SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Latanoprost 50micrograms/ml and Timolol 5mg/ml Eye Drops Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 50 micrograms latanoprost and 6.8 mg timolol maleate equivalent to 5 mg timolol.

Excipient with known effect: Benzalkonium chloride 0.2 mg/ml eye drops.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution (eye drops).

The solution is a clear, colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Adults (including the elderly):
Recommended therapy is one eye drop in the affected eye(s) once daily.

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

Paediatric population
The safety and efficacy of Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution in children and adolescents has not been established.

Method of administration
Ocular use.
Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes (see section 4.4).
If more than one topical ophthalmic drug is being used, the medicinal products should be administered at least five minutes apart.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution is contraindicated in patients with:

- 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 pace-maker. Overt cardiac failure, cardiogenic shock
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Systemic effects
Like other topically applied ophthalmic agents, Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution is absorbed systemically. Due to the 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 disorder
In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina, cardiac failure) and hypotension the 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 reactions, and rarely, death in association with cardiac failures have been reported following administration of timolol.

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. Latanoprost / Timolol 0.005% w/v / 0.5% w/v 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 insulin-dependent 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

Concomitant therapy
Timolol may interact with other drugs (see section 4.5).

The use of two local beta-blockers or two local prostaglandins is not recommended.

Other beta-blocking agents
The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to 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 doses of adrenaline used to treat anaphylactic reactions.

Ocular effects
Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Similar to experience with latanoprost eye drops, increased iris pigmentation was seen in 16-20% of all patients treated with latanoprost/timolol eye drops for up to one year (based on photographs). This effect has predominantly been seen in patients with mixed coloured irides, i.e. green-brown, yellow-brown or blue/grey-brown, and is due to increased melanin content in the stromal melanocytes of the iris.

Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. In patients with homogeneously blue, grey, green or brown eyes, the change has only rarely been seen during two years of treatment in clinical trials with latanoprost.

The change in iris colour occurs slowly and may not be noticeable for several months to years and it has not been associated with any symptom or pathological changes. No further increase in brown pigment has been observed after discontinuation of treatment, but the resultant colour change may be permanent.

Neither naevi nor freckles of the iris have been affected by the treatment. Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed but patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased iris pigmentation ensues.

Before treatment is instituted patients should be informed of the possibility of a change in eye colour. Unilateral treatment can result in permanent heterochromia.

There is no documented experience with latanoprost in inflammatory, neovascular, chronic angle closure or congenital glaucoma, in open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. Latanoprost has no or little effect on the pupil but there is no documented experience in acute attacks of closed angle glaucoma. Therefore it is recommended that { Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution } should be used with caution in these conditions until more experience is obtained.

Latanoprost should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.

Macular oedema, including cystoid macular oedema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema. Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution should be used with caution in these patients.

<u>Choroidal detachment</u>
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

<u>Surgical anaesthesia</u>
β-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution.

<u>Use of contact lenses</u>
Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctuate keratopathy and/or toxic ulcerative keratopathy, may cause eye irritation and is known to discolour soft contact lenses. Close monitoring is required with frequent or prolonged use of Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution in dry eye

patients, or in conditions where the cornea is compromised. Contact lenses may absorb benzalkonium chloride and these should be removed before applying Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution but may be reinserted after 15 minutes (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No specific medicinal product interaction studies have been performed with Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution.

There have been reports of paradoxical elevations in intraocular pressure following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues, or prostaglandin derivatives is not recommended.

The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution is given to patients already receiving an oral beta-adrenergic blocking agent, and the use of two or more topical beta-adrenergic blocking agents is not recommended.

There is a potential for additive effects resulting in hypotension, and/or marked bradycardia when ophthalmic beta-blocker solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

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.

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

Beta-blockers may increase the hypoglycaemic effect of anti-diabetic 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

Latanoprost

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

Timolol
There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary. 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 Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution is administered until delivery, the neonate should be carefully monitored during the first days of life.
Consequently Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution should not be used during pregnancy (see section 5.3).

Breast-feeding

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 4.2.
Latanoprost and its metabolites may pass into breast milk.
Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution should therefore not be used in women who are breast feeding.

Fertility
Neither Latanoprost nor timolol have been found to have any effect on male or female fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution has a moderate influence on the ability to drive and use machines.

Instillation of eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines.

4.8 Undesirable effects

For latanoprost, the majority of adverse events relate to the ocular system.

In data from the extension phase of the latanoprost/timolol eye drops pivotal trials, 16 - 20% of patients developed increased iris pigmentation, which may be permanent. In an open 5 year latanoprost safety study, 33% of patients developed iris pigmentation (see section 4.4). Other ocular adverse events are generally transient and occur on dose administration.

For timolol, the most serious adverse events are systemic in nature, including bradycardia, arrhythmia, congestive heart failure, bronchospasm and allergic reactions.

Like other topically applied ophthalmic drugs, timolol 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. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with Latanoprost / Timolol 0.005% w/v / 0.5% w/v eye drops, solution:

Adverse events are categorized by frequency as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000).

Nervous System Disorders:
Uncommon: headache.

Eye Disorders:
Very common: increased iris pigmentation.
Common: eye irritation (including stinging, burning and itching), eye pain.
Uncommon: eye hyperaemia, conjunctivitis, blurred vision, lacrimation increased, blepharitis, corneal disorders.

Skin and Subcutaneous Tissue Disorders:
Uncommon: skin rash, pruritus

Additional adverse events have been reported specific to the use of the individual components of latanoprost/timolol eye drops either in clinical studies, spontaneous reports or in the available literature.

For latanoprost, these are:
Infections and Infestations:
Herpetic keratitis.

Nervous System Disorders:
Dizziness.

Eye Disorders:

Eyelash and vellus hair changes (increased length, thickness, pigmentation, and number), punctate epithelial erosions, periorbital oedema, iritis/uveitis, macular oedema (in aphakic, pseudophakic patients with torn posterior lens capsules or in patients with known risk factors for macular oedema), dry eye, keratitis, corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation, iris cyst, photophobia, periorbital and lid changes resulting in deepening of the eyelid sulcus.

Cardiac Disorders:
Aggravation of angina in patients with pre-existing disease, palpitations.

Gastrointestinal disorders:
Nausea; vomiting (frequency: uncommon)

Respiratory, Thoracic and Mediastinal Disorders:
Asthma, asthma aggravation, dyspnoea,

Skin and Subcutaneous Tissue Disorders:
Darkening of palpebral skin.

Musculoskeletal and Connective Tissue Disorders:
Joint pain, muscle pain.

General disorders and Administration Site Conditions:
Chest pain.

For timolol, these are:
Immune System Disorders:

Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylactic reaction.

Metabolism and nutrition disorders:
Hypoglycaemia

Psychiatric Disorders:
Depression, memory loss, insomnia, nightmares.

Nervous System Disorders:
Dizziness, paraesthesia, cerebral ischaemia, cerebrovascular accident, increase in signs and symptoms of myasthenia gravis, syncope and headache.

Eye Disorders:
Signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), blepharitis, keratitis, blurred vision and choroidal detachment following filtration surgery (see section 4.4), decreased corneal sensitivity, dry eyes, corneal erosion, diplopia, ptosis.

Ear and Labyrinth Disorders:
Tinnitus.

Cardiac Disorders:
Palpitation, arrhythmia, bradycardia, chest pain, cardiac arrest, oedema, congestive heart failure, atrioventricular block, cardiac failure.

Vascular Disorders:
Hypotension, Raynaud's phenomenon, cold hands and feet.

Respiratory, Thoracic and Mediastinal Disorders:
Bronchospasm (predominately in patients with pre-existing bronchospastic disease), dyspnoea, cough.

Gastrointestinal Disorders:
Dysgeusia, nausea, diarrhoea, dyspepsia, dry mouth, 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:
Asthenia/fatigue.

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; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No data are available in humans with regard to overdose with Latanoprost/Timolol 50 microgram/ml + 5 mg/ml eye drops, solution.

Symptoms of systemic timolol overdose are: bradycardia, hypotension, bronchospasm and cardiac arrest. If such symptoms occur the treatment should be symptomatic and supportive. Studies have shown that timolol does not dialyse readily.

Apart from ocular irritation and conjunctival hyperaemia, no other ocular or systemic side effects are known if latanoprost is overdosed.

If latanoprost is accidentally ingested orally the following information may be useful:

Treatment: Gastric lavage if needed. Symptomatic treatment. Latanoprost is extensively metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers induced no symptoms, but a dose of 5.5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. These events were mild to moderate in severity and resolved without treatment, within 4 hours after terminating the infusion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmological-betablocking agents - timolol, combinations

ATC code: S01ED51

Mechanism of action

Latanoprost/timolol eye drops consists of two components: latanoprost and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by different mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone.

Latanoprost, a prostaglandin F2alpha analogue, is a selective prostanoid FP receptor agonist that reduces the IOP by increasing the outflow of aqueous humour. The main mechanism of action is increased uveoscleral outflow. Additionally, some increase in outflow facility (decrease in trabecular outflow resistance) has been reported in man. Latanoprost has no significant effect on the production of aqueous humour, the blood-aqueous barrier or the intraocular blood circulation. Chronic treatment with latanoprost in monkey eyes, which had undergone extracapsular lens extraction did not affect the retinal blood vessels as determined by fluorescein angiography. Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short term treatment.

Timolol is a beta-1 and beta-2 (non-selective) adrenergic receptor blocking agent that has no significant intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Timolol lowers IOP by decreasing the formation of

aqueous in the ciliary epithelium. 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. Timolol has not been found to significantly affect the permeability of the blood-aqueous barrier to plasma proteins. In rabbits, timolol was without effect on the regional ocular blood flow after chronic treatment.

Pharmacodynamic effects

Clinical effects

In dose finding studies, latanoprost/timolol eye drops produced significantly greater decreases in mean diurnal IOP compared to latanoprost and timolol administered once daily as monotherapy. In two well controlled, double masked six-month clinical studies the IOP reducing effect of latanoprost/timolol eye drops was compared with latanoprost and timolol monotherapy in patients with an IOP of at least 25 mm Hg or greater. Following a 2-4 week run-in with timolol (mean decrease in IOP from enrollment of 5 mm Hg), additional decreases in mean diurnal IOP of 3.1, 2.0 and 0.6 mm Hg were observed after 6 months of treatment for latanoprost/timolol eye drops, latanoprost and timolol (twice daily), respectively. The IOP lowering effect of latanoprost/timolol eye drops was maintained in 6 month open label extension of these studies.

Existing data suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, when considering a recommendation of either morning or evening dosing, sufficient consideration should be given to the lifestyle of the patient and their likely compliance. It should be kept in mind that in case of insufficient efficacy of the fixed combination, results from studies indicate that the use of unfixed administration of timolol bid and latanoprost once a day might be still efficient.

Onset of action of latanoprost/timolol eye drops is within one hour and maximal effect occurs within six to eight hours. Adequate IOP reducing effect has been shown to be present up to 24 hours post dosage after multiple treatments.

5.2 Pharmacokinetic properties

Latanoprost

Latanoprost is an isopropyl ester prodrug, which per se is inactive but after hydrolysis by esterases in the cornea to the acid of latanoprost, becomes biologically active. The prodrug is well absorbed through the cornea and all drug that enters the aqueous humor is hydrolysed during the passage through the cornea. Studies in man indicate that the maximum concentration in the aqueous humour, approximately 15-30 ng/ml, is reached about 2 hours after topical administration of latanoprost alone.After topical application in monkeys latanoprost is distributed primarily in the anterior segment, the conjunctiva and the eye lids.

The acid of latanoprost has a plasma clearance of 0.40 l/h/kg and a small volume of distribution, 0.16 l/kg, resulting in a rapid half life in plasma, 17 minutes.After topical ocular administration the systemic bioavailability of the acid of latanoprost is 45%. The acid of latanoprost has a plasma protein binding of 87%.

There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. The main metabolites, the 1,2-dinor and 1,2,3,4-tetranor metabolites, exert no or only weak biological activity in animal studies and are excreted primarily in the urine.

Timolol

The maximum concentration of timolol in the aqueous humour is reached about 1 hour after topical administration of eye drops. Part of the dose is absorbed systemically and a maximum plasma concentration of 1 ng/ml is reached 10-20 minutes after topical administration of one eye drop to each eye once daily (300 micrograms/day). The half life of timolol in plasma is about 6 hours. Timolol is extensively metabolised in the liver. The metabolites are excreted in the urine together with some unchanged timolol.

Latanoprost/timolol eye drops

No pharmacokinetic interactions between latanoprost and timolol were observed, although there was an approximate 2-fold increased concentration of the acid of latanoprost in aqueous humour 1-4 hours after administration of latanoprost/timolol eye drops compared to monotherapy.

5.3 Preclinical safety data

The ocular and systemic safety profile of the individual components is well established. No adverse ocular or systemic effects were seen in rabbits treated topically with the fixed combination or with concomitantly administered latanoprost and timolol ophthalmic solutions. Safety pharmacology, genotoxicity and carcinogenicity studies with each of the components revealed no special hazards for humans. Latanoprost did not affect corneal wound healing in the rabbit eye, whereas timolol inhibited the process in the rabbit and the monkey eye when administered more frequently than once a day.

For latanoprost, no effects on male and female fertility in rats and no teratogenic potential in rats and rabbits have been established. No embryotoxicity was observed in rats after intravenous doses of up to 250 micrograms/kg/day. However, latanoprost caused embryofetal toxicity, characterised by increased incidence of late resorption and abortion and by reduced fetal weight, in rabbits at intravenous doses of 5 micrograms/kg/day (approximately 100 times the clinical dose) and above.

Timolol showed no effects on male and female fertility in rats or teratogenic potential in mice, rats and rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Sodium chloride

Sodium dihydrogen phosphate dihydrate

Disodium phosphate dodecahydrate

Purified water

6.2 Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with latanoprost. If such drugs are used concomitantly with Latanoprost/Timolol, the eye drops should be administered with an interval of at least five minutes.

6.3 Shelf life

3 years
After first opening of container: 28 days

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Opened bottle: Do not store above 25°C.

Keep the bottle in the outer carton in order to protect from light.

For storage conditions after first opening, see section 6.3.

6.5 Nature and contents of container

5 ml LDPE bottle with HDPE dropper applicator, HDPE screw cap and tamper evident LDPE overseal.

Each bottle contains 2.5 ml eye drop solution.

Pack sizes: 1 bottle x 2.5ml eye drops, 3 bottles x 2.5ml eye drops, 6 bottles x 2.5ml eye drops.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/1042

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/10/2012

10 DATE OF REVISION OF THE TEXT

04/05/2022