SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

XTANDI 40 mg soft gelatine capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 40 mg of enzalutamide.

Contains sugar: Each capsule contains 57,8 mg sorbitol.

For the full list of excipients, (see section 6.1).

3. PHARMACEUTICAL FORM

Soft capsule.

Opaque white to off-white oblong soft gel capsule, printed with “ENZ” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xtandi is indicated:

- as monotherapy or in combination with androgen deprivation therapy (ADT) for the treatment of adult men with high-risk biochemical recurrent (BCR) non-metastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage-radiotherapy.
- in combination with androgen deprivation therapy (ADT) for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC).
- for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC).
- for the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

- for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

4.2 Posology and method of administration

Posology

The recommended dose of Xtandi is 160 mg (four 40 mg capsules) as a single oral daily dose. Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients with CRPC or mHSPC who are not surgically castrated. Patients with high-risk BCR nmHSPC may be treated with Xtandi with or without a LHRH analogue. For patients who receive Xtandi with or without a LHRH analogue, treatment can be suspended if PSA is undetectable (< 0,2 ng/mL) after 36 weeks of therapy. Treatment should be reinitiated when PSA has increased to ≥ 2,0 ng/mL for patients who had prior radical prostatectomy or ≥ 5,0 ng/mL for patients who had prior primary radiation therapy. If PSA is detectable (≥ 0,2 ng/mL) after 36 weeks of therapy, treatment should continue.

If a patient misses taking Xtandi 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.

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at a reduced dose (120 mg or 80 mg) if warranted. The patient then requires frequent monitoring for the return of that adverse reaction.

Concomitant use with strong CYP2C8 inhibitors

The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of Xtandi should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, the Xtandi dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor (see section 4.5).

Special Populations

Elderly patients

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

Hepatic impairment

No dose adjustment is necessary for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C, respectively). An increased drug half-life has however been observed in patients with severe hepatic impairment (see sections 4.4 and 5).

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

Xtandi is for oral use. The soft capsules should not be chewed, dissolved or opened but should be swallowed whole with water, and can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Uncontrolled seizures (see section 4.4).

Not to be used in women.

4.4 Special warnings and precautions for use

Risk of Seizure:

Caution should be used in administering Xtandi 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. Permanently discontinue Xtandi in patients who develop a seizure during treatment (see section 4.3).

Posterior reversible encephalopathy syndrome:

There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving Xtandi (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 Xtandi in patients who develop PRES is recommended.

Second Primary Malignancies

Cases of second primary malignancies have been reported in patients treated with enzalutamide in clinical studies. In phase 3 clinical studies, the most frequently reported events in enzalutamide treated patients, and greater than placebo, were bladder cancer (0,3 %), adenocarcinoma of the colon (0,2 %), transitional cell carcinoma (0,2 %) ,and malignant melanoma (0,2 %).

Patients should be advised to promptly seek the attention of their healthcare provider if they notice signs of gastrointestinal bleeding, macroscopic haematuria, or other symptoms such as dysuria or urinary urgency develop during treatment with enzalutamide.

Renal Impairment

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

Severe Hepatic Impairment

An increased drug half-life has been observed in patients with severe hepatic impairment, possibly related to increased tissue distribution. 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.

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 Xtandi treatment. Concomitant use of Xtandi with medicines that are sensitive substrates of many metabolising enzymes or transporters (see section 4.5) should 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 should be avoided. If Xtandi 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).

Recent cardiovascular disease

The phase 3 studies excluded patients with recent myocardial infarction (in the past 6 months) or unstable angina (in the past 3 months), New York Heart Association Class (NYHA) III or IV heart failure except if Left Ventricular Ejection Fraction (LVEF) ≥ 45 %, bradycardia or uncontrolled hypertension. This should be taken into account if Xtandi is prescribed in these patients.

Androgen deprivation therapy may prolong the QT interval

Androgen deprivation, as with Xtandi 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 Xtandi (see section 4.5).

Use with chemotherapy

The safety and efficacy of concomitant use of Xtandi with cytotoxic chemotherapy has not been established. Co-administration of Xtandi 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 and pharyngeal oedema have been observed with enzalutamide. Advise patients who experience any symptoms of hypersensitivity to discontinue enzalutamide and promptly seek medical care. (see section 4.8). Severe cutaneous adverse reactions (SCARs) have been reported with Xtandi. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

Xtandi as monotherapy in patients with high-risk BCR nmHSPC

Results of the EMBARK study suggest that Xtandi as monotherapy and in combination with androgen deprivation therapy are not equivalent treatment options in patients with high-risk BCR nmHSPC (see section 4.8). Xtandi in combination with androgen deprivation therapy is considered the preferred treatment option except for cases in which the addition of androgen deprivation therapy may result in unacceptable toxicity or risk.

Excipients

Xtandi contains 57.8 mg sorbitol (E420) per soft capsule.

4.5 Interaction with other medicines and other forms of interaction

Potential for other medicines to affect enzalutamide exposures:

CYP2C8 inhibitors

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 by 326 % while the C_{max} decreased by 18 %. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 77 % while C_{max} decreased by 19 %. Strong inhibitors (e.g. gemfibrozil) of CYP2C8 are to be avoided or used with caution during enzalutamide treatment. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily (see section 4.2).

CYP3A4 inhibitors

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 41 % while the C_{max} was unchanged. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 27 % while C_{max} was again unchanged. No dose adjustment is necessary when Xtandi is co-administered with inhibitors of CYP3A4.

CYP2C8 and CYP3A4 inducers

Following oral administration of the moderate CYP2C8 and strong CYP3A4 inducer rifampin (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 Xtandi is co-administered with inducers of CYP2C8 or CYP3A4.

Potential for Xtandi to affect exposures 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). Some transporters may also be induced, e.g. multidrug resistance-associated protein 2 (MRP2) and the organic anion transporting polypeptide 1B1 (OATP1B1).

In vivo studies have shown that Xtandi is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of Xtandi (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. In a clinical study in patients with metastatic CRPC, Xtandi (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)].

Interactions with certain medicines that are eliminated through metabolism or active transport are expected. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicines are to be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.

Groups of medicines that can be affected include, but are not limited to:

- Analgesics (e.g. fentanyl, tramadol)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anticancer agents (e.g. cabazitaxel)
- Anticoagulants (e.g. warfarin)
- Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- 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)
- Immunosuppressants (e.g. tacrolimus)
- Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

The full induction potential of Xtandi 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 or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicine may be necessary when stopping enzalutamide treatment.

CYP1A2 and CYP2C8 substrates

Xtandi (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). The AUC of pioglitazone increased by 20 %

while C_{max} decreased by 18 %. The AUC and C_{max} of caffeine decreased by 11 % and 4 %, respectively. No dose adjustment is indicated when a CYP1A2 or CYP2C8 substrate is co-administered with Xtandi.

P-gp substrates

In vitro data indicate that enzalutamide may be an inhibitor of the efflux transporter P-gp. A mild inhibitory effect of enzalutamide, at steady-state, on P-gp was observed in a study in patients with prostate cancer that received a single oral dose of the probe P-gp substrate digoxin before and concomitantly with enzalutamide (concomitant administration followed at least 55 days of once daily dosing of 160 mg enzalutamide). The AUC and C_{max} of digoxin increased by 33% and 17%, respectively. Medicines with a narrow therapeutic range that are substrates for P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with Xtandi and may require dose adjustment to maintain optimal plasma concentrations.

BCRP substrates

At steady-state, enzalutamide did not cause a clinically meaningful change in exposure to the probe breast cancer resistance protein (BCRP) substrate rosuvastatin in patients with prostate cancer that received a single oral dose of rosuvastatin before and concomitantly with enzalutamide (concomitant administration followed at least 55 days of once daily dosing of 160 mg enzalutamide). The AUC of rosuvastatin decreased by 14% while C_{max} increased by 6%. No dose adjustment is necessary when a BCRP substrate is co-administered with Xtandi.

MRP2, OAT3 and OCT1 substrates

Based on *in vitro* data, inhibition of MRP2 (in the intestine), as well as organic anion transporter 3 (OAT3) and organic cation transporter 1 (OCT1) (systemically) cannot be excluded. Theoretically, induction of these transporters is also possible, and the net effect is presently unknown.

Medicines which prolong the QT interval

Since androgen deprivation, as with Xtandi treatment may prolong the QT interval, the concomitant use of Xtandi 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) antidysrhythmic medicines, methadone, moxifloxacin, antipsychotics, etc. should be used with caution and the patient should be monitored (see section 4.4).

Effect of Food on Enzalutamide Exposures:

Food has no clinically significant effect on the extent of exposure to enzalutamide. In clinical trials, Xtandi was administered without regard to food.

4.6 Fertility, pregnancy and lactation

Xtandi is contraindicated for use by women.

Contraception in males and females

A condom is required during and for 3 months after treatment with Xtandi 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.

Pregnancy

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

Lactation

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

Fertility

Based on findings in animal studies, enzalutamide may impair fertility in males of reproductive potential, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of Xtandi.

4.7 Effects on ability to drive and use machines

Xtandi may have 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 warned to ascertain their individual side effect profile before driving or using machinery.

4.8 Undesirable effects

The most common adverse reactions seen are asthenia/fatigue, hot flushes, hypertension, fractures, and fall. Other important adverse reactions include ischemic heart disease and seizure.

Seizure occurred in 0,6 % of Xtandi-treated patients, 0,1 % of placebo-treated patients and 0,3 % of bicalutamide-treated patients (see section 4.4).

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

Adverse reactions in clinical trials are listed below by frequency category. Frequency categories are defined as follows:
Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Adverse reactions identified in controlled clinical trials and post-marketing

MedDRA System organ class	Adverse reaction and frequency
Blood and lymphatic system disorders	Uncommon: leucopenia, neutropenia Not known*: thrombocytopenia
Immune system disorders	Not known*: face oedema, tongue oedema, lip oedema, pharyngeal oedema

MedDRA System organ class	Adverse reaction and frequency
Psychiatric disorders	Common: anxiety Uncommon: visual hallucination
Nervous system disorders	Common: headache, memory impairment, amnesia, disturbance in attention, dysgeusia, restless legs syndrome, cognitive disorder Uncommon: seizure¥ Not known*: posterior reversible encephalopathy syndrome
Cardiac disorders	Common: ischemic heart disease† Not known*: QT-prolongation (see sections 4.4 and 4.5)
Vascular disorders	Very common: hot flush, hypertension
Gastrointestinal disorders	Not known*: nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Common: dry skin, pruritus Not known*: erythema multiforme, rash
Musculoskeletal and connective tissue disorders	Very common: fractures‡ Not known*: myalgia, muscle spasms, muscular weakness, back pain
Reproductive system and breast disorder	Common: gynaecomastia, nipple pain#, breast tenderness#
General disorders and administration site conditions	Very common: asthenia, fatigue
Injury, poisoning and procedural complications	Very common: fall

* Spontaneous reports from post-marketing experience.

¥ As evaluated by narrow 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.

Adverse reactions for enzalutamide as monotherapy.

Description of selected adverse reactions

Seizure

In controlled clinical studies, 31 patients (0,6 %) experienced a seizure out of 5110 patients treated with a daily dose of 160 mg Xtandi. Dose appears to be an important predictor of the risk of seizure. In the controlled clinical studies, patients with prior seizure or risk factors for seizure were excluded.

In a single-arm trial to assess incidence of seizure in patients with predisposing factors for seizures, 8 of 366 (2,2 %) patients treated with Xtandi experienced as seizure. The median duration of treatment was 9,3 months.

The mechanism by which Xtandi 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.

Ischaemic Heart Disease

In randomised placebo-controlled clinical studies, ischaemic heart disease occurred in 3,5 % of patients treated with enzalutamide plus ADT compared to 2 % of patients treated with placebo plus ADT. Fourteen (0,4 %) patients treated with enzalutamide plus ADT and 3 (0,1 %) patients treated with placebo plus ADT had an ischemic heart disease event that led to death.

In the EMBARK study, ischemic heart disease occurred in 5,4% of patients treated with enzalutamide plus leuprolide and 9% of patients treated with enzalutamide as monotherapy. No patients treated with enzalutamide plus leuprolide and one (0,3%) patient treated with enzalutamide as monotherapy had an ischemic heart disease event that led to death.

Gynaecomastia

In the EMBARK study, gynaecomastia (all grades) was observed in 29 of 353 patients (8,2%) who were treated with enzalutamide plus leuprolide and 159 of 354 patients (44,9%) who were treated with enzalutamide as monotherapy. Grade 3 or higher gynaecomastia was not observed in any patients who were treated with enzalutamide plus leuprolide, and was observed in 3 patients (0,8%) who were treated with enzalutamide as monotherapy.

Nipple pain

In the EMBARK study, nipple pain (all grades) was observed in 11 of 353 patients (3,1%) who were treated with enzalutamide plus leuprolide and 54 of 354 patients (15,3%) who were treated with enzalutamide as monotherapy. Grade 3 or higher nipple pain was not observed in any patients who were treated with enzalutamide plus leuprolide or with enzalutamide as monotherapy.

Breast tenderness

In the EMBARK study, breast tenderness (all grades) was observed in 5 of 353 patients (1,4%) who were treated with enzalutamide plus leuprolide and 51 of 354 patients (14,4%) who were treated with enzalutamide as monotherapy. Grade 3 or higher breast tenderness was not observed in any patients who were treated with enzalutamide plus leuprolide or with enzalutamide as monotherapy.

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 SAHPRA via the “6.04 Adverse Drugs Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/index/8.

4.9 Overdose

There is no antidote for Xtandi. In the event of an overdose, stop treatment with Xtandi and initiate general supportive measures 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

Pharmacotherapeutic group: hormone antagonists and related agents, anti-androgens.

ATC code: L02BB04

South African Pharmacological classification: A.26 Cytostatic Agents

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 ($t_{1/2}$) 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 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 %; coefficient of variation [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 metabolized. There are two major metabolites in human plasma: N-desmethyl enzalutamide (active) and a carboxylic acid derivative (inactive). Enzalutamide is metabolized 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. *In vitro*, N-desmethyl enzalutamide is metabolized to the carboxylic acid metabolite by carboxylesterase 1, which also plays a minor role in the metabolism of enzalutamide to the carboxylic acid metabolite. N-desmethyl enzalutamide was not metabolized by CYPs *in vitro*.

Under conditions of clinical use, enzalutamide is a strong inducer of CYP3A4, a moderate inducer of 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 ^{14}C-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. Patients with serum creatinine > 177 µmol/L (2 mg/dL) were excluded from clinical studies. 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 can not 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

Hepatic impairment did not have a pronounced effect on the total exposure to enzalutamide or its active metabolite. In patients with severe hepatic impairment the half-life of enzalutamide was doubled to 10,4 days compared with healthy controls.

The pharmacokinetics of enzalutamide were examined in subjects with baseline mild (N=6), moderate (N=8) or severe (N=8) hepatic impairment (Child-Pugh Class A B or C, respectively) and in 22 matched control subjects with normal hepatic function. Following a single oral 160 mg dose of enzalutamide, exposure parameters for enzalutamide increased by 5 % and 24 % respectively and the AUC and Cmax of enzalutamide in subjects with moderate impairment increased by 29 % and decreased by 11 % and the AUC and C_{max} of enzalutamide in subjects with severe impairment increased by 5 % and decreased by 41 %, respectively, compared to healthy control subjects. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC and C_{max} in subjects with mild impairment increased by 14 % and 19 %, respectively, the AUC and C_{max} in subjects with moderate impairment increased by 14 % and decreased by 17 %, respectively, and the AUC and C_{max} in subjects with severe hepatic impairment increased by 34 % and decreased by 27 %, respectively, compared to healthy control subjects.

Elderly

Of the 5110 patients in the controlled clinical trials who received enzalutamide, 3988 patients (78 %) were 65 years and over and 1703 patients (33 %) 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents:

Butylhydroxyanisole (BHA)(E320), butylhydroxytoluene (BHT)(E321), caprylocaproyl macrogolglycerides.

Capsule Shell:

Gelatin, glycerol, sorbitol sorbitan solution, titanium dioxide (E171).

Black Printing Ink containing:

Macrogol 400, iron oxide black (E172), polyvinyl acetate phthalate, propylene glycol.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

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

Xtandi is presented as PVC/PCTFE/Al laminate blister trays containing 28 capsules in 7 blister wells. Each blister well contains 4 capsules (1 daily dose). These blister trays are glued into cardboard wallets to form an inseparable unit. Four wallet/blister trays are packaged as a 112 capsule carton. This provides four weeks' supply.

6.6 Special precautions for disposal and other handling

Xtandi should not be handled by persons other than the patient or his caregivers. Based on its mechanism of action and embryo-foetal toxicity observed in mice, Xtandi may harm a developing foetus. Women who are on may become pregnant should not be handle damaged or opened Xtandi capsules without protection, e.g. gloves.

Any unused medicinal product or waste material shold be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Astellas Pharma (Pty) Ltd, 7 Mirage Road, Bedfordview, 2007, South Africa

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8. REGISTRATION NUMBER

48/26/0404

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 September 2016

10. DATE OF REVISION OF THE TEXT

31 July 2024