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.

Renal failure
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 administrated to this patient group.

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.

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.

Precations of use
Patient s with hypersensitivity to alpha-1-blockers.
Prostalen should be administered carefully to patients who have had a pronounced hypotensive reaction to another alpha-1-blocker (see section 4.5).
In coronary patients, the specific treatment for coronary insufficiency should be continued. If angina pectoris reappears or worsens Prostalen should be discontinued.
It is necessary to exclude any prostate cancer before the start of treatment especially since the first symptoms are closed to those observed in case of benign prostatic hypertrophy.
As other alpha-1-blockers, alfuzosin should be used with caution in patient with acute heart failure.
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 penile tissue damage and permanent loss of potency, therefore the patient should seek immediate medical assistance (see section 4.8).
The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with alpha-1-blockers. Although the risk of this event with alfuzosin appears very low, ophthalmic surgeons should be informed in advance of cataract surgery of current or past use of alpha-1-blockers, as IFIS may lead to increased procedural complications. The ophthalmologists should be prepared for possible modifications to their surgical technique
Concomitant use of alfuzosin and potent CYP3A4 inhibitors (such as itraconazole, ketoconazole, protease inhibitors, clarithromycin, telithromycin and nefazodone) should be avoided (see section 4.5). Alfuzosin should not be used concomitantly with CYP3A4 inhibitors that are known to increase the QTc interval (e.g. itraconazole and clarithromycin) and a temporary interruption of alfuzosin treatment is recommended if treatment with such medicinal products is initiated.
Concomitant use of phosphodiesterase 5 inhibitors (sildenafil, vardenafil, tadalafil) and alfuzosin hydrochloride might result in symptomatic hypotension in some patients. In order to reduce the risk of developing postural hypotension, the patient on α1-receptor blocker should be stable before starting taking phosphodiesterase 5 inhibitors.
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.

Elderly patient
Prostalen should be prescribed carefully to the elderly patient

4.5 Interaction with other medicinal products and other forms of interaction

Combinations contra-indicated:
- Other α_1-receptor blockers (see section 4.3 contraindications).

Combination not recommended
Potent CYP3A4 inhibitors (such as itraconazole, ketoconazole, proteases inhibitors, clarithromycin, telithromycin and nefazodone) as the alfuzosin blood levels might increase (see section 4.4 special warning for use).

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.
- Concomitant treatment with phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafim) may lead to symptomatic hypotension in some patients (see section 4.4 special warning for use).
- Drugs that are known to cause QTc prolongation (see section 4.4 special warning for use)

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).

- ***Nervous system disorders***

Common: faintness/dizziness, headache, weakness, lightheadedness, fatigue.
Uncommon: syncope, vertigo.

- ***Cardiac disorders***

Unknown: tachycardia.
Very rare: angina pectoris in patients with pre-existing coronary artery disease (see section 4.4).
Not known: atrial fibrillation.

- ***Vascular disorders***

Uncommon: hypotension (postural), flushing.

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

Not known: neutropenia, thrombocytopenia

- ***Gastro-intestinal disorders***

Common: nausea, abdominal pain, gastralgia.
Uncommon: diarrhoea, vomiting

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

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

- ***Hepatobiliary disorders***

Not known: hepatocellular injury, cholestatic liver disease.

- ***Reproductive system***

Not known: priapism

- ***Eye disorders***

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

- ***Respiratory disorders***

Uncommon: rhinitis

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

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

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

The main manifestation of overdose is hypotension and its potential complications.
In case of overdosage, the patient should be hospitalised, kept in the supine position, and conventional treatment of hypotension should take place (vascular filing and vasopressor treatment).
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

Intensity of clinical manifestations in Benign Prostatic Hypertrophy is not only related to prostate volume but also to sympathetic nervous tone.
An α_1-adrenergic innervation has been demonstrated in the smooth muscle fibers of the prostatic stroma. Alfuzosin follows a selective distribution in the prostatic tissue. Hypertrophy of the prostatic stroma involves smooth muscle fibers. Stimulation of postsynaptic α_1- receptors increases the muscle tone of the urinary tract: inhibition by alfuzosin of these receptors leads to relaxation of the smooth muscle fibers.

Alfuzosin is also slightly uro-selective as it inhibits the hypertonic response of the urethra before inducing dilattation of blood vessels.

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.

In treated patients, the occurrence frequency of accute urinary retention is reduced compared to untreated pateints. Moreover, alfuzosin significantly increases the success rate of urination after catheter removal in men with an episode of acute urinary retention associated with benign prostatic hypertrophy.

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

Absorption:
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.
Studies have shown that consistent pharmacokinetic profiles are obtained when the product is administered after a meal.

Distribution:
The binding of alfuzosin to plasma proteins is about 90 %, 68.2% to albumin serum and 52.5% to α_1-glycoproteine serum.

Biotransformation:
Alfuzosin undergoes extensive metabolism by the liver, with only 11 % of the parent compound being excreted unchanged in the urine.
CYP3A4 is the main hepatic enzyme isoform involved in the metabolism of alfuzosin. Ketoconazole is a potent CYP3A4 inhibitor. A daily doses of 200 mg of ketoconazole during 7 days have increased the C_{max} (2.11x) and the AUC (2.46x) after administration of 10mg of afuzosin after the meal. Others parameters, like

T_{max} and $T_{1/2}$, were not modified. A daily doses of 400 mg of ketoconazole during 8 days have increased the alfuzosin C_{max} (2.3x), the AUC_{last} (3.2x) and the AUC (3.0x) (see section 4.5).

Elimination:
The majority of the metabolites (which are inactive) are excreted in the faeces (75 to 91 %).
The apparent elimination half-life is 9.1 hours.

Renal failure:
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.
In renal failure, necessiting dialysis or not, the distribution volume and the alfuzosin clearance increase due to the elevation of the free fraction.

Hepatic failure:
Compared to subjects with normal hepatic functions, the elimination half-life is increased, the C_{max} values are doubled, the AUC tripled and the biodisponibility is increased.

Elderly patient:
Compared to healthy middle aged volunteers, the pharmacokinetic parameters (Cmax and AUC) are not increased in elderly patients.

In patients over 75, absoprtion of alfuzosin is faster and peak concentrations higher. Bioavailability may be increased and a reduction in the volume of distribution is observed in some patients. The elimination half-life remains unchanged.

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

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

3 years.

6.4 Special precautions for storage

Store in the original container, below 30 °C.

6.5 Nature and contents of container

Prostalen prolonged-release 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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