ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AZARGA 10 mg/ml + 5 mg/ml eye drops, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of suspension contains 10 mg brinzolamide and 5 mg timolol (as timolol maleate).

Excipient with known effect

One ml of suspension contains 0.10 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension (eye drops)

White to off-white uniform suspension, pH 7.2 (approximately).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction (see section 5.1).

4.2 Posology and method of administration

Posology

Use in adults, including the elderly
The dose is one drop of AZARGA in the conjunctival sac of the affected eye(s) twice daily.

When using nasolacrimal occlusion or closing the eyelids, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity (see section 4.4).

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye (s) twice daily.

When substituting another ophthalmic antiglaucoma medicinal product with AZARGA, the other medicinal product should be discontinued and AZARGA should be started the following day.

Special populations

Paediatric population
The safety and efficacy of AZARGA in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Hepatic and renal impairment
No studies have been conducted with AZARGA or with timolol 5 mg/ml eye drops in patients with hepatic or renal impairment. No dosage adjustment is necessary in patients with hepatic impairment or in patients with mild to moderate renal impairment.

AZARGA has not been studied in patients with severe renal impairment (creatinine clearance <30 ml/min) or in patients with hyperchloraemic acidosis (see section 4.3). Since brinzolamide and its main metabolite are excreted predominantly by the kidney, AZARGA is therefore contraindicated in patients with severe renal impairment (see section 4.3).

AZARGA should be used with caution in patients with severe hepatic impairment (see section 4.4).

Method of administration

For ocular use.

Patients should be instructed to shake the bottle well before use. After cap is removed, if tamper evident snap collar is loose, remove before using product.

To prevent contamination of the dropper tip and the suspension, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Instruct patients to keep the bottle tightly closed when not in use.

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Hypersensitivity to other beta-blockers.
- Hypersensitivity to sulphonamides (see section 4.4).
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.
- Severe allergic rhinitis
- Hyperchloraemic acidosis (see section 4.2).
- Severe renal impairment.

4.4 Special warnings and precautions for use

Systemic effects

- Brinzolamide and timolol are absorbed systemically. Due to the beta-adrenergic blocking component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. The incidence of systemic adverse reactions after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.
- Hypersensitivity reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) reported with sulphonamide derivates can occur in patients receiving AZARGA as it is absorbed systemically. At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs of serious reactions or hypersensitivity occur, AZARGA should be withdrawn immediately.

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 watched 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.

Hyperthyroidism

Beta-blockers may also mask the signs of hyperthyroidism.

Muscle weakness

Beta-adrenergic blocking medicinal products have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalised weakness).

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. AZARGA 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.

Acid/base disturbances

AZARGA contains brinzolamide, a sulphonamide. The same types of adverse reactions that are attributable to sulphonamides may occur with topical administration. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. This medicinal product should be used with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis. If signs of serious reactions or hypersensitivity occur, discontinue the use of this medicinal product.

Mental alertness

Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination. AZARGA is absorbed systemically and therefore this may occur with topical administration.

Anaphylactic reactions

While taking beta-blockers, patients with a 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 doses of adrenaline 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 ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Concomitant therapy

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents or two local carbonic anhydrase inhibitors is not recommended (see section 4.5).

There is potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and AZARGA. The concomitant administration of AZARGA and oral carbonic anhydrase inhibitors has not been studied and is not recommended (see section 4.5).

Ocular effects

There is limited experience with AZARGA in the treatment of patients with pseudoexfoliative glaucoma or pigmentary glaucoma. Caution should be utilised in treating these patients and close monitoring of IOP is recommended.

AZARGA has not been studied in patients with narrow-angle glaucoma and its use is not recommended in these patients.

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

The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count). Specifically, patients wearing contact lenses have not been studied and careful monitoring of these patients when using brinzolamide is recommended, since carbonic anhydrase inhibitors may affect corneal hydration. This may lead to a corneal decompensation and oedema and wearing contact lenses might increase the risk for the cornea. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.

AZARGA may be used while wearing contact lenses with careful monitoring (see below under ‘Benzalkonium chloride’).

Benzalkonium chloride

AZARGA contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses should be avoided. Patients must be instructed to remove contact lenses prior to the application of AZARGA and wait 15 minutes after instillation of the dose before reinsertion.

Benzalkonium chloride has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent or prolonged use.

Hepatic impairment

AZARGA should be used with caution in patients with severe hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with AZARGA.

AZARGA contains brinzolamide, a carbonic anhydrase inhibitor and, although administered topically, is absorbed systemically. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. The potential for interactions must be considered in patients receiving AZARGA.

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide eye drops. The concomitant administration of eye drops containing brinzolamide and oral carbonic anhydrase inhibitors is not recommended.

The cytochrome P-450 isozymes responsible for metabolism of brinzolamide include CYP3A4 (main), CYP2A6, CYP2B6, CYP2C8 and CYP2C9. It is expected that inhibitors of CYP3A4 such as ketoconazole, itraconazole, clotrimazole, ritonavir and troleandomycin will inhibit the metabolism of brinzolamide by CYP3A4. Caution is advised if CYP3A4 inhibitors are given concomitantly. However, accumulation of brinzolamide is unlikely as renal elimination is the major route. Brinzolamide is not an inhibitor of cytochrome P-450 isozymes.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when an ophthalmic beta-blocker solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.
Beta blockers can decrease the response to adrenaline used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy or anaphylaxis (see section 4.4).

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers. Caution is recommended in the concomitant use of this medicinal product with clonidine.

Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol. Caution is recommended.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data regarding the use of ophthalmic brinzolamide and timolol in pregnant women. Studies in animals with brinzolamide have shown reproductive toxicity following systemic administration, see section 5.3. AZARGA should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see 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 neonate when beta-blockers have been administered until delivery. If AZARGA is administered until delivery, the neonate should be carefully monitored during the first days of life.

Breast-feeding

It is not known whether ophthalmic brinzolamide is excreted in human breast milk. Studies in animals have shown that following oral administration brinzolamide is excreted in breast milk, see section 5.3.

Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in 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 the systemic absorption, see section 4.2.

However, a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from AZARGA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of Azarga on human fertility.

Non-clinical data do not show any effects of either brinzolamide or timolol on male or female fertility following oral dosing. No effects on male or female fertility are anticipated from the use of AZARGA.

4.7 Effects on ability to drive and use machines

AZARGA has minor influence on the ability to drive and use machines.

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines.

Carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

In clinical trials, the most common adverse reactions were blurred vision, eye irritation and eye pain, occurring in approximately 2% to 7% of patients.

Tabulated summary of adverse reactions

The following adverse reactions have been reported during clinical studies and post-marketing surveillance with AZARGA and the individual components brinzolamide and timolol. They are classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	MedDRA Preferred Term (v. 18.0)
Infections and infestations	Not known: nasopharyngitis[3], pharyngitis[3], sinusitis[3], rhinitis[3]
Blood and lymphatic system disorders	Uncommon: white blood cell count decreased[1] Not known: decreased red blood cell count[3], increased blood chloride[3]
Immune system disorders	Not known: anaphylaxis[2], anaphylactic shock[1], systemic allergic reactions including angioedema, [2] localised and generalised rash[2], hypersensitivity[1], urticaria[2], pruritus[2]
Metabolism and nutrition disorders	Not known: hypoglycaemia[2]
Psychiatric disorders	Rare: insomnia[1] Not known: hallucinations[2], depression[1], memory loss[2], apathy[3], depressed mood[3], decreased libido[3], nightmare[2,3], nervousness[3]
Nervous system disorders	Common: dysgeusia[1] Not known: cerebral ischaemia[2], cerebrovascular accident[2], syncope[2], increases in the signs and symptoms of myasthenia gravis[2], somnolence[3], motor dysfunction[3], amnesia[3], memory impairment[3], paraesthesia[2,3], tremor[3], hypoaesthesia[3], ageusia[3], dizziness[1], headache[1]
Eye disorders	Common: punctate keratitis[1], blurred vision[1], eye pain[1], eye irritation[1] Uncommon: keratitis[1,2,3], dry eye[1], vital dye staining cornea present[1], eye discharge[1], eye pruritus[1], foreign body sensation in eyes[1], ocular hyperaemia[1], conjunctival hyperaemia[1] Rare: corneal erosion[1], anterior chamber flare[1], photophobia[1], lacrimation increased[1], scleral hyperaemia[1], erythema of eyelid[1], eyelid margin crusting[1] Not known: increased optic nerve cup/disc ratio[3], choroidal detachment following filtration surgery[2] (see section 4.4 Special warnings and precautions for use), keratopathy[3], corneal epithelium defect[3], corneal epithelium disorder[3], increased intraocular pressure[3], eye deposit[3], corneal staining[3], corneal oedema[3], decreased corneal sensitivity[2], conjunctivitis[3], meibomianitis[3], diplopia[2, 3], glare[3], photopsia[3], reduced visual acuity[3], visual impairment[1], pterygium[3], ocular discomfort[3], keratoconjunctivitis sicca[3], hypoaesthesia of the eye[3], scleral pigmentation[3], subconjunctival cyst[3], visual disturbance[3], eye swelling[3], eye allergy[3], madarosis[3], eyelid disorder[3], eyelid oedema[1], ptosis[2]
Ear and labyrinth disorders	Not known: vertigo[3], tinnitus[3]
Cardiac disorders	Common: heart rate decreased[1] Not known: cardiac arrest[2], cardiac failure[2], congestive heart failure[2], atrioventricular block[2], cardio-respiratory distress[3], angina pectoris[3], bradycardia[2,3], irregular heart rate[3], arrhythmia[2,3], palpitations[2,3], tachycardia[3], increased heart rate[3], chest pain[2], oedema[2]
Vascular disorders	Uncommon: decreased blood pressure[1] Not known: hypotension[2], hypertension[3], blood pressure increased[1], Raynaud's phenomenon[2], cold hands and feet[2]
Respiratory, thoracic and mediastinal disorders	Uncommon: cough[1] Rare: oropharyngeal pain[1], rhinorrhoea[1] Not known: bronchospasm[2] (predominantly in patients with pre-existing bronchospastic disease), dyspnoea[1], asthma[3], epistaxis[1], bronchial hyperactivity[3], throat irritation[3], nasal congestion[3], upper respiratory tract congestion[3], postnasal drip[3], sneezing[3], nasal dryness[3]

Gastrointestinal disorders	Not known: vomiting[2,3], abdominal pain upper[1], abdominal pain[2], diarrhoea[1], dry mouth[1], nausea[1], oesophagitis[3], dyspepsia[2,3], abdominal discomfort[3], stomach discomfort[3], frequent bowel movements[3], gastrointestinal disorder[3], oral hypoaesthesia[3], oral paraesthesia[3], flatulence[3]
Hepatobiliary disorders	Not known: abnormal liver function test[3]
Skin and subcutaneous tissue disorders	Not known: Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (see section 4.4), urticaria[3], maculo-papular rash[3], generalised pruritus[3], skin tightness[3], dermatitis[3], alopecia[1], psoriasiform rash or exacerbation of psoriasis[2], rash[1], erythema[1]
Musculoskeletal and connective tissue disorders	Not known: myalgia[1], muscle spasms[3], arthralgia[3], back pain[3], pain in extremity[3]
Renal and urinary disorders	Uncommon: blood urine present[1] Not known: renal pain[3], pollakiuria[3]
Reproductive system and breast disorders	Not known: erectile dysfunction[3], sexual dysfunction[2], decreased libido[2]
General disorders and administration site conditions	Uncommon: malaise[1,3] Not known: chest pain[1], pain[3], fatigue[1], asthenia[2,3], chest discomfort[3], feeling jittery[3], irritability[3], peripheral oedema[3], medication residue[3]
Investigations	Uncommon: blood potassium increase[1], blood lactate dehydrogenase increased[1]

[1] adverse reactions observed for Azarga
[2] additional adverse reactions observed with timolol monotherapy
[3] additional adverse reactions observed with brinzolamide monotherapy

Description of selected adverse reactions

Dysgeusia (bitter or unusual taste in the mouth following instillation) was a frequently reported systemic adverse reaction associated with the use of AZARGA during clinical trials. It is likely to be caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal and is attributable to brinzolamide. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the occurrence of this effect (see section 4.2).

AZARGA contains brinzolamide which is a sulphonamide inhibitor of carbonic anhydrase with systemic absorption. Gastrointestinal, nervous system, haematological, renal and metabolic effects are generally associated with systemic carbonic anhydrase inhibitors. The same type of adverse reactions attributable to oral carbonic anhydrase inhibitors may occur with topical administration.

Timolol is absorbed into the systemic circulation. This may cause similar adverse reactions as seen with systemic beta-blocking medicinal products. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers. Additional adverse reactions associated with the use of the individual components that may potentially occur with AZARGA are included in the table above. The incidence of systemic adverse reactions after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Paediatric population

AZARGA is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.

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 the national reporting system listed in Appendix V.

4.9 Overdose

In case of accidental ingestion, symptoms of overdose from beta blockade may include bradycardia, hypotension, cardiac failure and bronchospasm.

If overdose with AZARGA eye drops occurs, treatment should be symptomatic and supportive. Due to brinzolamide, electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyse readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, Antiglaucoma preparation and miotics, ATC code: S01ED51

Mechanism of action

AZARGA contains two active substances: brinzolamide and timolol maleate. These two components decrease elevated IOP primarily by reducing aqueous humour secretion, but do so by different mechanisms of action. The combined effect of these two active substances results in additional IOP reduction compared to either compound alone.

Brinzolamide is a potent inhibitor of human carbonic anhydrase II (CA-II), the predominant iso-enzyme in the eye. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humour secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.

Timolol is a non-selective adrenergic-blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

Pharmacodynamic effects

Clinical effects
In a twelve-month, controlled clinical trial in patients with open-angle glaucoma or ocular hypertension who, in the investigator's opinion could benefit from a combination therapy, and who had baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of AZARGA dosed twice daily was 7 to 9 mmHg. The non-inferiority of AZARGA as compared to dorzolamide 20 mg/ml + timolol 5 mg/ml in the mean IOP reduction was demonstrated across all time-points at all visits.

In a six-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of AZARGA dosed twice daily was 8 to 9 mmHg, and was up to 3 mmHg greater than that of brinzolamide 10 mg/ml dosed twice daily and up to 2 mmHg greater than that of timolol 5 mg/ml dosed twice daily. A statistically superior reduction in mean IOP was observed compared to both brinzolamide and timolol at all time-points and visits throughout the study.

In three controlled clinical trials, the ocular discomfort upon instillation of AZARGA was significantly lower than that of dorzolamide 20 mg/ml + timolol 5 mg/ml.

5.2 Pharmacokinetic properties

Absorption

Following topical ocular administration, brinzolamide and timolol are absorbed through the cornea and into the systemic circulation. In a pharmacokinetic study, healthy subjects received oral brinzolamide (1 mg) twice daily for 2 weeks to shorten the time to reach steady-state prior to starting AZARGA administration. Following twice daily dosing of AZARGA for 13 weeks, red blood cell (RBC) concentrations of brinzolamide averaged 18.8 ± 3.29 µM, 18.1 ± 2.68 µM and 18.4 ± 3.01 µM at weeks 4, 10 and 15, respectively, indicating that steady-state RBC concentrations of brinzolamide were maintained

At steady state, following administration of AZARGA, the mean plasma C_{max} and $AUC_{0\text{-}12h}$ of timolol were 27% and 28% lower (C_{max}: 0.824 ± 0.453 ng/ml; $AUC_{0\text{-}12h}$: 4.71 ± 4.29 ng·h/ml), respectively, in comparison to the administration of timolol 5 mg/ml (C_{max}: 1.13 ± 0.494 ng/ml; $AUC_{0\text{-}12h}$: 6.58 ± 3.18 ng·h/ml). The lower systemic exposure to timolol following AZARGA administration is not clinically relevant. Following administration of AZARGA, mean C_{max} of timolol was reached at 0.79 ± 0.45 hours.

Distribution

Plasma protein binding of brinzolamide is moderate (about 60%). Brinzolamide is sequestered in RBCs due to its high affinity binding to CA-II and to a lesser extent to CA-I. Its active N-desethyl metabolite also accumulates in RBCs where it binds primarily to CA-I. The affinity of brinzolamide and metabolite to RBC and tissue CA results in low plasma concentrations.

Ocular tissue distribution data in rabbits showed that timolol can be measured in aqueous humour up to 48 hours after administration of AZARGA. At steady-state, timolol is detected in human plasma for up to 12 hours after administration of AZARGA.

Biotransformation

The metabolic pathways for the metabolism of brinzolamide involve N-dealkylation, O-dealkylation and oxidation of its N-propyl side chain. N-desethyl brinzolamide is a major metabolite of brinzolamide formed in humans, which also binds to CA-I in the presence of brinzolamide and accumulates in RBCs. *In vitro* studies show that the metabolism of brinzolamide mainly involves CYP3A4 as well as at least four other isozymes (CYP2A6, CYP2B6, CYP2C8 and CYP2C9).

Timolol is metabolised by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring and the other giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. Timolol metabolism is mediated primarily by CYP2D6.

Elimination

Brinzolamide is eliminated primarily by renal excretion (approximately 60%). About 20% of the dose has been accounted for in urine as metabolite. Brinzolamide and N-desethyl-brinzolamide are the predominant components found in the urine along with trace levels (<1%) of the N-desmethoxypropyl and O-desmethyl metabolites.

Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20% of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites. The plasma $t_{1/2}$ of timolol is 4.8 hours after administration of AZARGA.

5.3 Preclinical safety data

Brinzolamide

Non-clinical data reveal no special hazard for humans with brinzolamide based on single-dose toxicity, repeated dose toxicity, genotoxicity, carcinogenic potential, and topical ocular irritation studies.

Developmental toxicity studies in rabbits with oral doses of brinzolamide of up to 6 mg/kg/day (214 times the recommended daily clinical dose of 28 μg/kg/day) revealed no effect on foetal development despite significant maternal toxicity. Similar studies in rats resulted in slightly reduced ossification of skull and sternebrae of foetuses of dams receiving brinzolamide at doses of 18 mg/kg/day (642 times the recommended daily clinical dose), but not 6 mg/kg/day. These findings occurred at doses that caused metabolic acidosis with decreased body weight gain in dams and decreased foetal weights. Dose-related decreases in foetal weights were observed in pups of dams receiving brinzolamide orally ranging from a slight decrease (about 5-6%) at 2 mg/kg/day to nearly 14% at 18 mg/kg/day. During lactation, the no adverse effect level in the offspring was 5 mg/kg/day.

Timolol

Non-clinical data reveal no special hazard for humans with timolol based on single-dose toxicity, repeated dose toxicity, genotoxicity, carcinogenic potential, and topical ocular irritation studies. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse effects on postnatal development (at 50 mg/kg/day or 3 500 times the daily clinical dose of 14 μg/kg/day) and increased foetal resorptions in rabbits (at 90 mg/kg/day or 6 400 times the daily clinical dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Mannitol (E421)
Carbopol 974P
Tyloxapol
Disodium edetate
Sodium chloride
Hydrochloric acid and/or sodium hydroxide (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

4 weeks after first opening.

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 round opaque low density polyethylene bottles with a dispensing plug and white polypropylene screw cap containing 5 ml suspension.

Cartons containing 1 or 3 bottles. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/482/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 25 November 2008
Date of latest renewal: 26 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Novartis Manufacturing NV
Rijksweg 14
2870 Puurs-Sint-Amands
Belgium

Novartis Farmacéutica, S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR SINGLE BOTTLE 5 ml + CARTON FOR 3 x 5 ml BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

AZARGA 10 mg/ml + 5 mg/ml eye drops, suspension
brinzolamide/timolol

2. STATEMENT OF ACTIVE SUBSTANCE

1 ml of suspension contains 10 mg brinzolamide and 5 mg timolol (as timolol maleate).

3. LIST OF EXCIPIENTS

Contains: benzalkonium chloride, mannitol (E421), carbopol 974P, tyloxapol, disodium edetate, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), purified water.

See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, suspension

1 x 5 ml
3 x 5 ml

5. METHOD AND ROUTE OF ADMINISTRATION

Shake well before use.
Read the package leaflet before use.
Ocular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard 4 weeks after first opening.
Opened:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/08/482/001	1 x 5 ml
EU/1/08/482/002	3 x 5 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

azarga

17. UNIQUE IDENTIFIER-2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

AZARGA 10 mg/ml + 5 mg/ml eye drops
brinzolamide/timolol
Ocular use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP
Discard 4 weeks after first opening.
Opened:

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6 OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

AZARGA 10 mg/ml + 5 mg/ml eye drops, suspension
brinzolamide/timolol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them even if their signs of illnesses are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AZARGA is and what it is used for
2. What you need to know before you use AZARGA
3. How to use AZARGA
4. Possible side effects
5. How to store AZARGA
6. Contents of the pack and other information

1. What AZARGA is and what it is used for

AZARGA contains two active substances, brinzolamide and timolol, which work together to reduce pressure within the eye.

AZARGA is used to treat high pressure in the eyes, also called glaucoma or ocular hypertension, in adult patients that are more than 18 years of age and in whom high pressure in the eyes cannot be controlled effectively by one medicine alone.

2. What you need to know before you use AZARGA

Do not use AZARGA
- If you are allergic to brinzolamide, medicines called sulphonamides (examples include medicines used to treat diabetes, infections and also diuretics (water tablets)), timolol, beta-blockers (medicines used to lower blood pressure or to treat heart disease) or any of the other ingredients of this medicine (listed in section 6).
- If you have now or have had in the past respiratory problems such as asthma, severe long lasting obstructive bronchitis (severe lung condition which may cause wheezing, difficulty in breathing and/or long standing cough) or other types of breathing problems.
- If you have severe hay fever
- If you have a slow heart beat, heart failure or disorders of heart rhythm (irregular heartbeats).
- If you have too much acidity in your blood (a condition called hyperchloraemic acidosis).
- If you have severe kidney problems.

Warnings and precautions
Only use AZARGA for dropping in your eye(s).

If signs of serious reactions or hypersensitivity occur, discontinue the use of this product and talk to your doctor.

Talk to your doctor or pharmacist before using AZARGA if you have or have had in the past:
- coronary heart disease (symptoms can include chest pain or tightness, breathlessness or choking), heart failure, low blood pressure
- disturbances of heart rate such as slow heart beat
- breathing problems, asthma or chronic obstructive pulmonary disease
- poor blood circulation disease (such as Raynaud's disease or Raynaud's syndrome)
- diabetes as timolol may mask signs and symptoms of low blood sugar
- overactivity of the thyroid gland as timolol may mask signs and symptoms of thyroid disease
- muscular weakness (myasthenia gravis)
- tell your doctor before you have an operation that you are using AZARGA as timolol may change effects of some medicines used during anaesthesia.
- if you have a history of atopy (a tendency to develop an allergic reaction) and severe allergic reactions you may be more sensitive to developing an allergic reaction whilst using AZARGA and adrenaline may not be as effective to treat an allergic reaction. When receiving any other treatment please tell the doctor or nurse that you are taking AZARGA.
- if you have liver problems.
- if you have dry eyes or cornea problems.
- if you have problems with your kidneys.
- if you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after using AZARGA or other related medicines.

Take special care with AZARGA:
Serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with brinzolamide treatment. Stop using AZARGA and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

Children and adolescents
AZARGA is not recommended for children and adolescents under 18 years.

Other medicines and AZARGA
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

AZARGA can affect, or be affected by, other medicines you are taking, including other eye drops for the treatment of glaucoma. Tell your doctor if you are taking or intent to take medicines to lower blood pressure like parasympathomimetics and guanetidine, or other heart medicines including quinidine (used to treat heart conditions and some types of malaria), amiodarone or other medicines to treat heart rhythm disorders and glycosides to treat heart insufficiency. Also tell your doctor if you are taking or intend to take medicines to treat diabetes, or to treat gastric ulcers, antifungal, antiviral or antibiotic medicines, or antidepressants such as fluoxetine and paroxetine.

If you are taking another carbonic anhydrase inhibitor (acetazolamide or dorzolamide), talk to your doctor.
Increase in pupil size when taking Azarga and adrenaline (epinephrine) together has been reported occasionally.

Pregnancy and breast-feeding
You should not use AZARGA if you are pregnant or might get pregnant, unless your doctor considers it necessary. Talk to your doctor before you use AZARGA.

Do not use AZARGA if you are breast feeding, timolol may get into your milk.
Ask your doctor for advice before taking any medicine during breastfeeding.

Driving and using machines
Do not drive or use machines until your vision is clear. You may find that your vision is blurred for some time just after using AZARGA.

One of the active ingredients may impair the ability to perform tasks requiring mental alertness and/or physical coordination. If affected take care when driving or using machines.

AZARGA contains benzalkonium chloride

This medicine contains 3.34 µg benzalkonium chloride per drop (= 1 dose) which is equivalent to 0.01% or 0.1 mg/ml.

AZARGA contains a preservative (benzalkonium chloride) which may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards. Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.

3. How to use AZARGA

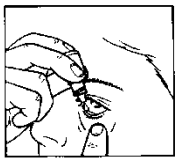
Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
If you are changing from another eye drop medicine used to treat glaucoma to AZARGA, you should stop using the other medicine and start using AZARGA the following day. Check with your doctor or pharmacist if you are not sure

To prevent contamination of the dropper tip and the suspension, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip. Keep the bottle tightly closed when not in use.

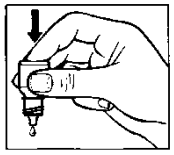
The following measure is useful to limit the amount of medicine that will come into the blood after application of eye drops:
- Keep the eyelid closed, while simultaneously applying gentle pressure to the corner of the eye next to the nose with a finger for at least 2 minutes.

The recommended dose is
One drop in the affected eye or eyes, twice a day.
Only use AZARGA in both eyes if your doctor told you to. Take it for as long as your doctor told you to.

How to use



1



2



3

- Get the AZARGA bottle and a mirror.
- Wash your hands.
- Shake well before use.
- Twist off the bottle cap. After the cap is removed, if the tamper evident snap collar is loose, remove before using product.
- Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Use the mirror if it helps.
- Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper. It could infect the drops.
- Gently press on the base of the bottle to release one drop of AZARGA at a time.
- Do not squeeze the bottle: it is designed so that a gentle press on the bottom is all that it needs (picture 2).
- After using AZARGA, press a finger into the corner of your eye, by the nose for 2 minutes (picture 3). This helps to stop AZARGA getting into the rest of the body.
- If you use drops in both eyes, repeat the steps for your other eye.
- Close the bottle cap firmly immediately after use.
- Use up one bottle before opening the next bottle.

If a drop misses your eye, try again.

If you are using other eye drop or eye ointment medicines leave at least 5 minutes between each medicine. Eye ointments should be administered last.

If you use more AZARGA than you should, rinse your eye with warm water. Do not put in any more drops until it is time for your next regular dose.

You may experience a decreased heart rate, decreased blood pressure, heart failure, difficulty breathing and your nervous system may be affected

If you forget to use AZARGA, continue with the next dose as planned. Do not use a double dose to make up for the forgotten dose. Do not use more than one drop in the affected eye(s) twice daily.

If you stop using AZARGA without speaking to your doctor, the pressure in your eye will not be controlled which could lead to loss of sight.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

Stop using AZARGA and seek medical attention immediately if you notice any of the following symptoms:

- severe redness and itching of the eye, reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis).

You can usually carry on taking the drops, unless the effects are serious. If you are worried, talk to your doctor or pharmacist. Do not stop using Azarga without speaking to your doctor first.

Common (may affect up to 1 in 10 people)

- **Effects in the eye**: eye surface inflammation, blurred vision, signs and symptoms of eye irritation (e.g. burning, stinging, itching, tearing, redness), eye pain.
- **General side effects**: heart rate decreased, taste disturbances.

Uncommon (may affect up to 1 in 100 people)

- **Effects in the eye**: corneal erosion (damage to the front layer of the eyeball), Eye surface inflammation with surface damage, inflammation inside the eye, corneal staining, abnormal sensation in the eyes, eye discharge, dry eye, tired eyes, itchy eye, eye redness, eyelid redness.
- **General side effects**: decrease in white blood cell count, decreased blood pressure, cough, blood in urine, body weakness.

Rare (may affect up to 1 in 1 000 people)

- **Effects in the eye:** corneal disorder, sensitivity to light, increased tear production, eyelid crusting
- **General side effects:** difficulty sleeping (insomnia), throat pain, running nose

Not known (frequency cannot be estimated from the available data)

- **Effects in the eye**: eye allergy, disturbance of vision, damage to the optic nerve, increased pressure in eye, deposits on the eye surface, decreased eye sensation, inflammation or infection of the conjunctiva (white of the eye), abnormal, double or reduced vision, increased pigmentation of the eye, growth on surface of eye, eye swelling, sensitivity to light, decreased growth or number of eyelashes, drooping of the upper eyelids (making the eye stay half closed), inflammation of the eyelid and eye lid glands, inflammation in the cornea and detachment of the layer below the retina that contains blood vessels following filtration surgery which may cause visual disturbances, decreased corneal sensitivity.
- **General side effects**: reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes, which can be preceded by fever and flu-like symptoms. These serious skin rashes can be potentially life-threatening (Stevens-Johnson syndrome, toxic epidermal necrolysis).
- **Heart and circulation**: changes in rhythm or rate of the heartbeat, slow heart rate, palpitations, a type of heart rhythm disorder, abnormal increase in heart rate, chest pain, reduced heart function, heart attack, increased blood pressure, reduced blood supply to the brain, stroke, oedema (fluid build up), congestive heart failure (heart disease with shortness of breath and swelling of the feet and legs due to fluid build up), swelling of the extremities, low blood pressure, discoloration of the fingers, toes, and occasionally other areas of the body (Raynaud's phenomenon), cold hands and feet.
- **Respiratory:** Constriction of the airways in the lungs (predominantly in patients with pre-existing disease) shortness of breath or difficulty breathing, cold symptoms, chest congestion, sinus infection, sneezing, stuffy nose, dry nose, nose bleeds, asthma, throat irritation.

- **Nervous system and general disorders:** hallucinations, depression, nightmares, memory loss, headache, nervousness, irritability, tiredness, shaking, feeling abnormal, fainting, dizziness, drowsiness, generalised or severe weakness, unusual sensations like pins and needles.
- **Gastric:** nausea, vomiting, diarrhoea, intestinal gas or abdominal discomfort, inflammation of the throat, dry or abnormal sensation in mouth, indigestion, stomach ache.
- **Blood:** abnormal liver function values, increased blood chlorine levels, or decreased red blood cell count as seen in a blood test.
- **Allergy:** increased allergic symptoms, generalised allergic reactions including swelling beneath the skin that can occur in areas such as the face and limbs and can obstruct the airway which may cause difficulty swallowing or breathing, hives, localised and generalised rash, itchiness, severe sudden life-threatening allergic reaction.
- **Ear:** ringing in the ears, sensation of spinning or dizziness.
- **Skin:** rash, skin redness or inflammation, abnormal or decreased skin sensation, hair loss, rash with white silvery coloured appearance (psoriasiform rash) or worsening of psoriasis.
- **Muscular:** generalised back, joint, or muscle pain not caused by exercise, muscle spasms, pain in extremities, muscle weakness/tiredness, increases in the signs and symptoms of myasthenia gravis (muscle disorder).
- **Kidney:** kidney pain such as lower back pain, frequent urination.
- **Reproduction:** sexual dysfunction, decreased libido, male sexual difficulty.
- **Metabolism:** low blood sugar levels.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AZARGA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Throw away the bottle 4 weeks after first opening to prevent infections, and use a new bottle. Write down the date of opening on the bottle label and carton label in the space provided.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AZARGA contains
- The active substances are brinzolamide and timolol. One ml of suspension contains 10 mg of brinzolamide and 5 mg of timolol (as maleate).
- The other ingredients are benzalkonium chloride (see section 2 ‘AZARGA contains benzalkonium’), carbopol 974P, disodium edetate, mannitol (E421), purified water, sodium chloride, tyloxapol, hydrochloric acid and/or sodium hydroxide.
  Tiny amounts of hydrochloric acid and/or sodium hydroxide are added to keep acidity levels (pH levels) normal.

What AZARGA looks like and contents of the pack
AZARGA is a liquid (white to off-white uniform suspension) supplied in a pack containing one 5 ml plastic bottle with a screw cap or in a pack containing three 5 ml bottles.
Not all pack sizes may be marketed.

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu