SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Brimonidine Tartrate/Timolol 2 mg/ml + 5 mg/ml eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains:

2.0 mg brimonidine tartrate, equivalent to 1.3 mg of brimonidine

5.0 mg timolol as 6.8 mg timolol maleate

Excipients with known effect:

Contains benzalkonium chloride 0.05 mg/mL.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Eye drops, solution.

Clear, greenish-yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers.

4.2 Posology and method of administration

To avoid contamination of the eye or eye drops do not allow the dropper tip to come into contact with any surface.

Posology

Recommended dosage in adults (including the elderly)

The recommended dose is one drop of Brimonidine Tartrate/Timolol in the affected eye(s) twice daily, approximately 12 hours apart. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart.

Method of administration

As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctual occlusion) or eyelids are closed for two minutes. This should be performed immediately following the instillation of each drop. This may result in a decrease of systemic side effects and an increase in local activity.

Use in renal and hepatic impairment

Brimonidine Tartrate/Timolol has not been studied in patients with hepatic or renal impairment. Therefore, caution should be used in treating such patients.

Paediatric population:

Brimonidine Tartrate/Timolol is contraindicated in neonates and infants (less than 2 years of age) (see sections 4.3, 4.4, 4.8 and 4.9).

The safety and effectiveness of brimonidine/timolol in children and adolescents (2 to 17 years of age) have not been established and therefore, its use is not recommended in children or adolescents (see sections 4.4 and 4.8).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Reactive airway disease including bronchial asthma or a history of bronchial
- asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome sino-atrial block, second or third degree
- atrioventricular block not controlled with a pace-maker, overt cardiac failure,
- cardiogenic shock.
- Use in neonates and infants (less than 2 years of age) (see section 4.8)
- Patients receiving monoamine oxidase (MAO) inhibitor therapy.
- Patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin)

4.4 Special warnings and precautions for use

Paediatric population

Children of 2 years of age and above, especially those in the 2-7 age range and/or weighing ≤20 Kg, should be treated with caution and closely monitored due to the high incidence and severity of somnolence. The safety and effectiveness of brimonidine/timolol in children and adolescents (2 to 17 years of age) have not been established (see sections 4.2 and 4.8).

Some patients have experienced ocular allergic type reactions (allergic conjunctivitis and allergic blepharitis) with brimonidine/timolol in clinical trials. Allergic conjunctivitis was seen in 5.2% of patients. Onset was typically between 3 and 9 months resulting in an overall discontinuation rate of 3.1%. Allergic blepharitis was uncommonly reported (<1%). If allergic reactions are observed, treatment with brimonidine/timolol should be discontinued.

Delayed ocular hypersensitivity reactions have been reported with brimonidine tartrate ophthalmic solution 0.2%, with some reported to be associated with an increase in IOP.

Like other topically applied ophthalmic agents, brimonidine/timolol may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed. 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 section 4.2.

Cardiac disorders:

Cardiac reactions have been reported including, rarely, death associated with cardiac failure following administration of timolol. 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, betablockers should only be given with caution to patients with first degree heart block.

As with systemic beta-blockers, if discontinuation of treatment is needed in patients with coronary heart disease, therapy should be withdrawn gradually to avoid rhythm disorders, myocardial infarct or sudden death.

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.

Brimonidine/timolol 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.

Hyperthyroidism

Beta-blockers may also mask the signs of hyperthyroidism.

Brimonidine/timolol must be used with caution in patients with metabolic acidosis and untreated phaeochromocytoma.

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 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).

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 dose 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 anaesthetist must be informed if the patient is receiving timolol.

The preservative in Brimonidine Tartrate/Timolol, benzalkonium chloride, may cause eye irritation. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Avoid contact with soft contact lenses.

Brimonidine Tartrate/Timolol has not been studied in patients with closed-angle glaucoma.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with the brimonidine/timolol fixed combination. Although specific drug interactions studies have not been conducted with brimonidine/timolol, the theoretical possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

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, anti-arrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics or guanethidine. Also, after the application of brimonidine, very rare (<1 in 10,000) cases of hypotension have been reported. Caution is therefore advised when using brimonidine/timolol with systemic antihypertensives.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally. Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents.

Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

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.

Concomitant use of a beta-blocker with anaesthetic drugs may attenuate compensatory tachycardia and increase the risk of hypotension (see section 4.4), and therefore the anaesthetist must be informed if the patient is using brimonidine/timolol.

Caution must be exercised if brimonidine/timolol is used concomitantly with iodine contrast products or intravenously administered lidocaine.

Cimetidine, hydralazine and alcohol may increase the plasma concentrations of timolol.

No data on the level of circulating catecholamines after brimonidine tartrate/timolol administration are available. Caution, however, is advised in patients taking medication which can affect the metabolism and uptake of circulating amines e.g. chlorpromazine, methylphenidate, reserpine.

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with α-adrenergic agonists or interfere with their activity i.e. agonists or antagonists of the adrenergic receptor e.g. (isoprenaline, prazosin).

Although specific drug interactions studies have not been conducted with brimonidine/timolol, the theoretical possibility of an additive IOP lowering effect with prostamides, prostaglandins, carbonic anhydrase inhibitors and pilocarpine should be considered.

Brimonidine is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenagic transmission (e.g. tricyclic antidepressants and mianserin), (see section 4.3). Patients who have been receiving MAOI therapy should wait 14 days after discontinuation before commencing treatment with brimonidine/timolol.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data for the use of the brimonidine timolol fixed combination in pregnant women. Brimonidine Tartrate/Timolol should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Brimonidine tartrate

There are no adequate data from the use of brimonidine tartrate in pregnant women. Studies in animals have shown reproductive toxicity at high maternotoxic doses (see section 5.3). The potential risk for humans is unknown.

Timolol

Studies in animals have shown reproductive toxicity at doses significantly higher than would be used in clinical practice (see section 5.3).

Epidemiological studies have not revealed malformative effects but have shown 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 brimonidine/timolol is administered in pregnancy up to the time of delivery, the neonate should be carefully monitored during the first days of life.

Breastfeeding

Brimonidine tartrate

It is not known if brimonidine is excreted in human milk but it is excreted in the milk of the lactating rat.

Timolol

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

Brimonidine Tartrate/Timolol should not be used by women breast-feeding infants.

4.7 Effects on ability to drive and use machines

Brimonidine/timolol has minor influence on the ability to drive and use machines. Brimonidine/timolol may cause transient blurring of vision, visual disturbance, fatigue and/or drowsiness which may impair the ability to drive or operate machines. The patient should wait until these symptoms have cleared before driving or using machinery.

4.8 Undesirable effects

Based on 12 month clinical data, the most commonly reported ADRs were conjunctival hyperaemia (approximately 15% of patients) and burning sensation in the eye (approximately 11% of patients). The majority of these cases was mild and led to discontinuation rates of only 3.4% and 0.5% respectively.

The following adverse drug reactions were reported during clinical trials with brimonidine/timolol and are ranked by system order class and using the following frequency:

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

Not known: cannot be estimated from the available data

Eye disorders

Very common: conjunctival hyperaemia, burning sensation

Common: stinging sensation in the eye, allergic conjunctivitis, corneal erosion, superficial punctate keratitis, eye pruritus, conjunctival folliculosis, visual disturbance, blepharitis, epiphora, eye dryness, eye discharge, eye pain, eye irritation, foreign body sensation

Uncommon: visual acuity worsened, conjunctival oedema, follicular conjunctivitis, allergic blepharitis, conjunctivitis, vitreous floater, asthenopia, photophobia, papillary hypertrophy, eyelid pain, conjunctival blanching, corneal oedema, corneal infiltrates, and vitreous detachment

Psychiatric disorders

Common: depression

Nervous system disorders

Common: somnolence, headache

Uncommon: dizziness, syncope

Cardiac disorders

Uncommon: congestive heart failure, palpitations

Vascular disorders

Common: hypertension

Respiratory, thoracic and mediastinal disorders

Uncommon: rhinitis, nasal dryness

Gastrointestinal disorders

Common: oral dryness

Uncommon: taste perversion, nausea, diarrhoea.

Skin and subcutaneous tissue disorders

Common: eyelid oedema, eyelid pruritus, eyelid erythema

Uncommon: allergic contact dermatitis

General disorders and administration site conditions

Common: asthenic conditions

The following adverse drug reactions have been reported since brimonidine tartrate/timolol has been marketed:

Eye disorders

Not known: vision blurred

Cardiac disorders

Not known: arrhythmia, bradycardia, tachycardia

Vascular disorders

Not known: hypotension

Skin disorders:

Not known: erythema facial

Additional adverse events that have been seen with one of the components and may potentially occur also with brimonidine/timolol:

Brimonidine

Eye disorders: iritis, iridocyclitis (anterior uveitis), miosis

Psychiatric disorders: insomnia

Respiratory, thoracic and mediastinal disorders: upper respiratory symptoms, dyspnoea

Gastrointestinal disorders: gastrointestinal symptoms

General disorders and administration site conditions: systemic allergic reactions

Skin and subcutaneous tissue disorders: skin reaction including erythema, face oedema, pruritus, rash and vasodilatation

In cases where brimonidine has been used as part of the medical treatment of congenital glaucoma, symptoms of brimonidine overdose such as loss of consciousness, lethargy, somnolence, hypotension, hypotonia, bradycardia, hypothermia, cyanosis, pallor, respiratory depression and apnoea have been reported in neonates and infants (less than 2 years of age) receiving brimonidine (see section 4.3).

A high incidence and severity of somnolence has been reported in children of 2 years of age and above, especially those in the 2-7 age range and/or weighing ≤ 20 Kg (see section 4.4).

Timolol

Like other topically applied ophthalmic drugs, brimonidine/timolol (brimonidine tartrate/ timolol) is absorbed into the systemic circulation. Absorption of timolol 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. To reduce the systemic absorption, see section 4.2.

Additional adverse reactions that have been seen with ophthalmic beta-blockers and may potentially occur also with brimonidine tartrate/timolol are listed below:

Immune system disorders: Systemic allergic reactions including angioedema, urticaria, localised and generalised rash, pruritis, anaphylactic reaction

Metabolism: hypoglycaemia

Psychiatric disorders: insomnia, nightmares, memory loss, hallucinations.

Nervous system disorders: cerebrovascular accident, cerebral ischemia, increases in signed and symptoms of myasthenia gravis, paraesthesia

Eye disorders: keratitis, choroidal detachment following filtration surgery (see section 4.4), decreased corneal sensitivity, corneal erosion, ptosis, diplopia

Cardiac disorders: chest pain, oedema, atrioventricular block, cardiac arrest, cardiac failure

Vascular disorders: Raynaud's phenomenon, cold hands and feet

Respiratory, thoracic, and mediastinal disorders: bronchospasm (predominantly in patients with pre-existing bronchospatic disease), dyspnoea, cough

Gastrointestinal disorders: dyspepsia, abdominal pain, vomiting

Skin and subcutaneous tissue disorders: alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash

Musculoskeletal and connective tissue disorders: myalgia

Reproductive system and breast disorders: sexual dysfunction, decreased libido

General disorders and administration site conditions: fatigue

Adverse reactions reported in eye drops containing phosphates:

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Rare reports of overdosage with brimonidine/timolol in humans resulted in no adverse outcome. Treatment of an overdose includes supportive and symptomatic therapy; a patient's airway should be maintained.

Brimonidine

Ophthalmic overdose(Adults):

In those cases received, the events reported have generally been those already listed as adverse reactions.

Systemic overdose resulting from accidental ingestion (Adults):

There is very limited information regarding accidental ingestion of brimonidine in adults. The only adverse event reported to date was hypotension. It was reported that the hypotensive episode was followed by rebound hypertension. Oral overdoses of other alpha-2-agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

Paediatric population

Reports of serious adverse effects following inadvertent ingestion of brimonidine by paediatric subjects have been published or reported. The subjects experienced symptoms of CNS depression, typically temporary coma or low level of consciousness, lethargy, somnolence, hypotonia, bradycardia, hypothermia, pallor, respiratory depression and apnoea, and required admission to intensive care with intubation if indicated. All subjects were reported to have made a full recovery, usually within 6-24 hours.

Timolol

Symptoms of systemic timolol overdose include: bradycardia, hypotension, bronchospasm, headache, dizziness and cardiac arrest. A study of patients showed that timolol did not dialyse readily.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmological – antiglaucoma preparations and miotics - beta-blocking agents – timolol, combinations

ATC code: S01ED51

Mechanism of action

Brimonidine Tartrate/Timolol consists of two active substances: brimonidine tartrate and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in

additional IOP reduction compared to either compound administered alone. Brimonidine Tartrate/Timolol has a rapid onset of action.

Brimonidine tartrate is an alpha-2 adrenergic receptor agonist that is 1000-fold more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoreceptor. This selectivity results in no mydriasis and the absence of vasoconstriction in microvessels associated with human retinal xenografts.

It is thought that brimonidine tartrate lowers IOP by enhancing uveoscleral outflow and reducing aqueous humour formation.

Timolol is a beta1 and beta2 non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

Clinical efficacy

In three controlled, double-masked clinical studies, brimonidine/timolol (twice daily) produced a clinically meaningful additive decrease in mean diurnal IOP compared with timolol (twice daily) and brimonidine (twice daily or three times a day) when administered as monotherapy. In a study in patients whose IOP was insufficiently controlled following a minimal 3-week run-in on any monotherapy, additional decreases in mean diurnal IOP of 4.5, 3.3 and 3.5 mmHg were observed during 3 months of treatment for brimonidine/timolol (twice daily), timolol (twice daily) and brimonidine (twice daily), respectively. In this study, at trough, a significant additional decrease in IOP could only be demonstrated on comparison with brimonidine but not with timolol, however a positive trend was seen with superiority at all other timepoints. In the pooled data of the other two trials statistical superiority versus timolol was seen throughout.

In addition, the IOP-lowering effect of brimonidine/timolol was consistently non- inferior to that achieved by adjunctive therapy of brimonidine and timolol (all twice daily).

The IOP-lowering effect of brimonidine/timolol has been shown to be maintained in double-masked studies of up to 12 months.

5.2 Pharmacokinetic properties

Brimonidine/Timolol

Plasma brimonidine and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to brimonidine/timolol treatment in healthy subjects. There were no statistically significant differences in brimonidine or timolol AUC between brimonidine/timolol and the respective monotherapy treatments. Mean plasma Cmax values for brimonidine and timolol following dosing with brimonidine/timolol were 0.0327 and 0.406 ng/ml respectively.

Brimonidine

After ocular administration of 0.2% eye drops solution in humans, plasma brimonidine concentrations are low. Brimonidine is not extensively metabolised in

the human eye and human plasma protein binding is approximately 29%. The mean apparent half-life in the systemic circulation was approximately 3 hours after topical dosing in man.

Following oral administration to man, brimonidine is well absorbed and rapidly eliminated. The major part of the dose (around 74% of the dose) was excreted as metabolites in urine within five days; no unchanged drug was detected in urine. In vitro studies, using animal and human liver, indicate that the metabolism is mediated largely by aldehyde oxidase and cytochrome P450. Hence, the systemic elimination seems to be primarily hepatic metabolism.

Brimonidine binds extensively and reversibly to melanin in ocular tissues without any untoward effects. Accumulation does not occur in the absence of melanin.

Brimonidine is not metabolised to a great extent in human eyes.

Timolol

After ocular administration of a 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/ml in the aqueous humour at one hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 7 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma protein.

5.3 Preclinical safety data

The ocular and systemic safety profile of the individual components is well established. Non-clinical data reveal no special hazard for humans based on conventional studies of the individual components in safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenicity studies. Additional ocular repeated dose toxicity studies on brimonidine/timolol also showed no special hazard for humans.

Brimonidine

Brimonidine tartrate did not cause any teratogenic effects in animals, but caused abortion in rabbits and postnatal growth reduction in rats at systemic exposures approximately 37-times and 134-times those obtained during therapy in humans, respectively.

Timolol

In animal studies, beta-blockers have been shown to produce reduced umbilical blood flow, reduced foetal growth, delayed ossification and increased foetal and postnatal death, but no teratogenicity. With timolol, embryotoxicity (resorption) in rabbit and foetotoxicity (delayed ossification) in rats have been seen at high maternal doses. Teratogenicity studies in mice, rats and rabbits, at oral doses of timolol up to 4200 times of that in the human daily dose of brimonidine/timolol, showed no evidence of foetal malformation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Sodium phosphate monobasic monohydrate

Sodium phosphate dibasic heptahydrate

Hydrochloric acid or sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening: use within 28 days.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

White opaque LDPE bottle with natural LDPE nozzle and white opaque HDPE cap.

The following pack sizes are available:

1 x 5 ml

3 x 5 ml

6 x 5 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd t/a Mylan

Station Close

Potters Bar

Hertfordshire

EN6 1TL

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/1631

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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