Applicant : Eurolab (Pty) Ltd
Proprietary name : Enzutix
Dosage form and strength : Soft capsules, 40 mg
Date of submission : 12 May 2022
Approval date : 24 January 2023

APPROVED PROFESSIONAL INFORMATION FOR ENZUTIX

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ENZUTIX 40 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 40 mg of enzalutamide.

Each soft capsule contains 91,6 mg sorbitol.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule.

White to off-white opaque, oblong-shaped soft gelatine capsule containing colourless to slightly yellow, transparent liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The recommended dose of **ENZUTIX** is 160 mg (4 x 40 mg capsules) as a single oral daily dose.

Special Populations

Elderly

No dose adjustment is necessary for elderly patients (see section 5.1).

Hepatic impairment

No dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B, respectively. 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)).

Renal impairment

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

Paediatric population

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

Method of administration

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

If a patient misses taking a dose 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 an entire 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 listed in section 6.1.

ENZUTIX is not for use in women (see sections 4.6 and 6.6).

4.4 Special warnings and precautions for use

Risk of seizure

Use of enzalutamide has been associated with seizure (see section 4.8). The risk of seizure may be increased in patients receiving concomitant medicines that lower the seizure threshold. Caution should be used in 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. The decision to continue treatment in patients who develop seizure should be taken on an individual basis.

Posterior reversible encephalopathy syndrome

There have been reports of posterior reversible encephalopathy syndrome (PRES) (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). Treatment discontinuation is recommended in patients who develop PRES.

Concomitant use with other medicines

Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicines (see examples in section 4.5). A review of concurrent medicines should therefore be conducted with enzalutamide treatment initiation. Concomitant use of enzalutamide with medicines that are sensitive substrates of many metabolising enzymes or transporters 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 (see section 4.5).

Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If **ENZUTIX** 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 is required in patients with severe renal impairment as enzalutamide has not been studied in this patient population.

Severe hepatic impairment

Caution is required in patients with severe 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 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.

Recent cardiovascular disease

Phase 3 studies excluded patients (there is no data on the use in 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 consideration when **ENZUTIX** is prescribed for these patients.

Androgen deprivation therapy may prolong the QT interval

In patients with a history of or risk factors for QT prolongation and in patients receiving concurrent 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 enzalutamide treatment.

Use with chemotherapy

The safety and efficacy of concomitant use of **ENZUTIX** 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

ENZUTIX contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take **ENZUTIX**.

4.5 Interactions 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. Studies documented following oral administration of strong CYP2C8 inhibitor gemfibrozil (600 mg twice daily) to healthy male subjects, the AUC of enzalutamide increased by 326 % while C_{max} of enzalutamide 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, if possible, or used with caution during enzalutamide treatment.

CYP3A4 inhibitors

CYP3A4 plays a minor role in the metabolism of enzalutamide. Studies documented 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 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 **ENZUTIX** is co-administered with CYP3A4 inhibitors.

CYP2C8 and CYP3A4 inducers

Studies documented following oral administration of 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 ENZUTIX is co-administered with inducers of CYP3A4.

<u>Potential for enzalutamide to affect exposures to other medicines</u>

Enzyme induction

Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many medicines 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-glucuronosyl-transferase (UGTs - glucuronide conjugating enzymes). The transport protein P-gp may also be induced, and probably other

transporters including multidrug resistance-associated protein 2 (MRP2), breast cancer resistance protein (BCRP) and the organic anion transporting polypeptide 1B1 (OATP1B1).

In vivo studies have shown that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of enzalutamide (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). UGT1A1 may have been induced as well.

Studies in patients with metastatic CRPC, enzalutamide (160 mg once daily) documented 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 %.

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.

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, irinotecan, sunitinib)
- Antiepileptics (e.g. carbamazepine, clonazepam, phenobarbitone, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Antithrombotics (e.g. 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. ciclosporin, tacrolimus)
- Proton pump inhibitor (e.g. omeprazole)
- Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

Medicines with a narrow therapeutic range that are substrates of CYP3A4, CYP2C9, CYP2C19, and UGT1A1 should be used with caution when administered concomitantly with **ENZUTIX** and may require dose adjustment to maintain therapeutic plasma concentrations.

The full induction potential of enzalutamide may not occur until approximately 1 month after treatment initiation, 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 **ENZUTIX** treatment and dose adjustment should be considered as appropriate.

In consideration of the long half-life of enzalutamide of 5,8 days (see section 5.2), effects on enzymes may persist for one month or longer after enzalutamide treatment discontinuation. A gradual dose reduction of the concomitant medicine may be necessary when stopping enzalutamide treatment.

The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.

CYP1A2 and CYP2C8 substrates

Enzalutamide (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 **ENZUTIX**.

P-gp substrates

In vitro data indicate that enzalutamide may be an inhibitor of the efflux transporter P-gp. The effect of enzalutamide on P-gp substrates has not been evaluated *in vivo*; however, under conditions of clinical use, enzalutamide may be an inducer of P-gp via activation of the nuclear pregnane receptor (PXR). 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 concurrently with **ENZUTIX** and may require dose adjustment to maintain optimal plasma concentrations.

BCRP, MRP2, OAT3 and OCT1 substrates

Based on *in vitro* data, inhibition of BCRP and 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. **ENZUTIX** may increase the plasma concentrations of co-administered medicines that are BCRP or MRP2 substrates. The effects of enzalutamide 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 concurrently with **ENZUTIX** 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 concurrent use of **ENZUTIX** 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 enzalutamide exposures

Food has no clinically significant effect on the extent of exposure to enzalutamide. **ENZUTIX** can be taken without regard to food.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

ENZUTIX is contraindicated for use by women. There is no human data on the use of enzalutamide during pregnancy and is not for use in women of childbearing potential. **ENZUTIX** may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant (see sections 4.3 and 6.6).

Contraception in males and females

It is unknown whether enzalutamide or its metabolites are present in semen. A condom is required during and for 3 months after treatment with **ENZUTIX** 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 documented reproductive toxicity.

Pregnancy

ENZUTIX is not for use in women and is contraindicated in women who are or may become pregnant (see sections 4.3 and 6.6). Considering the pharmacological consequences of androgen receptor signalling inhibition, maternal use of enzalutamide is expected to produce changes in hormone levels that could affect the development of the foetus.

Breastfeeding

ENZUTIX is not for use in women (see section 4.3). It is unknown if enzalutamide or its metabolites are excreted in human milk. Studies in animals have documented enzalutamide and/or its metabolites are secreted in rat milk.

Fertility

Studies in animals have documented that enzalutamide affected the reproductive system in male rats and dogs.

4.7 Effects on ability to drive and use machines

Enzalutamide may influence a patient's ability to drive and operate machinery as psychiatric and neurologic events including seizures 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.

4.8 Undesirable effects

a. Summary of the safety profile

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

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

b. Tabulated summary of adverse reactions

System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Leukopenia and neutropenia.
	Frequency unknown	Thrombocytopenia
Immune system disorders	Frequency unknown	Face oedema, tongue oedema, lip oedema and pharyngeal oedema.
Psychiatric disorders	Frequent	Anxiety.
	Less frequent	Visual hallucination.
Nervous system disorders	Frequent	Headache, memory impairment, amnesia, disturbance in attention and restless legs syndrome.
	Less frequent	Cognitive disorder and 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 flushes and hypertension.
Gastrointestinal disorders	Frequency unknown	Nausea, vomiting and diarrhoea.
Skin and subcutaneous tissue disorders	Frequent	Dry skin and pruritus.
	Frequency unknown	Rash.
Musculoskeletal and	Frequent	Fractures‡.

connective tissue disorders	Frequency unknown	Myalgia, muscle spasms, muscular weakness, and back pain.
Reproductive System and breast disorders	Frequent	Gynaecomastia.
General disorders and administration site disorders	Frequent	Asthenia and fatigue.
Injury, poisoning and procedural complications	Frequent	Falls.

¥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 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.

c. Description of selected adverse reactions

Seizure

Studies documented that 0,4 % of patients treated with a daily dose of 160 mg enzalutamide experienced a seizure. Dose appears to be an important predictor of the risk of seizure.

Studies documented in patients with predisposing factors for seizure (of which 1,6 % had a history of seizures), 2,2 % patients treated with enzalutamide (with a median treatment duration of 9,3 months) experienced a seizure.

The mechanism by which enzalutamide may lower the seizure threshold is unknown.

However, based on data from *in vitro* studies it could be related to enzalutamide and its active metabolite that bind to and can inhibit the activity of the GABA-gated chloride channel.

Ischemic Heart Disease

Studies documented 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.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.26 Cytostatic Agents

Pharmacotherapeutic group: hormone antagonists and related agents, anti-androgens; ATC code: L02BB04.

Mechanism of action

Prostate cancer is known to be androgen sensitive and responds to inhibition of androgen receptor signalling. Despite low or even undetectable levels of serum androgen, androgen receptor signalling continues to promote disease progression. Stimulation of tumour cell growth via the androgen receptor requires nuclear localisation and DNA binding.

Enzalutamide is an androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors, and consequently; inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression 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.

Elderly

Studies documented no overall differences in safety or effectiveness were observed between elderly patients and younger patients.

5.2 Pharmacokinetic properties

Pharmacokinetic studies documented 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, enzalutamide accumulates about 8,3-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 is equally as active as enzalutamide and circulates at approximately the same plasma concentration as enzalutamide.

Absorption

Maximum enzalutamide plasma concentrations (C_{max}) are observed 1 to 2 hours after administration. 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 after a single oral dose is 110 L (29 % CV). The enzalutamide volume of distribution 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 % plasma proteins bound, primarily to albumin. The active metabolite is 95 % bound to plasma proteins. There was no protein binding displacement between enzalutamide and other highly bound medicines (warfarin, ibuprofen and salicylic acid) *in vitro*.

Biotransformation

Enzalutamide is extensively metabolised. There are two major metabolites in human plasma: the active N-desmethyl enzalutamide metabolite and an inactive carboxylic acid derivative. 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. *In vitro*, N-desmethyl enzalutamide is metabolised 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 metabolised 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).

In vitro data indicate that enzalutamide is not a substrate for OATP1B1, OATP1B3, or OCT1; and N-desmethyl enzalutamide is not a substrate for P-gp or BCRP.

In vitro data indicate that enzalutamide and its major metabolites do not inhibit the following transporters at clinically relevant concentrations: OATP1B1, OATP1B3, OCT2, or OAT1.

Linearity

No major deviations from dose proportionality are documented over the dose range 40 mg to 160 mg. The steady-state C_{min} values of enzalutamide and the active metabolite in individual patients remained constant during more than one year of chronic therapy, demonstrating time-linear pharmacokinetics once steady-state is achieved.

Special Populations

Renally impaired patients

No formal renal impairment study for enzalutamide are documented. Based on a population pharmacokinetic analysis, no dose adjustment was 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 this patient group. It is unlikely that enzalutamide will be significantly removed by intermittent haemodialysis or continuous ambulatory peritoneal dialysis.

Hepatically impaired patients

Hepatic impairment does not have a pronounced effect on the total exposure to enzalutamide or its active metabolite. Studies documented the half-life of enzalutamide is doubled in

patients with severe hepatic impairment compared with healthy controls (10,4 days compared to 4,7 days), which is possibly related to an increase in tissue distribution. Caution is advised when used in in patients with severe hepatic impairment (Child-Pugh Class C). Studies concluded that no dose adjustment is necessary for patients with baseline mild or moderate hepatic impairment.

Race

Enzalutamide has been studied in Caucasian, Japanese and Chinese patients with prostate cancer. There are insufficient data to evaluate potential differences in the pharmacokinetic profile of enzalutamide in other races.

Elderly

Studies performed on patients over 65 and 75 years of age demonstrate that there is no overall difference in safety or efficacy between older and younger patients. Therefore, based on pharmacokinetic analysis on age, no dose adjustment is necessary in the elderly.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Caprylocaproyl macrogolglycerides

Butylhydroxyanisole

Butylhydroxytoluene

Capsule shell

Gelatin 160

Glycerol

Sorbitol, liquid partially dehydrated

Titanium dioxide (E171)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

ENZUTIX is packed in transparent PVC / ACLAR-aluminium blisters packed in carton boxes containing 112 capsules.

6.6 Special precautions for disposal and other handling

ENZUTIX should not be handled by persons other than the patient and his caregivers.

ENZUTIX must not be handled by women who are or may become pregnant (refer section 4.6).

The soft capsules should not be dissolved or opened.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

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3 Stirrup Lane, Van Reenens Avenue,

Woodmead,

2144

8 REGISTRATION NUMBERS

55/26/0125

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 January 2023

10 DATE OF REVISION OF TEXT