Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

RESCULA 1.5 mg/ml eye drops solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Unoprostone isopropyl 1.5 mg/ml.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution
Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

RESCULA is indicated for the reduction of elevated intraocular pressure in patients with ocular hypertension or chronic open angle glaucoma:

- as monotherapy in patients who are insufficiently responsive to, intolerant of or contraindicated to another intraocular pressure lowering medicinal product.
- as a second line adjunctive therapy to topical beta-blocking agents.

4.2 Posology and method of administration

Ocular use.

Adults (including the elderly):
The recommended dosage is one drop of RESCULA in the conjunctival sac of the affected eye(s), twice daily (morning and evening).

If one dose is missed, treatment must continue with the next dose as normal.

Patients should be instructed to avoid any contact between the tip of the bottle and the eye or surrounding structures to avoid an ocular contamination with common micro-organisms.

When used concomitantly with other eye drops, an interval of at least five minutes must be kept between instillation of each medicinal product.

Children and adolescents:
The tolerability and efficacy of RESCULA in children and adolescents have not been established. Consequently, RESCULA is not recommended for use in children or adolescents.

Patients with hepatic or renal impairment:
No specific studies in patients with hepatic or renal impairment have been performed. Taking into consideration the pharmacokinetic profile of this medicinal product no accumulation of the active substance is expected in these patients. (see 5.2 Pharmacokinetic properties).

4.3 Contraindications

Hypersensitivity to unoprostone isopropyl or to any of the excipients.

4.4 Special warnings and precautions for use

RESCULA may gradually change eye colour, by increasing the amount of brown pigments in the iris. Before treatment, patients must be informed of the possibility of permanent eye colour change. Unilateral treatment may result in a permanent heterochromia.

The change in iris colour occurs slowly (around the 8th month). This effect has been demonstrated by successive photos of the irides, and was seen in 1.06% of all patients treated with RESCULA in monotherapy clinical trials for up to 24 months.

The incidence of iris colour change observed was slightly higher in patients with heterochromic irides, i.e. blue-grey/brown or green/brown (1.9%), than in patients with monochromic irides (0.7%).

RESCULA has not been evaluated for the treatment of other primary or secondary glaucoma Therefore it is not recommended to use RESCULA in patients exhibiting these pathologies.

There is no experience in patients with severe asthma. Such patients should therefore be treated with caution until there is sufficient experience available.

RESCULA contains benzalkonium chloride as a preservative. Benzalkonium chloride may cause eye irritation.

Contact lens wearers:

Contact lenses must be removed prior to application of RESCULA and may be reinserted after 15 minutes at the earliest.
Benzalkonium chloride may be absorbed by soft contact lenses and is known to discolour soft contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction

RESCULA has not undergone any specific interaction study with other medicinal products.

4.6 Pregnancy and lactation

Pregnancy:

There are no adequate data from the use of RESCULA in pregnant women.
Unoprostone isopropyl was not teratogenic in rats and rabbits, but prostaglandin-like effects on maintenance of pregnancy were observed at high dose levels (see 5.3 Preclinical safety data).
Given the pharmacological properties, although the route of administration is local, an oxytocic effect at the end of pregnancy cannot be excluded. Therefore, RESCULA should not be used during pregnancy.

Lactation:

Drug-related compounds are excreted into the milk of lactating rats (see 5.3 Preclinical safety data), but it is not know whether drug-related compounds pass into human milk. Therefore, it is preferable to avoid the use of RESCULA during breast-feeding.

4.7 Effects on ability to drive and use machines

As with any eye drops, the instillation of RESCULA. *can induce temporary visual disturbances which may affect the ability to drive or use machines (see also 4.8 Undesirable effects).* Patients who experience these signs must wait for

normal vision to return before driving or operating machinery.

4.8 Undesirable effects

RESCULA has been studied in over 961 patients, 659 of whom were treated for up to 12 months.

The most commonly reported adverse events are burning/stinging and burning/stinging upon instillation, both of which may occur in up to 25% of patients. These reactions are usually mild and transient.
After up to 24 months of administration of RESCULA in monotherapy clinical trials, the incidence of iris hyperpigmentation rises to 1.06%.

The adverse events observed in the clinical trials up to 12 months of treatment considered to be related - or probably related - to the treatment are classified below according to their incidence:

Ocular:

Very common (> 1/10):
sensation of burning/stinging upon or after instillation.

Common (> 1/100 and < 1/10):
itching, hyperaemia, dry eye sensation, foreign body sensation, lacrimation disorder, abnormal vision, eyelid disorder, photophobia, conjunctivitis, keratitis, discharge, corneal lesions, eye pain.

Uncommon (> 1/1 000 and < 1/100):
irreversible hyperpigmentation of the iris, eyelash growth, irritation, iritis, blepharitis.

On account of the presence of benzalkonium chloride, risk of contact eczema and irritation.

Systemic:

Common (> 1/100 and <1/10):
cutaneous allergic reaction (rash), headaches.

Uncommon (> 1/1 000 and < 1/100):
allergic reactions, rhinitis.

With a different formulation marketed in Japan containing 0.12% unoprostone isopropyl, (instead of 0.15%) the following adverse events have been reported:

- spontaneous cases of corneal lesions, hyperpigmentation of the iris, allergic conjunctivitis, visual disorders, iritis/iridocyclitis, eye pain;
- rare spontaneous cases of chemosis, sub-conjunctival haemorrhage, dry mouth, taste perversion, nausea, vomiting, palpitations, sickness, asthenia, pigmentation of the eyelid, increase in the number of eyelashes.

4.9 Overdose

No case of overdose is known to date. In the event of an overdose, a symptomatic treatment should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Prostaglandin Analogues.
ATC code: S01 EE02.

The active substance, unoprostone isopropyl, is a docosanoid whose biochemical structure is similar to derivatives of the eicosanoid/prostanoid family; it is an analogue of biosynthetic derivatives of arachidonic acid or of docosahexanoic acid containing 22 carbon atoms, which acts to lower the intraocular pressure (IOP).

Experimental evidence suggests that unoprostone isopropyl acts mainly by increasing the aqueous humour outflow. The assumed mechanism of action is believed to involve the opening of the trabecular meshwork. However, this mechanism is not fully elucidated.

The maximum reduction in intraocular pressure is observed within 12 hours after a single day of dosing.

When administered at therapeutic doses, RESCULA:

- lowers the intraocular pressure without affecting the cardiovascular function;
- does not result in any change in pulmonary function in patients with mild to moderate asthma;
- does not result in mydriasis or myosis and has no effect on accommodation.

Clinical studies performed in monotherapy have shown that the reduction in the IOP obtained with RESCULA (2 instillations/24 hours) was:

- less than that obtained with timolol ophthalmic solution 0.5% after 6 months and after 1 year of treatment (2 instillations/24 hours);
- equivalent to the one obtained with betaxolol 0.5% eye drops after 6 months of treatment, however, this equivalence was not confirmed, by the results at 1 year (2 instillations/24 hours);
- less than that reported in publications for latanoprost 0.005% eye drops (1 instillation/24 hours).

Two clinical studies have demonstrated that the addition of RESCULA to timolol provides an additional lowering of the intraocular pressure of -2.9 and -2.6 mm Hg, respectively. The IOP-lowering effect of RESCULA in adjunctive therapy to timolol was comparable to that of dorzolamide (-3.0 mm Hg) and brimonidine (-3.1 mm Hg), but less than that of latanoprost (-5.3 mm Hg).

5.2 Pharmacokinetic properties

Absorption: After application to the eye, unoprostone isopropyl is absorbed into ocular tissues through the cornea and conjunctival epithelium where it is hydrolysed by esterases to its biologically active metabolite unoprostone free acid, which subsequently reaches the systemic circulation. Studies in animals indicate that peak concentrations in the cornea and conjunctiva are reached in less than 15 minutes and in the aqueous humour, iris and ciliary body about 1 hour after ocular instillation. Peak concentrations in the retina and choroid occur at about 30 minutes post-dose. A 14 days study in humans demonstrated little systemic absorption of unoprostone isopropyl after single or repeated ocular administration. The systemic exposure of its metabolite unoprostone free acid was minimal following the ocular instillation. Mean peak unoprostone free acid concentration was less than 1.5 nanograms/ml (tmax = 15 min). No accumulation of unoprostone free acid was observed.

Distribution: Ocular instillation of unoprostone isopropyl to rabbits lead to significant distribution to ocular tissues with highest concentrations in cornea (2.4% of dose at t_{max}) and conjunctiva followed by aqueous humour (0.5% of dose at t_{max}), iris, ciliary body, choroid and retina.

Metabolism: Following ocular application, unoprostone isopropyl is hydrolysed by esterases in the cornea to its biological active metabolite, unoprostone free acid. Unoprostone free acid is further metabolized to several inactive metabolites with lower molecular weight and increased polarity via a-chain and w-chain b-oxidation. No secondary conjugation is found and no significant effect on hepatic microsomal enzyme activity has been observed.

Elimination: Elimination of unoprostone free acid from human plasma is rapid, with a half-life of 14 minutes. Plasma levels of unoprostone free acid dropped below the lower limit of quantitation (<0.250 nanograms/ml) 1 hour following ocular administration.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, ocular and systemic repeated dose toxicity, genotoxicity and carcinogenic potential.

Unoprostone isopropyl did not affect fertility and reproductive performance in rats and was non-teratogenic in rats and rabbits.

However, animal studies showed prostaglandin-like action on maintenance of pregnancy at high dose levels. In particular, during organogenesis, subcutaneous administration of unoprostone isopropyl caused abortions and reduced birth index at maternally toxic doses in rats (5mg/kg/day) and maternally non-toxic doses in rabbits (0.3 mg/kg/day). In the rat peri-postnatal study, subcutaneous doses of 1.25 mg/kg/day caused premature deliveries, shortened gestation and reduced live birth index. Toxicokinetic analysis was not carried out, but these effects were seen at doses >100 times the maximum human daily dose.

Drug-related compounds were excreted in milk of lactating rats. The maximum concentration in milk was 3.3 times the maternal plasma concentrations within 2 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate
Mannitol
Polysorbate 80
Sodium hydroxide
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.
After opening: 4 weeks.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Bottle (polypropylene) with dropper applicator (polypropylene) containing 5ml solution.
Boxes of 1 or 3 bottles.

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

After opening, RESCULA should not be used for more than 4 weeks and any remaining contents must be discarded. The medicinal product must not be used after the expiry date.

7 MARKETING AUTHORISATION HOLDER

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