necessary, a suspension of 48 hours is considered to be sufficient to allow the reappearance of sensitivity to catecholamines.

In certain cases, the beta-blocker treatment may not be interrupted:

- In patients affected with coronary insufficiency, it is advisable to continue the treatment up to the surgical procedure, in view of the risk associated with the sudden discontinuation of beta-blockers.
- In the event of emergencies or the impossibility of discontinuation, the patient must be protected from vagal predominance by adequate premedication of atropine, repeated as necessary.
- The anaesthesia must make use of products which cause as little myocardial depression as possible, and blood loss must be compensated.

The increase in the anaphylactic risk associated with the intake of beta-blockers must be taken into consideration.

Thyrotoxicosis
Beta-blockers are capable of masking certain signs of thyrotoxicosis, in particular cardiovascular signs.

4.5 Interaction with other medicinal products and other forms of interaction

1) Eye drops solution

Ophthalmologic monitoring is necessary in the event of concomitant treatment with eye drops solution containing epinephrine (risk of mydriasis).

2) Other medicinal products

Although the quantities of beta-blockers passing through the systemic circulation are low after ocular instillation, the risk of drug interactions exists. It is therefore appropriate to take account the interactions observed with beta-blockers administered by general route.

Contraindicated co-administrations

Floctafenine
In the event of shock or hypotension due to floctafenine, reduction of cardiovascular compensation reactions by beta-blockers.

Sultopride
Increased risk of ventricular rhythm disorders, notably torsade de pointes (atypical rapid ventricular tachycardia).

Co-administration not recommended

Amiodarone
Contractility, automatism and conduction disorders (suppression of compensatory sympathetic mechanisms).

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

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

Beta-blockers used in cardiac insufficiency
Risk of increase of undesirable effects of beta-blockers, notably with excessive risk of bradycardia.

Co-administrations requiring precautions for use

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

Anti-cholinesterases:
Donezepil, galantamine, rivastigmine, neostigmine, pyridostigmine, tacrine, ambenonium. Risk of excessive bradycardia (addition of bradycardiogenic effects). Regular clinical monitoring.

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 with the *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 (described for timolol).

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

Clonidine and other central anti-hypertensives (alphamethyldopa, guanfacine, moxonidine, rilmenidine)
Significant increase in arterial pressure in the event of sudden discontinuation of the treatment by the central anti-hypertensive. Avoid the sudden discontinuation of the central anti-hypertensive. Clinical monitoring.

Insulin, hypoglycemic sulfamides
All beta-blockers can mask certain symptoms of hypoglycemia: palpitations and tachycardia. The majority of non-cardioselective beta-blockers increase the incidence and severity of hypoglycemia. Warn the patient and strengthen blood glucose self-monitoring, especially at the start of the treatment.

Medicinal products causing torsade de pointes
Class Ia anti-arrhythmics (quinidine, hydroquinidine, disopyramide) and class III anti-arrhythmics (amiodarone, dofetilide, ibutilide, sotalol), certain neuroleptics: Phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide), and other medicinal products such as: bepridil, cisapride, diphenamil, erythromycin IV, vincamine IV, mizolastrine, halofantrine, sparfloxacine, petamidine, moxifloxacine etc. Increased risk of ventricular rhythm disorders, notably torsade de pointes. Clinical and electrocardiographic monitoring.

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

Co-administrations to be taken into consideration

NSAIDs (general route) including selective cox-2 inhibitors
Reduction of the anti-hypertensive effect (inhibition of vasodilatory prostaglandins by NSAIDs and fluid and salt retention with pyrazole NSAIDs).

Alpha blockers for urological purposes: Alfuzosine, doxazosine, prazosine, tamsulosine, terazosine
Increase in the hypotensive effect, risk of increased orthostatic hypotension.

Amifostine
Increase in the anti-hypertensive effect.

Calcium antagonists (dihydropyridines)
Hypotension, heart failure in patients suffering from latent or uncontrolled cardiac insufficiency (*in vitro* negative inotropic effect of dihydropyridines, varying in degree with the products, and likely to be to add to the negative inotropic effects of beta-blockers). The presence of a beta-blocker can also minimize the sympathetic reflex reaction that comes into play in the event of excessive hemodynamic repercussions.

Anti-depressants of the imipramine family (tricyclics), anti-psychotics
Anti-hypertensive effect and increased risk of orthostatic hypotension (additive effect).

Mefloquine
Risk of excessive bradycardia (addition of bradycardiogenic effects).

4.6 Pregnancy and lactation

The systemic passage of beta-blockers administered by the ocular route is lower than by the general route, but nevertheless it does occur.

Pregnancy

There are no adequate data from the use of Carteol L.P. in pregnant women. Reproductive toxicity studies in animals do not indicate any adverse effects relevant to the clinical use of Carteol L.P. (see section 5.3).

After systemic use, the beta-blocking action persists for several days after birth in the newborn baby of a treated mother, and may manifest itself in the form of a bradycardia, respiratory difficulty, or hypoglycemia. But in general, this is of no clinical consequence.

Nevertheless, due to the reduction of the cardiovascular compensation reactions, heart failure may occur, requiring hospitalization in intensive care (see 4.9 Overdose), in which case the use of filler solutions must be avoided (risk of acute pulmonary oedema).

Carteol L.P. may be prescribed during pregnancy if necessary. In the event of treatment up to delivery, attentive monitoring of the newborn (heart rate and glycemic index during the first 3 to 5 days of life) is recommended.

Lactation

It is unknown whether carteolol is excreted in human breast milk. Animal studies have shown excretion of carteolol in breast milk.

A decision on whether to continue/discontinue therapy with Carteol L.P. should be made taking into account the benefit of breast-feeding to the child and the benefit of Carteol L.P. therapy to the mother.

In case of treatment during lactation, take into account the pharmacological properties of Carteol L.P. (hypoglycaemia, bradycardia).

4.7 Effects on ability to drive and use machines

These eye drops are associated with undesirable effects (in particular, visual disturbances), which may impair the ability to drive and use machines.

4.8 Undesirable effects

Like other topically applied ophthalmic medicinal products, carteolol eye drops may be absorbed systemically and adverse reactions seen with oral beta-blockers may occur.

Benzalkonium chloride may cause eye and skin irritation (see Section 4.4. Special warnings and special precautions for use).

Cardiac and vascular disorders
Ocular: Syncope, palpitation, arrhythmia, heart block.
Systemic: Bradycardia, hypotension, cardiac insufficiency, slowing in atrioventricular conduction or intensification of an existing atrioventricular block, claudication, Raynaud's phenomenon, cold hands and feet.

Eye disorders
Ocular: Signs and symptoms of ocular irritation, including mild burning or stinging sensation at the beginning of treatment, blurred vision, conjunctival hyperaemia, conjunctivitis, blepharitis, keratitis, decreased corneal sensitivity, and dry eyes.
Systemic: Visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), ptosis, diplopia, choroidal detachment (following filtration surgery).

Gastrointestinal disorders
Ocular: Dyspepsia, dry mouth.
Systemic: Nausea, vomiting, diarrhea, gastralgia.

General disorders and administration site disorders
Ocular: Fatigue, chest pain.
Systemic: Asthenia.

Immune system disorders
Ocular: Systemic lupus erythematosus.
Systemic: Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localized and generalized rash.

Metabolism and nutrition disorders
Systemic: Hypoglycaemia.

Nervous system and psychiatric disorders
Ocular: Headache, dizziness, increase in signs and symptoms of myasthenia gravis.
Systemic: Depression, insomnia, nightmares, libido decreased, impotence.

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

Skin and subcutaneous tissue disorders
Ocular: Alopecia.
Systemic: Various skin symptoms, including urticaria, anaphylaxis, angio-œdema (angioneurotic oedema), cutaneous rash, psoriasiform rash or exacerbation of psoriasis (see Section 4.4. Special warnings and special precautions for use).

Biologically
Rare cases of antinuclear antibodies have been observed, only exceptionally accompanied by clinical symptoms such as lupus syndrome, which regress at treatment discontinuation.

4.9 Overdose

Although the quantities of beta-blockers passing into the systemic circulation are low after ocular instillation, the risk of overdose must be kept in mind.

Limited experience from ocular overdosing.

In the event of accidental overdose via the ocular route, rinse the eyes with a sterile sodium chloride 9 mg/ml (0.9%) solution.

In the event of accidental oral intake or mis-usage, the symptoms and the steps to be taken are identical to those for overdose on beta-blockers via the general route.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class: Beta-blocking agent.

ATC code: S01ED05

At the general level

Carteolol is a non-cardioselective beta-blocker, with partial agonist potential [moderate intrinsic sympathomimetic activity (ISA)], and a non-significant membrane-stabilizing effect (local or quinidine-like anaesthetic).

At the ocular level

- Carteolol hydrochloride eye drops reduce intraocular pressure, whether associated with glaucoma or not, by reducing the secretion of aqueous humour.
- Its activity becomes apparent usually approximately 30 minutes after instillation, peaks between 2 and 4 hours and is still present after 24 hours.
- Stability of the hypotensive effect over time: the effect can remain constant for one year.
- However, a reduction in sensitivity to carteolol hydrochloride remains possible, especially after a more prolonged treatment.
- There is practically no change in the pupillary diameter or accommodation.
- The excipient of Carteol L.P. 1% contains a hydrosoluble polymer (alginic acid) which possesses physical properties (such as bioadhesivity, ionic interactions etc.) which permit the frequency of daily instillations to be reduced to one instillation.

5.2 Pharmacokinetic properties

Mean plasmatic concentrations observed after 2 months of repeated instillations of Carteol 2% in glaucomatous patients are lower with the prolonged-release formulation given once a day (Cmax = 1.72ng/ml) than with the regular formulation given twice a day (Cmax = 3.64 ng/ml).

Although the renal function is important for elimination, no study has been conducted on patients suffering from renal insufficiency.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity.

In reproductive toxicity studies, embryotoxicity was seen at high oral doses resulting in systemic exposure levels considered sufficiently in excess of systemic exposure at clinical use of Carteol eye-drops. Carteolol was not teratogenic in reproductive toxicity studies.

In rats, it has been reported that carteolol hydrochloride is capable of passing through the placental barrier and was excreted in small quantities in breast milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride solution
Alginic acid (E 400)
Sodium dihydrogen phosphate dihydrate (E 339)
Disodium phosphate dodecahydrate (E 339)
Sodium chloride
Sodium hydroxide (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

Shelf-life after first opening of the container: 28 days.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

3 ml in dropper-container (PE) with screw cap (polypropylene).

3 x 3 ml in dropper-container (PE) with screw cap (polypropylene).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Chauvin Pharmaceuticals Limited.
106 London Road
Kingston-Upon- Thames
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8 MARKETING AUTHORISATION NUMBER

PA 0118/048/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd December 2004

Date of last renewal: 9th November 2006

10 DATE OF REVISION OF THE TEXT

March 2007