Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Timolol 0.25 % w/v Eye Drops, Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of eye drops contains 2.5 mg of timolol (as 3.4 mg of timolol maleate).

Excipient(s) with known effect:

Benzalkonium chloride 0.1mg/ml eye drops, solution.

1ml of eye drops contains 16.72 mg of disodium hydrogen phosphate dodecahydrate, equivalent to 4.43 mg of phosphates.

1ml of eye drops contains 3.12 mg of sodium dihydrogen phosphate dehydrate, equivalent to 1.9 mg of phosphates.

The total content of phosphates in each 1ml of eye drops is 6.33 mg.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.
Clear, colourless to light yellow, eye drops solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Timolol is a beta-adrenoreceptor blocking agent used topically in the reduction of elevated intra-ocular pressure in various conditions including the following: patients with ocular hypertension; patients with chronic open-angle glaucoma including aphakic patients; some patients with secondary glaucoma.

4.2 Posology and method of administration

Posology
Recommended therapy is one drop of timolol 0.25% w/v eye drops, solution in the affected eye(s) twice a day.

Another strength (timolol 0.5% w/v eye drops, solution) is available. If clinical response is not adequate, dosage may be changed to one drop timolol 0.5% w/v eye drops, solution in each affected eye twice a day. If needed, timolol may be used with other agent(s) for lowering intra-ocular pressure. The use of two topical beta-adrenergic blocking agents is not recommended (see 4.4 'Special warnings and precautions for use').

Intra-ocular pressure should be reassessed approximately four weeks after starting treatment because response to timolol may take a few weeks to stabilise.

Provided that the intra-ocular pressure is maintained at satisfactory levels, many patients can then be placed on once-a-day therapy.

Transfer from other topical beta-blocking agents
The other topical beta-blocking agent should be used as normal for a final day. Then, the next day, treatment with only timolol 0.25% w/v eye drops, solution should be started. Initially, one drop of timolol 0.25% w/v eye drops, solution in each affected eye, twice a day, should be used. If the response is not adequate, the dosage may be increased to one drop of timolol 0.5% w/v eye drops, solution in each affected eye twice a day.

Transfer from non-beta-blocking topical agents or oral anti-glaucoma preparations

On the day of transfer, the non-beta-blocking topical agent, or oral anti-glaucoma preparation, should be used as normal together with one drop of timolol 0.25% w/v eye drops, solution in each affected eye, twice in the day. The following day, discontinue the non-beta-blocking topical agent, or oral anti-glaucoma preparation, and continue with timolol 0.25% w/v eye drops, solution. If a higher dosage of timolol is required, substitute timolol 0.25% w/v eye drops, solution with one drop of timolol 0.5% w/v eye drops, solution in each affected eye twice a day.

Elderly
There has been wide experience with the use of timolol maleate in elderly patients. The dosage recommendations given above reflect the clinical data derived from this experience.

Paediatric Population
Due to limited data, Timolol could only be recommended for use in Primary congenital and primary juvenile glaucoma for a transitional period while decision is made on a surgical approach and in case of failed surgery while awaiting further options.

Posology: Clinicians should strongly evaluate the risks and benefits when considering medical therapy with Timolol in paediatric patients. A detailed paediatric history and examination to determine the presence of systemic abnormalities should precede the use of Timolol.
No specific dosage recommendations can be given as there is only limited clinical data (see also section 5.1).
However, if a benefit outweighs the risk, it is recommended to use the lowest active agent concentration available once daily. If IOP could not be sufficiently controlled, a careful up titration to a maximum of two drops daily per affected eye has to be considered. If applied twice daily, an interval of 12 hours should be preferred.
Furthermore the patients, especially neonates, should be strongly observed after the first dose for one to two hours in the office and closely monitored for ocular and systemic side effects until surgery is performed.
With regards to paediatric use, the 0,1% active agent concentration might already be sufficient.

Duration of treatment: For a transient treatment in the paediatric population (see also section 4.2 'paediatric population').

Method of administration: To limit potential adverse effects only one drop should be instilled per dosing time.
Systemic absorption of topically administered β-blockers can be reduced by nasolacrimal occlusion and by keeping the eyes closed as long as possible (e.e. for 3-5 minutes) after instillation of drops. See also section 4.4, 5.2.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also 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.

Patients should be informed of the correct handling of the dropper bottles.

4.3 Contraindications

Reactive airway disease including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, sick sinus syndrome sino-atrial block, second- and third-degree atrioventricular block not controlled with pace-maker, overt cardiac failure, and cardiogenic shock.

Hypersensitivity to the active substance (substances) or to any of the excipients in this product (see section 6.1) or other beta-blocking agents.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic agents, timolol maleate is absorbed systemically. Due to beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see 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 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.

Cardiac failure should be adequately controlled before beginning therapy with timolol. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates monitored.

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.

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

Timolol 0.25% wv Eye Drops Solution 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.

Beta-blockers may also mask the signs of hyperthyroidism.

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

Other beta-blocking agents:
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol maleate 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 is not recommended (see section 4.5).

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoreceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn.

Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy involving beta-blockade should be gradual.

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 (epinephrine). The anaesthesiologist should be informed when the patient is receiving timolol.

Contact lenses:
Timolol has been generally well tolerated in glaucoma patients wearing conventional hard contact lenses. Timolol has not been studied in patients wearing lenses made with material other than polymethylmethacrylate (PMMA), which is used to make hard contact lenses.

Timolol Eye Drops Solution contains benzalkonium chloride as a preservative which may be deposited in soft contact lenses; therefore Timolol should not be used while wearing these lenses

The lenses should be removed before application of the drops and not reinserted earlier than 15 minutes after use.

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

Timolol Eye Drops Solution contains disodium hydrogen phosphate dodecahydrate and Sodium dihydrogen phosphate dehydrate as buffering agents, these excipients can cause the undesirable side effect corneal calcification, please reference section 4.8 (Undesirable effects) eye disorders for further information.

Angle-closure glaucoma
In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol has little or no effect on the pupil. When timolol is used to reduce elevated intra-ocular pressure in angle-closure glaucoma it should be used with a miotic and not alone.

Patients should be advised that if they develop an intercurrent ocular condition (e.g. trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container (see 6.6 'Special precautions for disposal and other handling'').

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

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 adrenaline used to treat anaphylactic reactions.

Paediatric Population:

Timolol solution should generally be used cautiously in young glaucoma patients (see also section 5.2).

It is important to notify the parents of potential side effects so they can immediately discontinue the drug therapy. Signs to look for are for example coughing and wheezing.

Because of the possibility of apnoea and Cheyne-Stokes breathing, the drug should be used with extreme caution in neonates, infants and younger children. A portable apnoea monitor may also be helpful for neonates on Timolol.

4.5 Interaction with other medicinal products and other forms of interactions

No specific drug interaction studies have been performed with timolol maleate.

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, rauwolfia alkaloids, parasympathomimetics, guanethidine.

Although timolol alone has little or no effect on pupil size, mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

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

Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Oral calcium antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function.

The potential exists for hypotension, AV conduction disturbances and left ventricular failure to occur in patients receiving a beta-blocking agent when an oral calcium entry blocker is added to the treatment regimen. The nature of any cardiovascular adverse effect tends to depend on the type of calcium blocker used. Dihydropyridine derivatives, such as nifedipine, may lead

to hypotension, whereas verapamil or diltiazem have a greater propensity to lead to AV conduction disturbances or left ventricular failure when used with a beta blocker.

Intravenous calcium channel blockers should be used with caution in patients receiving beta adrenergic blocking agents.

The concomitant use of beta adrenergic blocking agents and digitalis with either diltiazem or verapamil may have additive effects in prolonging AV conduction time.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no adequate data for the use of timolol maleate in pregnant women. Timolol maleate should not be used during pregnancy unless clearly necessary. The use of timolol requires that the anticipated benefit be weighed against possible hazards. To reduce the systemic absorption, see 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 Timolol 0.25% wv Eye Drops Solution is administered until delivery, the neonate should be carefully monitored during the first days of life.

Breast-feeding:

Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol maleate 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. A decision for breast-feeding mothers, either to stop taking timolol or stop nursing, should be based on the importance of the drug to the mother. To reduce the systemic absorption see 4.2.

4.7 Effects on ability to drive and use machines

Possible side effects such as dizziness and visual disturbances may affect some patients' ability to drive or operate machinery.

4.8 Undesirable effects

Like other topically applied ophthalmic drugs, timolol maleate 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.

The following adverse reactions have been reported with *ocular* administration of this or other timolol maleate formulations, either in clinical trials or since the drug has been marketed.

Additional side effects have been reported in clinical experiences with *systemic* timolol maleate, and may be considered potential effects of ophthalmic timolol maleate. Also listed are adverse reactions seen within the class of ophthalmic beta-blockers and may potentially occur with Timolol w/v Eye Drops.

Blood and lymphatic system disorders:
Systemic: non-thrombocytopenic purpura.

Immune system disorders:
Ocular: systemic lupus erythematosus, pruritus
Systemic: signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash, anaphylactic reaction.

Metabolism and nutrition disorders:
Ocular: hypoglycaemia
Systemic: hyperglycaemia

Psychiatric disorders:

Ocular: depression, insomnia, nightmares, memory loss, hallucination.
Systemic: diminished concentration, increased dreaming.

Nervous system disorders:
Ocular: cerebrovascular accident, cerebral ischemia, dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, syncope, headache.
Systemic: vertigo, local weakness

Eye disorders:
Ocular: signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), conjunctivitis, blepharitis, keratitis, dry eyes, corneal erosion and decreased corneal sensitivity. Visual disturbances, including blurred vision, refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis and choroidal detachment following filtration surgery (see 4.4 'Special warnings and precautions for use'). 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.

Ear and labyrinth disorders:
Ocular: tinnitus

Cardiac disorders:
Ocular: bradycardia, chest pain, arrhythmia, heart block, congestive heart failure, palpitation, cardiac arrest, cardiac failure, oedema.
Systemic: AV block (second- or third-degree), sino-atrial block, pulmonary oedema, worsening of arterial insufficiency, worsening of angina pectoris and vasodilation

Vascular disorders:
Ocular: claudication, hypotension, Raynaud's phenomenon, cold hands and feet.

Respiratory, thoracic and mediastinal disorders:
Ocular: bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnoea, cough.
Systemic: rales.

Gastrointestinal disorders:
Ocular: dysgeusia, nausea, diarrhoea, dyspepsia, dry mouth, abdominal pain, vomiting.

Skin and subcutaneous tissue disorders:
Ocular: alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.
Systemic: sweating, exfoliative dermatitis.

Musculoskeletal and connective tissue disorders:
Ocular: myalgia
Systemic: arthralgia

Reproductive system and breast disorders:
Ocular: decreased libido, Peyronie's disease, sexual dysfunction such as impotence
Systemic: micturition difficulties.

General disorders and administrative site conditions:
Ocular: asthenia, fatigue
Systemic: extremity pain, decreased exercise tolerance.

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

Symptoms:
There have been reports of inadvertent overdose with timolol resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see Section 4.8 'Side effects').

Management :
If overdose occurs, the following measures should be considered:

1. Gastric lavage, if ingested. Studies have shown that timolol does not dialyse readily.
2. Symptomatic bradycardia: atropine sulphate, 0.25 to 2 mg intravenously, should be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline hydrochloride should be administered cautiously. In refractory cases, the use of a cardiac pacemaker may be considered.
3. Hypotension: a sympathomimetic pressor agent such as dopamine, dobutamine or noradrenaline should be used. In refractory cases, the use of glucagon has been reported to be useful.
4. Bronchospasm: isoprenaline hydrochloride should be used. Additional therapy with aminophylline may be considered.
5. Acute cardiac failure: conventional therapy with digitalis, diuretics, and oxygen should be instituted immediately. In refractory cases, the use of intravenous aminophylline is suggested. This may be followed, if necessary, by glucagon, which has been reported useful.
6. Heart block (second- or third-degree): isoprenaline hydrochloride or a pacemaker should be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-glaucoma preparations and miotics, beta blocking-agents, selective
ATC code: S01ED01

Mechanism of Action
Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic activity. Timolol maleate combines reversibly with the beta-adrenergic receptor, and this inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source.
Reversal of this blockade can be accomplished by increasing the concentration of the agonist which will restore the usual biological response.

Clinical efficacy and safety
Unlike miotics, timolol reduces IOP with little or no effect on accommodation or pupil size. In patients with cataracts, the inability to see around lenticular opacities when the pupil is constricted is avoided. When changing patients from miotics to timolol a refraction might be necessary when the effects of the miotic have passed.

Diminished response after prolonged therapy with timolol has been reported in some patients.

Paediatric Population: There is only very limited data available on the use of Timolol (0, 25%, 0, 5% twice daily one drop) in the paediatric population for a treatment period up to 12 weeks. One small, double blinded, randomized, published clinical study conducted on 105 children (n=71 on Timolol) aged 12 days – 5 years show to some extent evidence, that Timolol is the indication *primary congenital and primary juvenile glaucoma* is effective in short term treatment.

5.2 Pharmacokinetic properties

The onset of reduction in intra-ocular pressure can be detected within one-half hour after a single dose. The maximum effect occurs in one or two hours; significant lowering of IOP can be maintained for as long as 24 hours with a single dose.

Paediatric Population: As already confirmed by adult data, 80% of each eye drop passes through the nasolacrimal system where it may be rapidly absorbed into the systemic circulation via the nasal mucosa, conjunctiva nasolacrimal duct, oropharynx and gut, or the skin from tear overflow. Due to the fact that the blood volume in children is smaller than that in adults a higher circulation concentration has to be taken into account. In addition, neonates have immature metabolic enzyme pathways and it may result in an increase in elimination half-life and potentiating adverse events.

Limited data show that plasma timolol levels in children after 0.25% greatly exceed those in adults after 0.5%, especially in infants and are presumed to increase the risk of side effects such as bronchospasm and bradycardia.

5.3 Preclinical safety data

No adverse ocular effects were observed in rabbits and dogs administered timolol topically in studies lasting one and two years, respectively. The oral LD_{50} of the drug is 1,190 and 900 mg/kg in female mice and female rats, respectively.

Carcinogenesis, mutagenesis, impairment of fertility
In a two-year oral study of timolol maleate in rats there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal phaeochromocytomas in male rats administered 300 mg/kg/day (300 times the maximum recommended human oral dose). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose.

In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinoma in female mice at 500 mg/kg/day (500 times the maximum recommended human dose), but not at 5 or 50 mg/kg/day. In a subsequent study in female mice, in which post-mortem examinations were limited to uterus and lungs, a statistically significant increase in the incidence of pulmonary tumours was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinoma was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumours has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant ($p \leq 0.05$) elevations of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose-response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate
Sodium chloride
Benzalkonium chloride
Sodium hydroxide (0.08 % w/v)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years (unopened).
Discard timolol 0.25% w/v eye drops, solution four weeks after first opening the bottle.

6.4 Special precautions for storage

Do not store above 25°C. Keep bottle in the outer carton in order to protect from light.

Any unused product or waste material should be disposed of in accordance with local requirements.

6.5 Nature and contents of container

5 ml natural LDPE (low density polyethylene) bottle, containing 5ml of timolol eye drop solution, fitted with a 13 mm natural LDPE plug and a 13 mm white HDPE (high density polyethylene) screw cap with a tamper-evident seal, contained within a cardboard carton.

Pack sizes: 1 x 5 ml solution.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1339/017/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th December 2010
Date of last renewal: 19th September 2015

10 DATE OF REVISION OF THE TEXT

May 2020