PROFESSIONAL INFORMATION FOR

XZALU

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

XZALU (40 mg soft gelatine capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40 mg Enzalutamide.

Contains sugar: Sorbitol 61, 671 mg per capsule.

For the full list of excipients, **see Section 6.1**.

3. PHARMACEUTICAL FORM

XZALU are soft gelatine capsules.

XZALU are Clear liquid filled in opaque, peach coloured, oblong shape, soft gelatin capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XZALU is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer (CRPC).

4.2 Posology and method of administration

Posology

The recommended dose of XZALU is 160 mg (four 40 mg capsules) orally as a single daily dose.

Special populations

Elderly patients

No dosage adjustment is necessary for elderly patients (**see section 5.2**).

Hepatic impairment

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Class A or B – **See section 5.2**). Caution is advised in patients with severe hepatic impairment (Child-Pugh class C – **See section 4.4**).

Renal impairment

No dosage adjustment is necessary for patients with mild or moderate renal impairment (**See section 5.2**). Caution is advised in patients with severe renal impairment or end stage renal disease (**see section 4.4**).

Paediatric population

There is no relevant use of this medicine in the paediatric population, as prostate cancer is not present in children and adolescents.

Method of administration:

XZALU soft gelatine capsules should be swallowed whole with water and can be taken with or without food.

If a patient miss taking XZALU at the usual time, the prescribed dose should be taken as close as possible to the usual time. If a patient misses a dose for a whole day, treatment should be resumed the following day with the usual daily dose.

4.3 Contraindications

XZALU is contra-indicated in:

- Patients with known hypersensitivity to enzalutamide or any of the excipients of XZALU listed in **section 6.1**.
- Women.

4.4 Special warnings and precautions for use

Risk of seizure

Caution should be used when administering XZALU to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism. In addition, the risk of seizures may be increased in patients receiving concomitant medicines that lower the seizure threshold. The decision to continue treatment in patients who develop seizure should be taken case by case.

Posterior reversible encephalopathy syndrome

There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving enzalutamide (**see section 4.8**). PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of XZALU in patients who develop PRES is recommended.

Concomitant use with other medicines

Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicines (**see section 4.5**). A review of concomitant medicines should therefore be conducted when initiating XZALU treatment. Concomitant use of XZALU with medicines that are sensitive substrates of many metabolising enzymes or transporters (**see section 4.5**) should generally be avoided if their therapeutic effect is of large importance to the patient, and

if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.

Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If XZALU is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin), additional International Normalised Ratio (INR) monitoring should be conducted (**see section 4.5**).

Renal impairment

Caution should be exercised in patients with severe renal impairment as XZALU has not been studied in this patient population.

Hepatic impairment

An increased half-life of enzalutamide has been observed in patients with severe hepatic impairment, possibly related to increased tissue distribution. The clinical relevance of this observation remains unknown. A prolonged time to reach steady state concentrations is however anticipated, and the time to maximum pharmacological effect as well as time for onset and decline of enzyme induction (**see section 4.5**) may be increased.

Androgen deprivation therapy may prolong the QT interval

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicines that might prolong the QT interval (**see section 4.5**), medical practitioners should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating XZALU.

Use with chemotherapy

The safety and efficacy of concomitant use of XZALU with cytotoxic chemotherapy has not been established. Co-administration of enzalutamide has no clinically relevant effect on the

pharmacokinetics of intravenous docetaxel (**see section 4.5**); however, an increase in the occurrence of docetaxel-induced neutropenia cannot be excluded.

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, rash, or face, tongue, lip, or pharyngeal oedema, have been observed with enzalutamide (**see section 4.8**).

Excipients

XZALU contains glycerol which may cause headache, stomach upset and diarrhoea.

XZALU contains sorbitol, patients with hereditary fructose intolerance (HFI) should not take/be given this medicine. Sorbitol may also cause gastrointestinal discomfort and a mild laxative effect.

4.5 interaction with other medicines and other forms of interaction

Potential for other medicines to affect enzalutamide exposure

CYP2C8 inhibitors and inducers

CYP2C8 plays an important role in the elimination of enzalutamide and in the formation of its active metabolite. Following oral administration of the strong CYP2C8 inhibitor gemfibrozil (600 mg twice daily) to healthy male subjects, the AUC of enzalutamide increased 4,26-fold while the C_{max} decreased by 18 %; the AUC and C_{max} of the active metabolite decreased by 25 % and-44 % respectively. Strong inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin) of CYP2C8 are to be avoided or used with caution during XZALU treatment.

If co-administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

CYP3A4 inhibitors and inducers

CYP3A4 plays a minor role in the metabolism of enzalutamide. Following oral administration of the strong CYP3A4 inhibitor itraconazole (200 mg once daily) to healthy male subjects, the AUC of enzalutamide increased by 1,41-fold while the C_{max} was essentially unaffected (decreased by 2 %); the AUC of the active metabolite increased by 1,21 fold while the C_{max} decreased by 14 %. No dose adjustment is necessary when XZALU is co-administered with inhibitors or inducers of CYP3A4.

CYP2C8 and CYP3A4 inducers

Following oral administration of the moderate CYP2C8 and strong CYP3A4 inducer rifampicin (600 mg once daily) to healthy male subjects, the AUC of enzalutamide plus the active metabolite decreased by 37 % while C_{max} remained unchanged. No dose adjustment is necessary when XZALU is co-administered with inducers of CYP2C8 or CYP3A4.

Potential for XZALU to affect exposure to other medicines

Enzyme induction

Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect. There is also a risk of increased formation of active metabolites. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C9, CYP2C19, and uridine 5'-diphospho glucuronosyltransferase (UGTs - glucuronide conjugating enzymes). The transport protein P-gp may also be induced, and probably other transporters as well, e.g. multidrug resistance-associated protein 2 (MRP2), breast cancer resistance protein (BCRP) and the organic anion transporting polypeptide 1B1 (OATP1B1).

XZALU is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of XZALU (160 mg daily) with single oral doses of sensitive CYP substrates

in prostate cancer resulted in an 86 % decrease in the AUC of midazolam (CYP3A4 substrate), a 56 % decrease in the AUC of S-warfarin (CYP2C9 substrate), and a 70 % decrease in the AUC of omeprazole (CYP2C19) substrate). Uridine 5'-diphospho-gluccuronosyltransferase (UGT1A1) may have been induced as well.

In a clinical study in patients with metastatic CRPC, enzalutamide (160 mg once daily) had no clinically relevant effect on the pharmacokinetics of intravenously administered docetaxel (75 mg/m^2 by infusion every 3 weeks). The AUC of docetaxel decreased by 12 % [geometric mean ratio (GMR) = 0,882 (90 % CI: 0,767, 1,02)] while C_{max} decreased by 4 % [GMR = 0,963 (90 % CI: 0,834, 1,11)].

Taken together, these results suggest that enzalutamide causes enzyme induction via activation of the nuclear pregnane receptor (PXR). Medicines with a narrow therapeutic range that are substrates of CYP3A4, CYP2C9, CYP2C19, and UGT1A1 should be used with caution when administered concomitantly with XZALU and may require dose adjustment to maintain therapeutic plasma concentrations.

Such substrates include, but are not limited to:

• Analgesics (e.g. fentanyl, tramadol).

• Antibiotics (e.g. clarithromycin, doxycycline).

• Anticancer medicines (e.g. cabazitaxel).

• Antiepileptics (e.g. phenobarbitone, carbamazepine, clonazepam, phenytoin, primidone, valproic acid).

• Antipsychotics (e.g. haloperidol).

• Antithrombotics (e.g. acenocoumarol, warfarin, clopidogrel).

• Betablockers (e.g. bisoprolol, propranolol).

• Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil).

• Cardiac glycosides (e.g. digoxin).

• Corticosteroids (e.g. dexamethasone, prednisolone).

• HIV antivirals (e.g. indinavir, ritonavir).

• Hypnotics (e.g. diazepam, midazolam, zolpidem).

• Immunosuppressant (e.g. tacrolimus).

• Proton pump inhibitor (e.g. omeprazole).

• Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin).

• Thyroid medicines (e.g. levothyroxine).

The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment, when steady-state plasma concentrations of enzalutamide are reached, although some induction effects may be apparent earlier. Patients taking medicines that are substrates of CYP2B6, CYP3A4, CYP2C9, CYP2C19 or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment and dose adjustment should be considered as appropriate. In consideration of the long half-life of enzalutamide (5.8 days see **section 5.2**), effects on enzymes may persist for one month longer after stopping XZALU.

CYP1A2 and CYP2C8 substrates

XZALU (160 mg once daily) did not cause a clinically relevant change in the AUC or C_{max} of caffeine (CYP1A2 substrate) or pioglitazone (CYP2C8 substrate) and no dose adjustment is indicated when a CYP1A2 orCYP2C8 substrate is co-administered with XZALU.

P-gp substrates

In vitro data indicate that enzalutamide may be an inhibitor of the efflux transporter P-gp. The effect of XZALU on P-gp substrates has not been evaluated *in vivo*; however, under conditions of clinical use, XZALU may be an inducer of P-gp via activation of PXR. Medicines with a narrow therapeutic range that are substrates of P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with XZALU and may require dose adjustment to maintain optimal plasma concentrations.

BCRP, MRP2, OAT3 and OCT1 substrates

In vitro data indicate that enzalutamide may be an inhibitor of breast cancer resistant protein (BCRP), organic anion transporter 3 (OAT3) and organic cation transporter 1 (OCT1) (systemically), as well as multidrug resistance-associated protein 2 (MRP2) at clinically relevant concentrations in the gastrointestinal wall during absorption. Thus, XZALU may increase the plasma concentrations of co-administered medicines that are BCRP, OAT3, OCT1 or MRP2 substrates (e.g. methotrexate) should be used with caution when administered concomitantly with XZALU and may require dose adjustments to maintain optimal plasma concentrations.

Medicines which prolong the QT interval

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of XZALU with medicines known to prolong the QT interval or medicines able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicines, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (**see section 4.4**).

Effect of food on XZALU exposure

Food has no clinically significant effect on the extent of exposure to enzalutamide.

4.6 Fertility, pregnancy and lactation

XZALU is contraindicated for use in women.

Contraception in males and females

It is not known whether XZALU or its metabolites are present in semen. A condom is required during and for 3 months after treatment with XZALU if the patient is engaged in sexual activity with a pregnant woman. If the patient engages in sexual intercourse with a woman of childbearing potential, a condom and another form of birth control must be used during and for 3 months after treatment. Studies in animals have shown reproductive toxicity.

Pregnancy

Considering the pharmacological consequences of androgen receptor signalling inhibition, maternal use of XZALU is expected to produce changes in hormone levels that could affect development of the foetus.

Breastfeeding

XZALU is not for use in women. It is unknown whether XZALU or its metabolites are excreted in human milk.

Fertility

Animal studies showed that enzalutamide affected the reproductive system in male rats and dogs.

4.7 Effects on ability to drive and use machines

XZALU has moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizure have been reported (**see section 4.8**). Patients should be advised of the potential risk of experiencing a psychiatric or neurological event while driving or operating machines. No studies to evaluate the effects of enzalutamide on the ability to drive and use machines have been conducted.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are asthenia/fatigue, hot flush, headache, fractures, and hypertension. Other important adverse reactions include fall, non-pathologic fractures, cognitive disorder, and neutropenia.

Seizure occurred in 0.4 % of enzalutamide-treated patients, 0.1 % of placebo-treated patients and 0.3 % in bicalutamide-treated patients.

Rare cases of posterior reversible encephalopathy syndrome have been reported in enzalutamide-treated patients (**see section 4.4**).

The following adverse effects have been classified as either being frequent, less frequent, or of an unknown frequency.

Blood and lymphatic system disorders

Less frequent: leukopenia, neutropenia.

Frequency unknown: thrombocytopenia.

Immune system disorders

Frequency unknown: face oedema, tongue oedema, lip oedema, pharyngeal oedema.

Psychiatric disorders

Frequent: anxiety.

Less frequent: visual hallucination.

Nervous system disorders

Frequent: headache, memory impairment, amnesia, disturbance in attention, restless legs syndrome.

Less frequent: cognitive disorder, seizure¥.

Frequency unknown: posterior reversible encephalopathy syndrome.

Cardiac disorders

Frequent: ischemic heart disease†.

Frequency unknown: QT-prolongation (**see sections 4.4 and 4.5**).

Vascular disorders

Frequent: hot flush, hypertension.

Gastrointestinal disorders

Frequency unknown: nausea, vomiting, diarrhoea.

Skin and subcutaneous tissue disorders

Frequent: dry skin, pruritus.

Frequency unknown: rash.

Musculoskeletal and connective tissue disorders

Frequent: fractures‡.

Frequency unknown: myalgia, muscle spasms, muscular weakness, back pain.

Reproductive system and breast disorder

Frequent: gynaecomastia.

General disorders and administration site conditions

Frequent: asthenia, fatigue.

Injury, poisoning and procedural Complications

Frequent: fall.

Adverse reactions identified post-marketing

Musculoskeletal and connective tissue disorders:

**Fractures

*myalgia, muscle spasms, muscular weakness, back pain.

Nervous System Disorders

*posterior reversible encephalopathy syndrome

* Spontaneous reports from post-marketing experience

** Includes all fractures with the exception of pathological fractures

¥ As evaluated by narrow Standardised MedDRA Queries (SMQs) of 'Convulsions' including convulsion, grand mal convulsion, complex partial seizures, partial seizures, and status epilepticus. This includes rare cases of seizure with complications leading to death.

† As evaluated by narrow SMQs of 'Myocardial Infarction' and 'Other Ischemic Heart Disease' including the following preferred terms observed in at least two patients in randomized placebo-controlled phase 3 studies: angina pectoris, coronary artery disease, myocardial infarctions, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischaemia, and arteriosclerosis coronary artery.

‡ Includes all preferred terms with the word 'fracture' in bones.

Description of selected adverse reactions

Seizure

Dose appears to be an important predictor of the risk of seizure.

The mechanism by which XZALU may lower the seizure threshold is not known but could be related to data from *in vitro* studies showing that enzalutamide and its active metabolite bind to and can inhibit the activity of the GABA-gated chloride channel.

Ischemic Heart Disease

In randomized placebo-controlled clinical studies, ischemic heart disease occurred in 2,5% of patients treated with enzalutamide plus ADT compared to 1,3 % patients treated with placebo plus ADT.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla Medpro (Pty) Ltd. via email: drugsafetysa@cipla.com

4.9 Overdose

There is no antidote for XZALU. In the event of an overdose, treatment with XZALU should be stopped and general supportive measures initiated taking into consideration the half-life of 5,8 days. Patients may be at increased risk of seizures following an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A. 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents – ENDOCRINE THERAPY

ATC code: L02BB04

Mechanism of action

Enzalutamide is an androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits binding of androgens to androgen receptors, inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor over expression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. Enzalutamide lacks androgen receptor agonist activity.

5.2 Pharmacokinetics properties

The pharmacokinetics of enzalutamide have been evaluated in prostate cancer patients and in healthy male subjects. The mean terminal half-life ($T_{1/2}$) for enzalutamide in patients after a single oral dose is 5,8 days (range 2,8 to 10,2 days), and steady state is achieved in approximately one month. With daily oral administration of approximate therapeutic doses, enzalutamide accumulates approximately 10,4-fold relative to a single dose. Daily fluctuations in plasma concentrations are low (peak to trough of 1,25). Clearance of enzalutamide is primarily via hepatic metabolism, producing an active metabolite that circulates at approximately the same plasma concentrations as enzalutamide.

Absorption

Maximum plasma concentrations (C_{max}) of enzalutamide in patients are observed 1 to 2 hours after administration. Based on a mass balance study in humans, oral absorption of enzalutamide is estimated to be at least 84,2 %. Enzalutamide is not a substrate of the efflux transporters P-gp or BCRP. At steady state, the mean C_{max} values for enzalutamide and its active metabolite are 16,6 µg/mL (23 % CV) and 12,7 µg/mL (30 % CV), respectively.

Food effect:

Food has no clinically significant effect on the extent of absorption.

Distribution

The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29 % CV). The volume of distribution of enzalutamide is greater than the volume of total body water, indicative of extensive extravascular distribution. Studies in rodents indicate that enzalutamide and its active metabolite can cross the blood brain barrier.

Enzalutamide is 97 % to 98 % bound to plasma proteins, primarily albumin. The active metabolite is 95 % bound to plasma proteins.

Biotransformation

Enzalutamide is extensively metabolised. There are two major metabolites in human plasma: N-desmethyl enzalutamide (active) and a carboxylic acid derivative (inactive). Enzalutamide is metabolised by CYP2C8 and to a lesser extent by CYP3A4/5 (**see section 4.5**), both of which play a role in the formation of the active metabolite. Enzalutamide is not metabolised *in vitro* by CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C18, CYP2C19, CYP2D6, or CYP 2E1.

In vitro studies show that enzalutamide and/or its active metabolite are inhibitors of CYP2C8 and CYP2C19, with lesser inhibitory effects on CYP2B6 and CYP2C9. Under conditions of clinical use, enzalutamide is a moderate inducer if CYP2C9 and CYP2C19 and has no clinically relevant effect on CYP2C8 (**see section 4.5**).

Elimination

The mean apparent clearance (CL/F) of enzalutamide in patients ranges from 0,520 and 0,564 L/h.

Following oral administration of 14C-enzalutamide, 84,6 % of the radioactivity is recovered by 77 days post dose: 71,0 % is recovered in urine (primarily as the inactive metabolite, with trace amounts of enzalutamide and the active metabolite), and 13,6 % is recovered in faeces (0,39 % of dose as unchanged enzalutamide).

Special populations

Renal impairment

No formal renal impairment study for enzalutamide has been completed. Based on a population pharmacokinetic analysis, no dose adjustment is necessary for patients with calculated creatinine clearance (CrCL) values ≥ 30 mL/min (estimated by the Cockcroft and Gault formula). Enzalutamide has not been evaluated in patients with severe renal impairment (CrCL < 30 mL/min) or end stage renal disease, and recommendations for treatment cannot

be made in that group of patients. It is unlikely that enzalutamide will be significantly removed by intermittent haemodialysis or continuous ambulatory peritoneal dialysis.

Hepatic impairment

The pharmacokinetics of enzalutamide were examined in subjects with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B respectively) as well as control subjects with normal hepatic function. Following a single oral dose of 160 mg enzalutamide, exposure parameters for enzalutamide increased by approximately 24 % and 29 % in subjects with mild and moderate hepatic impairment respectively, compared to healthy control subjects. Hepatic impairment had similar minimal effects on the AUC of the active metabolite. Overall, the results indicate that no dose adjustment is necessary for patients with baseline mild or moderate impairment.

Enzalutamide has not been evaluated in patients with baseline severe hepatic impairment (Child-Pugh C). No recommendations can be made with respect to dose for those patients.

Elderly

Based on the population pharmacokinetic analysis for age, no dose adjustment is necessary in the elderly.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Butyl Hydroxy Anisole
- Butyl Hydroxy Toluene
- Caprylocaproyl Polyoxylglycerides (Labrasol ALF)
- Gelatin (Gelita RXL)
- Glycerin
- Sorbitol sorbitan solution (Sorbitol special)
- Medium Chain Triglyceride (Miglyol 812 N)

- Purified water
- Titanium dioxide
- Ferric oxide Red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep container tightly closed.

6.5 Nature and contents of container

XZALU is packed in HDPE bottle with a child resistant cap containing 120’s capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du cap

Mispel street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

56/26/0921.920

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 March 2023

10. DATE OF REVISION OF THE TEXT

Not applicable.