SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

ALFUWIN® XL (prolonged release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each prolonged release tablet contains 10 mg alfuzosin hydrochloride.

Contains sugar (mannitol): 10 mg

Excipients with known effects: Hydrogenated castor oil 41,4 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Prolonged release tablets.

Round biconvex, three layer tablet: one white layer between two yellow layers; diameter about 8 mm.

4 CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Treatment of functional symptoms of Benign Prostatic Hyperplasia (BPH).

Adjunctive therapy with urethral catheterisation for Acute Urinary Retention (AUR) related to BPH.

4.2 Posology and method of administration:

Posology:

The recommended dose for ALFUWIN XL is:

BPH: One ALFUWIN XL tablet daily to be taken after meals (as bioavailability in the fasting state is less than half that after a meal).

AUR: One ALFUWIN XL tablet daily after a meal to be taken from the first day of catheterisation.

Method of administration: The ALFUWIN XL tablet must be swallowed whole (see section 4.4).

Special populations

ALFUWIN XL is contraindicated in patients with severe renal impairment (creatinine clearance ≥ 30 ml/min), hepatic impairment and children below 18 years of age (see section 4.3).

4.3 Contraindications:

- Hypersensitivity to alfuzosin or any of the excipients of ALFUWIN XL (see section 6.1)
- Orthostatic hypotension (see section 4.4)
- Combination with other alpha-1-blockers (alpha-1-adrenoceptor blockers or antagonists)
- Hepatic impairment
- Severe renal impairment (see section 4.4)
- Children below 18 years of age
- Concomitant administration with potent CYP3A4 inhibitors (see section 4.5).

4.4 Special warnings and precautions for use:

Hypotension:

In some patients, in particular those receiving antihypertensive medication and nitrates (see section 4.5), postural hypotension with or without symptoms (dizziness, fatigue, sweating) may develop within a few hours following administration. In such cases, the patient should lie down until the symptoms have completely disappeared. These effects are usually transient, occur at the beginning of treatment, and do not usually prevent the continuation of treatment.

Pronounced drop in blood pressure has been reported in post-marketing surveillance in patients with pre-existing risk factors (such as underlying cardiac disease and/or concomitant treatment with anti-hypertensive medication).

The risk of developing hypotension and related adverse reactions may be greater in elderly patients.

The patient should be warned of the possible occurrence of such events.

QT prolongation:

Patients with acquired or congenital QT prolongation or who are taking medication that prolong the QT interval, should be evaluated before and during the administration of ALFUWIN XL.

Priapism:

Alpha-1-blockers, such as ALFUWIN XL, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Because this condition can lead to permanent impotence if not properly treated, patients should be advised about the seriousness of the condition (see section 4.8).

Care should be taken when ALFUWIN XL who have had a pronounced hypotensive response to another alpha-1-blocker.

Ischaemic heart disease:

In coronary patients, ALFUWIN XL should not be prescribed alone. In patients with ischaemic heart disease/angina pectoris, the specific treatment for coronary insufficiency should be continued. If angina pectoris reappears or gets worse, ALFUWIN XL should be discontinued.

Potent CYP3A4 inhibitors:

Concomitant use of ALFUWIN XL and potent CYP3A4 inhibitors (such as itraconazole, ketoconazole, protease inhibitors, clarithromycin, telithromycin and nefazodone) must be avoided (see section 4.3 and 4.5). ALFUWIN XL must not be used concomitantly with CYP3A4 inhibitors that are known to increase the QT interval (e.g. itraconazole and clarithromycin) and a temporary interruption of ALFUWIN XL treatment is recommended if treatment with such medicinal products is initiated.

Intraoperative Floppy Iris Syndrome:

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 some alpha-1-blockers (including ALFUWIN XL).

Although the risk of this event with ALFUWIN XL 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.

Mode of administration:

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 medicine and therefore possible early adverse reactions.

Excipients statement:

The excipient hydrogenated castor oil may cause stomach upset and diarrhoea.

4.5 Interactions with other medicines and other forms of interaction:

Combinations contraindicated:

- Alpha-1-blockers (see section 4.3).
- Potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, clarithromycin, telithromycin and nefazodone since ALFUWIN XL blood levels are increased (see section 4.3 and 4.4).

Combinations to be taken into account:

- Antihypertensive medicines (see section 4.4)
- Nitrates (see section 4.4)
- General anaesthetics: Administration of general anaesthetics to a patient treated with ALFUWIN XL may lead to a decrease in blood pressure.

4.6 Fertility, pregnancy and lactation:

Due to the indication area this section is not applicable.

4.7 Effects on the ability to drive and use machines:

There are no data available on the effect on driving vehicles. Adverse reactions such as vertigo, dizziness**,** asthenia and hypotension may occur, especially at the beginning of treatment. This should be taken into account when driving vehicles and operating machinery (see section 4.4).

4.8 Undesirable effects:

The following frequency rating is used, when applicable:

Very common (≥ 1/10); *common* (≥ 1/100, < 1/10); *uncommon* (≥ 1/1000, < 1/100); *rare* (≥ 1/10 000, < 1/1000); *very rare* (≤ 1/10 000), including isolated reports.

Frequency not known: Frequency cannot be estimated from available data.

Blood and the lymphatic system disorders:

Frequency not known: thrombocytopenia

Nervous system disorders:

Common: faintness/dizziness, headache

Uncommon: syncope, vertigo, drowsiness, malaise

Eye disorders:

Uncommon: vision abnormal

Frequency not known: Intraoperative Floppy Iris Syndrome (IFIS) (see section 4.4)

Cardiac disorders:

Uncommon: tachycardia

Very rare: angina pectoris in patients with pre-existing coronary artery disease (see section 4.4)

Frequency not known: atrial fibrillation, palpitations

Vascular disorders:

Uncommon: symptomatic hypotension (postural) (see section 4.4), flushing

Respiratory, thoracic and mediastinal disorders:

Uncommon: rhinitis

Gastrointestinal disorders:

Common: nausea, gastralgia

Uncommon: diarrhoea, dry mouth**,** vomiting

Hepato-biliary disorders:

Frequency not known: hepatocellular injury, cholestatic liver disease

Skin and subcutaneous tissue disorders:

Uncommon: rash, pruritus,

Very rare: urticaria, angioedema

Reproductive system and breast disorders:

Frequency not known: priapism

General disorders and administrative site conditions:

Common: asthenia

Uncommon: oedema, chest pain.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: Email: za.drugsafety@sanofi.com or Tel: 011 256-3700, or
- SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

In case of over dosage, the patient should be hospitalised, kept in the supine position, and conventional treatment of hypotension should take place.

ALFUWIN XL is not dialysable because of its high degree of protein binding. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES:

A 5.2 Adrenolytics (sympatholytics)

Pharmacotherapeutic group: Drugs used in benign prostatic hypertrophy. ATC code: G04C A01

5.1 Pharmacodynamic properties:

Alfuzosin hydrochloride is an orally active quinazoline derivative. It is a selective peripherally-acting antagonist of post-synaptic alpha-1-adrenoceptors.

In vitro pharmacological studies have documented the selectivity of alfuzosin hydrochloride for the alpha-1-adrenoceptors located in the prostate, bladder base and prostatic urethra. Alpha-1-adrenoceptor blockade decreases infra-vesical obstruction via a direct action on prostatic smooth muscle.

In vivo animal studies have shown that alfuzosin hydrochloride decreases urethral pressure and therefore, resistance to urine flow during micturition. Moreover, alfuzosin hydrochloride inhibits the hypertonic response of the urethra more readily than that of vascular muscle, and shows functional uroselectivity in experimental animals.

In man, alfuzosin hydrochloride improves voiding parameters by reducing urethral tone and bladder outlet resistance, and facilitates bladder emptying.
In addition, alfuzosin significantly increases the success rate of spontaneous voiding after catheter removal in men with an episode of AUR related to BPH.

5.2 Pharmacokinetic properties:

Absorption: Alfuzosin hydrochloride is absorbed after oral administration, with a mean absolute bioavailability of 64 %. The bioavailability of alfuzosin hydrochloride 10 mg once daily was similar to the immediate release formulation, 2,5 mg given three times daily, in middle aged healthy volunteers and the maximum plasma concentration was being achieved 9 hours after administration compared to 1,0 hour for the immediate release formulation.
CYP 3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin.
The apparent elimination half-life is 9,1 hours.

Maximum blood levels and bioavailability are not affected by food intake.

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

Compared to subjects with normal renal function, mean Cmax and AUC values were about 5 % and 7 % increased in patients with mild to moderate renal impairment, without modification of the apparent elimination half-life. There are no data available on severe renal impairment.

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

In subjects aged over 75 years, absorption of alfuzosin hydrochloride is more rapid and the peak levels are higher. Bioavailability may be increased and in some patients the volume of distribution is reduced. The elimination half-life remains unchanged.

The volume of distribution and clearance of alfuzosin are increased in renal insufficiency, with or without dialysis, owing to an increase in the free fraction.

The pharmacokinetic profile of alfuzosin hydrochloride 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:

Ethylcellulose

Hydrogenated castor oil

Hypromellose

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone

Silica colloidal hydrated

Yellow ferric oxide (E172).

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 months

6.4 Special precautions for storage:

Store at or below 25 °C. Protect from moisture. Keep tablets in the blister until required for use.

6.5 Nature and contents of container:

ALFUWIN XL is packed in printed aluminium foil and clear, colourless, rigid polyvinyl chloride (PVC) film blister packs inserted into an outer cardboard printed carton containing 30 tablets (3 blister strips of 10 tablets each).

6.6 Special precautions for disposal:

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION:

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1685

South Africa

8 REGISTRATION NUMBER(S):

41/5.2/0740

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