1.3.1.1 Approved Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZILADE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZILADE:

Each capsule contains 40 mg Enzalutamide.

Contains sugar: 52.4 mg sorbitol. See section 6.1 full list of excipients.

3. PHARMACEUTICAL FORM

ZILADE:

White to off white, oblong shape soft gelatine capsule imprinted in black ink with “E40” containing pale yellow to yellow colour solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ZILADE 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 ZILADE is 160 mg (four 40 mg capsules) as a single oral daily dose.

SPECIAL POPULATIONS

Elderly patients

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

Patients with hepatic impairment

No dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B; see section 5.2). Caution is advised in patients with severe hepatic impairment as an increased half-life of enzalutamide has however been observed (Child-Pugh Class C, see section 4.4).

Patients with renal impairment

No dose 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

ZILADE should be swallowed whole with water, and can be taken with or without food.

If a patient misses taking ZILADE 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

Hypersensitivity to enzalutamide or to any of the excipients.

Not to be used in women.

4.4. Special warnings and precautions for use

Risk of Seizure

Caution should be used in administering ZILADE 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 seizure may be increased in patients receiving concomitant medicines that lower the seizure threshold.

Posterior reversible encephalopathy syndrome

There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients

receiving ZILADE (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 ZILADE in patients who develop PRES is recommended.

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 medicinal products that might prolong the QT interval (see section 4.5) medical practitioners should assess the risk including the potential for Torsade de pointes prior to initiating ZILADE.

Renal Impairment

Caution is required in patients with severe renal impairment as ZILADE has not been studied in this patient population.

Hepatic Impairment

Caution is required in patients with severe hepatic impairment as ZILADE has not been studied in this patient population.

Excipients

ZILADE contains sorbitol (E420). Patients with the rare hereditary condition of sorbitol intolerance should not take ZILADE.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicines to affect enzalutamide exposures:

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 ZILADE treatment. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. 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 1 ,21-fold while the C_{max} decreased by 14 %. No dose adjustment is necessary when ZILADE is co-administered with inhibitors or inducers of CYP3A4.

Potential for ZILADE to affect exposures to other medicines:

Enzyme induction

ZILADE is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of ZILADE (160 mg once daily) with single oral doses of sensitive CYP substrates in prostate cancer patients 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-glucuronosyltransferase (UGT1A1) may have been induced as well.

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 UGT1A 1 should be used with caution when administered concomitantly with ZILADE and may require dose adjustment to maintain therapeutic plasma concentrations.

Such substrates include, but are not limited to:

- Macrolide antibiotics (e.g. clarithromycin)
- Benzodiazepines (e.g. diazepam, midazolam)
- Immune modulators (e.g. ciclosporin, tacrolimus)

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

- Anti-epileptics (e.g. phenobarbitone, phenytoin)

- Coumarins (e.g. warfarin)

- Certain anticancer agents (e.g. cabazitaxel, irinotecan, sunitinib)

In consideration of the long half-life of enzalutamide (5,8 days, section Pharmacokinetic Properties), effects on enzymes may persist for one month or longer after stopping ZILADE.

CYP2C8 substrates

ZILADE (160 mg once daily) did not cause a clinically relevant change in the AUC of pioglitazone (CYP2C8 substrate) and no dose adjustment is indicated when a CYP2C8 substrate is co-administered with ZILADE.

P -gp substrates

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

BCRP and MRP2 substrates

In vitro data indicate that enzalutamide may be an inhibitor of breast cancer resistant protein (BCRP) and multidrug resistance-associated protein '2 (MRP2) at clinically relevant concentrations in the gastrointestinal wall during absorption. Thus, ZILADE may increase the plasma concentrations of co-administered medicines that are BCRP or MRP2 substrates. The effects of ZILADE on BCRP and MRP2 substrates have not been evaluated in vivo. Oral medicines with a narrow therapeutic range that are BCRP or MRP2 substrates (e.g. methotrexate) should be used with caution when administered concomitantly with ZILADE and may require dose adjustments to maintain optimal plasma concentrations.

Medicinal products which prolong the QT interval

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

4.6 Fertility, pregnancy and lactation

ZILADE is contraindicated for use by women.

Contraception in males and females

It is not known whether ZILADE or its metabolites are present in semen. A condom is required during and for ~~3~~ 4 months after treatment with ZILADE 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 4 months after treatment.

The recommended duration of contraception in female patients should be until the end of relevant systemic exposure to the genotoxic compound incl. potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 6 months. The duration of folliculogenesis is described as 6 to 12 months. The 7-month contraception recommendation for genotoxic pharmaceuticals after cessation of therapy covers the growth and maturation phase of folliculogenesis and is expected to allow elimination of most damaged follicles and oocytes

Pregnancy

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

Lactation

ZILADE is not for use in women.

It is unknown whether ZILADE or its metabolites are excreted in human milk.

Fertility

The recommended duration of contraception in male patients should be until the end of relevant systemic exposure to the genotoxic compound incl. potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 90 days. Use of contraception for a period of 4 months after cessation of therapy will minimize the risk of adverse embryo-fetal effects from genotoxic pharmaceuticals. The 4 months cover the period of spermatogenesis and the epididymal maturation.

4.7 Effects on ability to drive and use machines

ZILADE may influence a patient's ability to drive and operate machinery. Patients should be warned to ascertain their individual side effect profile before driving or using machinery.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent adverse reactions seen are asthenia/fatigue, hot flushes, headache and hypertension. Other important adverse reactions include falls, non- pathologic fractures, cognitive disorder, and neutropenia.

Seizure occurred in 0,4 % of ZILADE - treated patients and in 0,1 % of placebo-treated patients.

Adverse reactions in clinical trials are listed below by frequency category.

Frequency categories are defined as follows:

Frequent – vey common, common;

Less frequent – uncommon, rare, very rare;

Frequency unknown – not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

b. Adverse Reactions Identified in Clinical Trials System

System organ class	Frequency and adverse reaction
Blood and lymphatic system disorders	Less frequent: leucopenia, neutropenia
General Disorders	Frequent: asthenia/fatigue
Psychiatric Disorders	Frequent: anxiety Less frequent: visual hallucinations
Nervous System Disorders	Frequent: headache, memory impairment, amnesia, disturbance in attention, restless legs syndrome Less common: cognitive disorder, seizure
Reproductive system and breast disorder	Frequent: gynaecomastia
Vascular Disorders	Frequent: hot flushes, hypertension
Skin and Subcutaneous Tissue Disorders	Frequent: dry skin, pruritus
Injury, Poisoning and Procedural Complications	Frequent: falls

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

c. Description of selected adverse reactions

Seizure

Seizure In controlled clinical studies, 10 patients (0.5%) experienced a seizure out of 2051 patients treated with a daily dose of 160 mg enzalutamide, whereas one patient (< 0.1%) receiving placebo and one patient (0.3%) receiving bicalutamide, experienced a seizure. Dose appears to be an important predictor of the risk of seizure, as reflected by preclinical data, and data from a dose-escalation study. In the controlled clinical studies, patients with prior seizure or risk factors for seizure were excluded.

The mechanism by which ZILADE 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.

d. Other special population

Elderly patients

No overall differences in safety or effectiveness were observed between the elderly patients and younger patients.

f. 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 to SAHPRA via The '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications:

https://www/sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no antidote for enzalutamide. In the event of an overdose, treatment with enzalutamide 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

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. Pharmacokinetic properties

The pharmacokinetics of enzalutamide have been evaluated in prostate cancer patients and in healthy male subjects. The mean terminal half-life (t1/2) 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 ratio of 1,25). Clearance of enzalutamide is primarily via hepatic metabolism, producing an active metabolite that circulates at approximately the same plasma concentration 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 has no clinically significant effect on the extent of absorption. In clinical trials, enzalutamide was administered without regard to food.

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. There was no protein binding displacement between enzalutamide and other highly bound drugs (warfarin, ibuprofen and salicylic acid) in vitro.

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 Interactions), both of which play a role in the formation of the active metabolite. Enzalutamide is not metabolised in vitro by CYP1A 1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2CI8, CYP2CI9, CYP2D6, or CYP2E1.

In vitro studies show that enzalutamide and/or its active metabolite are inhibitors of CYP2C8 and CYP2CI9, with lesser inhibitory effects on CYP2B6 and CYP2C9. Under conditions of clinical use, enzalutamide is a moderate inducer of CYP2C9 and CYP2C19 and has no clinically relevant effect on CYP2C8 (see Interactions).

Elimination

The mean apparent clearance (CL/F) of enzalutamide in patients ranges from 0,520 and 0,584 L/h. Following oral administration of I4C-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 impaired patients

No formal renal impairment study for enzalutamide has been completed. Patients with serum creatinine > 177 µmol/L (2 mg/dl) were excluded from clinical trials. 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 impaired patients

The pharmacokinetics of enzalutamide were examined in subjects with baseline mild (N=6) or moderate (N=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 14 matched control subjects with normal hepatic function. Following a single oral 160 mg dose of 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 hepatic impairment. Patients with baseline severe hepatic impairment (ChildPugh C) were excluded from clinical trials. No recommendations can be made with respect to dose for those patients.

Elderly

Of the 1671 patients in the pivotal clinical trials who received enzalutamide, 1261 patients (75 %) were 65 years and over and 516 patients (31 %) were 75 years and over. No overall differences in safety or effectiveness were observed between these older patients and younger patients. Based on the population pharmacokinetic analysis for age, no dose adjustment is necessary in the elderly.

5.3 Preclinical safety data

Not applicable

Environmental Risk Assessment

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Medicament Preparation

Caprylocaproyl Polyoxylglycerides Ph. Eur.## (Labrasol ALF)

Butylhydroxyanisole Ph. Eur.

Butylhydroxytoluene Ph. Eur.

Gelatine preparation:

Gelatine (GELATIN 160 BLOOM) Ph. Eur.

Sorbitol Sorbitan Solution Ph. Eur. (POLYSORB 85/70/00)

Glycerol Ph. Eur. (OPTIM GLYCERIN 99.7%)

Titanium dioxide Ph. Eur. (KRONOS 1171)

Purified water Ph. Eur

Imprinting:

Opacode WB Black NS-78-17821 IH:

Purified Water (USP, PhEur, JP)

Ferrosoferric Oxide (NF)/BLACK IRON OXIDE (JPE)

Isopropyl Alcohol (USP, PhEur, JP)

Propylene Glycol (USP, FCC, Ph.Eur, JP, JSFA)

HPMC 2910/Hypromellose (USP, PhEur, JP)

Colourants

Titanium dioxide & Ferrosoferric Oxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25°C.

KEEP OUT OF REACH OF CHILDREN.

Keep in the original container until required for administration.

6.5 Nature and contents of container

Blister Pack

a) Clear PVC film coated with 51 micron Aclar film - Aluminium foil blister pack:

Blister pack comprises of clear 250 micron PVC film coated with 51 micron Aclar film as the forming material and 25 micron Aluminium foil with 7 g/m2 heat seal lacquer as the lidding material.

Enzalutamide Capsules 40 mg packed in above blisters shall be further packed in pre-printed cartons with professional information according to the approved pack size.

Pack sizes: 112

Enzalutamide Capsules 40 mg 4 x 28's (Blister)

b) Clear PVC/PVDC film- Aluminium foil blister pack:

Blister pack comprises of clear 250 micron PVC film coated with 90 gsm PVDC as the forming material and 25 micron Aluminium foil with 7 g/m2 heat seal lacquer as the lidding material.

Enzalutamide Capsules 40 mg packed in above blisters shall be further packed in pre-printed cartons with professional information according to the approved pack size.

Pack sizes: 112

Enzalutamide Capsules 40 mg 4 x 28's (Blister)

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER

55/26/0176.174

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF TEXT

24 APRIL 2024