ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prostalen 10 mg prolonged release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of alfuzosin hydrochloride.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged release tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the functional symptoms of benign prostatic hypertrophy (BPH).
Adjuvant therapy for the insertion of a uretral catheter associated with acute urinary retention (AUR) related to benign prostatic hyperplasia.

4.2 Posology and method of administration

The recommended dose is one 10 mg tablet per day to be taken after a meal.
For AUR, one 10 mg tablet daily after a meal to be taken from the first day of catheterisation.
Prostalen should be swallowed whole.

Paediatric population
Efficacy of Alfuzosin 10 mg prolonged release tablet has not been demonstrated in children aged 2 to 16 years (see section 5.1). Therefore, Alfuzosin 10 mg prolonged release tablet is not indicated for use in the paediatric population.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see section 6.1 list of excipients).
- History of orthostatic hypotension.
- Combination with other α_1-receptor blockers.
- Hepatic insufficiency.

4.4 Special warnings and precautions for use

Special warnings
As with all α_1-receptor blockers in some subjects, in particular patients receiving antihypertensive medications or nitrates, postural hypotension with or without symptoms (dizziness, fatigue, sweating) may develop within a few hours following administration. In such cases, the patients should lie until the symptoms have completely disappeared.

These effects are transient, occur at the beginning of treatment and do not usually prevent the continuation of treatment. Advanced age contributes to the risk of developping severe hypotension. Pronounced drop in blood pressure has been reported in post-marketing surveillance in patient with pre-existing risk factors (such as underlying cardiac diseases and/or concomitant treatment with anti-hypertensive medication). The patient should be warned of the possible occurence of such events.

As with all α_1-receptor blockers, alfuzosin should be used with caution in patients with acute cardiac failure.

Care should probably be taken when Alfuzosin 10 mg prolonged release tablet is administered to patients who have had a pronounced hypotensive response to another α_1-receptor blockers.

Precautions for use

- Alfuzosin hydrochloride 10 mg should be prescribed with caution to elderly patients.
- Patients with history of hypersensitivity to α_1-receptor blockers.
- Alfuzosin chlorhydrate should be administered cautiously in patients treated with antihypertensives and nitro derivatives and the blood pressure should be monitored frequently, especially at the beginning of the treatment.
- In coronary patients, the specific treatment for coronary insufficiency should be continued. If angina reappears or worsens, Alfuzosin 10 mg prolonged released tablet should be discontinuated.
- It is crucial to exclude prostatic cancer prior to start the treatment, especially because the first symptoms are closed to these of benign prostatic hyperplasia.
- Afluzosin should be administered cautiously in patients who have had a strong hypotensive reaction to other α1-receptor blockers.
- Patients with congenital QTc prolongation, with a known history of acquired QTc prolongation or who are taking drugs known to increase the QTc interval should be evaluated before and during the administration of alfuzosin.
- Prolonged erections and priapism have been reported with alpha-1 blockers including alfuzosin in post marketing experience. If priapism is not treated immediately, it could result in permanent loss of potency, therefore the patient should seek immediate assistance (see section 4.8).
- The "Intraoperative Floppy Iris Syndrome" (IFISS, a variant of pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with α1-receptor blockers. Although the risk of this event with alfuzosin appears very low, ophtalmic surgeons should be informed in advance of cataract surgery of current or past use of α1-receptor blockers, as IFIS may lead to increased procedural complications. The ophtalmologists should be prepared for possible modifications to their surgical technique.
- Patients should be warned that the tablet should be swallowed whole. Any other mode of administration, such as crunching, crushing, chewing, grinding or pounding to powder should be prohibited. These actions may lead to inappropriate release and absorption of the drug and therefore possible early adverse reactions.
- Concomitant use of phosphodiesterase 5 inhibitors (sildenafil, vardenafil, tadalafil) and alfuzosin hydrochloride migh result in symptomatic hypotension in some patients. In order to reduce the risk of developping postural hypotension, the patient on α1-receptor blocker should be stable before starting taking phosphodiesterase 5 inhibitors.
- As there are no clinical safety data available in patients with severe renal impairment (creatinine clearance < 30 mL/min), alfuzosin 10 mg prolonged released tablets should not be administred to this patient group.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations contra-indicated:

- α_1-receptor blockers (see section 4.3 contraindications).

Combination to be taken into account:

- Antihypertensive drugs (see section 4.4 special warnings and precautions for use).
- Nitrates (see section 4.4 special warnings for use).
- The administration of general anaesthetics to patients treated with Alfuzosin 10 mg prolonged release tablet may lead to blood pressure instability.
- Potent CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir.
  Repeated 200 mg daily dosing of ketoconazole, for seven days resulted in a 2.1-fold increase in Cmax and a 2.5-fold increase in exposure of alfuzosin 10 mg when administered as a single dose under fed conditions (high fat meal). Other parameters such as tmax and t1/2 were not notified.

Cmax and AUC of alfuzosin 10 mg, when administered as a single dose under fed conditions, increased 2.3-fold and 3.0 fold, respectively following 8-day repeated 400 mg ketoconazole daily dosing (see section 5.2 pharmacokinetics properties).

Concomitant treatment with phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafim) may lead to symptomatic hypotension in some patients.

No pharmacodynamic or pharmacokinetic interaction has been observed in healthy volunteers between alfuzosin and the following drugs: warfarin, digoxin, hydrochlorothiazide and atenolol.

4.6 Fertility, pregnancy and lactation

Due to the type of indication this section is not applicable.

4.7 Effects on ability to drive and use machines

There are no data available on the effect on driving vehicles. Adverse reactions such as vertigo, dizziness and asthenia may occur essentially at the beginning of treatment. This has to be taken into account when driving vehicles and operating machinery.

4.8 Undesirable effects

Classification of expected frequencies
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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

- ***Nervous system disorders***

Common: faintness/dizziness, headache.
Uncommon: syncope, vertigo, malaise, drowsiness.

- ***Cardiac disorders***

Unknown: tachycardia, hypotension (postural).
Very rare: new onset, aggravation or recurrence of angina pectoris in patients with pre-existing coronary artery disease (see section 4.4).
Not known: atrial fibrillation.

- ***Vascular disorders***

Uncommon: hypotension (postural), flushing.
Not known: vomiting

- ***Blood and lymphatic system disorders***

Not known: neutropenia

- ***Gastro-intestinal disorders***

Common: nausea, abdominal pain, gastralgia.
Uncommon: diarrhoea
Not known: vomiting

- ***Skin and subcutaneous tissue disorders***

Uncommon: rash, pruritus.
Very rare: urticaria, angioedema.

- ***Hepatobiliary disorders***

Not known: hepatocellular injury, cholestatic liver disease.

- ***Reproductive system and breast disorders***

Not known: priapism

- ***General disorders and administration site conditions***

Common: asthenia.
Uncommon: flushes, oedema, chest pain

- ***Eye disorders***

Not known: intraoperative floppy iris syndrome (see section 4.4).

- ***Respiratory disorders***

Uncommon: rhinitis

Other effects cannot be excluded:

- ***Nervous system disorders***

Uncommon: sleepiness.

- ***Eye disorders***

Uncommon: vision abnormal.

- ***General disorders and administration site conditions***

Common: malaise

- ***Cardiac disorders***

Uncommon: palpitations.

- ***Gastro-intestinal disorders***

Common: dry mouth.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal products is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professional are asked to report any suspected adverse reactions via their national reporting system.

4.9 Overdose

In case of overdosage, the patient should be hospitalised, kept in the supine position, and conventional treatment of hypotension should take place.
In case of significant hypotension, the appropriate corrective treatment may be a vasoconstrictor that acts directly on vascular muscle fibres.
Alfuzosin is not dialysable because of its hygh degree of protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: α_1-adrenoreceptor antagonists, ATC code: G04CA01.

Alfuzosin is an orally active quinazoline derivative. It is a selective peripherally active antagonist of postsynaptic α_1-adrenoreceptors.
In vitro pharmacological studies have documented the selectivity of alfuzosin for the α_1-adrenoreceptors located in the prostate, bladder and prostatic urethra.

In vivo, animal studies have shown that alfuzosin decreases urethral pressure and therefore, resistance to urine flow during micturition

Clinical manifestations of Benign Prostatic Hypertrophy are associated with infra vesical obstruction which is triggered by both anatomical (static) and functional (dynamic) factors. The functional component of obstruction arises from the tension of prostatic smooth muscle which is mediated by α_1-adrenoreceptors. Activation of α_1-adrenoreceptors stimulates smooth muscle contraction, thereby increasing the tone of the prostate, prostatic capsule, prostatic urethra and bladder base, and, consequently, increasing the resistance to bladder outflow. This in turn leads to outflow obstruction and possible secondary bladder instability.

α_1-blockade decreases infra vesical obstruction via a direct action on prostatic smooth muscle.

. Moreover, alfuzosin inhibits the hypertonic response of the urethra more readily in conscious normotensive rats by decreasing urethral pressure at doses that do not affect blood pressure.

In man, alfuzosin improves voiding parameters by reducing urethral tone and bladder outlet resistance, and facilitates bladder emptying.

In placebo controlled studies in BPH patients, alfuzosin:

- Significantly increases peak flow rate (Q_{max}) in patients with $Q_{max} \leq 15$ mL/s by a mean of 30 %. This is observed from the first dose.
- Significantly reduces the detrusor pressure and increases the volume producing a strong desire to void.
- Significantly reduces the residual urine volume.

These favourable urodynamic effects lead to an improvment of lower urinary tract symptoms i.e. filling (irritative) as well as voiding (obstructive) symptoms.

Alfuzosin may cause moderate antihypertensive effects.

A lower frequency of acute urinary rentention is observed in the alfuzosin treated patitent than in untreated patients.

AUR (related to BPH):
In the ALFAUR study, the effect of alfuzosin on the return of normal voiding was evaluated in 357 men over 50 years, presenting with a first episode of acute urinary rentention (AUR), related to BPH. In this multicentre randomised double blind parallel group study comparing alfuzosin 10 mg/day and placebo, the evaluation of voiding was performed 24 hours after catheter removal, the morning after 2-3 days of treatment.

In men aged 65 years and over, alfuzosin significantly increased the success rate of spontaneous voiding after catheter removal – see table. No benefit has been established in patients under 65 year of age or if treatment is extended beyond 4 days.

ALFAUR study: percentage of pateints (ITT population) successfully voiding post-catheter removal

Age	**Placebo N (%)**	**Alfuzosin N (%)**	**Relative difference vs. placebo 95 % CI**	**P value**
65 years and above	30 (35.7 %)	88 (56.1 %)	1.57 (1.14 – 2.16)	0.03
Below 65 years	28 (75.7 %)	58 (73.4 %)	0.97 (0.77 – 1.22)	0.80
all patients (50 years and above)	58 (47.8 %)	146 (61.9 %)	1.29 (1.04 – 1.60)	0.012

Paediatric population
Alfuzosin 10 mg prolonged release tablet is not indicated for use in paediatric population (see section 4.2).

Efficacy of alfuzosin hydrochloride was not demonstrated in the two studies conducted in 197 pateitn 2 to 16 years of age with elevated detrusor leak point pressure (LPP $\geq$ 40 cm H_2O) of neurologic origin. Patients

were treated with alfuzosin hydrochloride 0.1 mg/kg/day or 0.2 mg/kg/day using adapted paediatric formulations).

5.2 Pharmacokinetic properties

Prolonged-release formulation:
The mean value of the relative bioavailability is 104.4 % versus the immediate release formulation (2.5 mg tid) in middle-aged healthy volunteers and the maximum plasma concentration is being achieved 9 hours after administration compared to 1 hour for the immediate release formulation.

The apparent elimination half-life is 9.1 hours.

Studies have shown that consistent pharmacokinetic profiles are obtained when the product is administered after a meal.
Under fed conditions, mean C_{max} and C_{trough} values are 13.6 (SD = 5.6) and 3.2 (SD = 1.6) ng/mL respectively. Mean AUC $_{0-24}$ is 194 (SD = 75) ng·h/mL. A plateau of concentration is observed from 3 to 14 h with concentrations above 8.1 ng/mL (C_{av}) for 11 h.

Compared to healthy middle aged volunteers, the pharmacokinetic parameters (C_{max} and AUC) are not increased in elderly patients.

Compared to subjects with normal renal functions mean C $_{max}$ and AUC values are moderately increased in pateints with renal impairment, without modification of the apparent elimination half-life. This change in the pharmacokinetic profile is not considered clinically relevant. Therefore, this does not necessitate a dosing adjustment.

The binding of alfuzosin to plasma proteins is about 90 %. Alfuzosin undergoes extensive metabolism by the liver, with only 11 % of the parent compound being excreted unchanged in the urine. The majority of the metabolites (which are inactive) are excreted in the faeces (75 to 91 %).

The pharmacokinetic profile of alfuzosin is not affected by chronic cardiac insufficiency.

Metabolic interactions: CYP3A4 is the main hepatic enzyme isoform involved in the metabolism of alfuzosin (see section 4.5).

5.3 Preclinical safety data

No data of therapeutic relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose, microcrystalline cellulose, anhydrous colloidal silica, magnesium stearate, Opadry II white.

6.2 Incompatibilities

None known.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original container, below 30 °C.

6.5 Nature and contents of container

Prostalen tablets are film-coated, white and round. The tablets are packaged in blister strips (PVC-Aluminium of 10 tablets). Each box contains 3 blisters of 10 tablets (30 tablets).

6.6 Special precautions for disposal

No special requirements for disposal.

7. CATEGORY OF DISTRIBUTION

☐ Over-the counter medicine ☒ Prescription only medicines
List I

8. MARKETING AUTHORISATION HOLDER

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10. DATE OF REVISION OF THE TEXT

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