

**DR. REDDY'S LABORATORIES (PTY) LTD.  
ENLUTOZA  
PROFESSIONAL INFORMATION**

**SCHEDULING STATUS**

S4

**1. NAME OF THE MEDICINE**

ENLUTOZA, 40 mg, Soft gelatin capsule

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each soft gelatin capsule contains 40 mg enzalutamide.

Contains sugar alcohol:

Each soft gelatin capsule contains 51,2 mg of sorbitol.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Soft capsule.

White to off-white coloured oblong shaped soft gelatin capsules filled with colourless to light yellow clear transparent solution.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

ENLUTOZA 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 ENLUTOZA 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

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during treatment of patients not surgically castrated.

If a patient experiences a  $\geq$  Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to  $\leq$  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 ENLUTOZA dose should be reduced to 80 mg once daily.

If co-administration of the strong CYP2C8 inhibitor is discontinued, the ENLUTOZA 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).

#### *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 (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**

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

If a patient miss taking ENLUTOZA 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 of ENLUTOZA.
- Not to be used in women.
- Uncontrolled seizures.

#### **4.4 Special warnings and precautions for use**

##### **Seizures**

Caution should be used in administering ENLUTOZA 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.

Advise patients of the risk of developing a seizure while receiving ENLUTOZA and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Permanently discontinue ENLUTOZA in patients who develop a seizure during treatment.

##### **Posterior Reversible Encephalopathy Syndrome (PRES)**

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving enzalutamide (see section 4.8). PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, 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). Discontinue ENLUTOZA in patients who develop PRES.

##### **Hypersensitivity**

Hypersensitivity reactions, including oedema of the face (0,5 %), tongue (0,1 %), or lip (0,1 %) have been observed with enzalutamide in seven randomized clinical studies. Pharyngeal oedema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue ENLUTOZA and promptly seek medical care. Permanently discontinue ENLUTOZA for serious

hypersensitivity reactions.

### **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 bladder transitional cell carcinoma (0,1 %).

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

### **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 enzalutamide treatment. Concomitant use of enzalutamide 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 ENLUTOZA is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), 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**

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

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increased.

**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 ENLUTOZA is prescribed in 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 concomitant medicines that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating ENLUTOZA.

**Use with chemotherapy**

The safety and efficacy of concomitant use of ENLUTOZA 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.

**Falls and Fractures**

Falls and fractures occurred in patients receiving ENLUTOZA. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted medicines.

In the combined data of four randomized, placebo-controlled clinical studies, falls occurred in 11 % of patients treated with ENLUTOZA compared to 4 % of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 10 % of patients treated with ENLUTOZA and in 4 % of patients treated with placebo. Grade 3 to 4 fractures occurred in 3 % of patients treated with ENLUTOZA and in 2 % of patients treated with placebo. The median time to onset of fracture was 336 days (range: 2 to 1914 days) for patients treated with ENLUTOZA. Routine bone density assessment and treatment of osteoporosis with bone-targeted medicines were not performed in the studies.

**Embryo-Foetal Toxicity**

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The safety and efficacy of ENLUTOZA have not been established in females. Based on animal reproductive studies and mechanism of action, ENLUTOZA can cause foetal harm and loss of pregnancy when administered to a pregnant female.

Female sexual partners (of childbearing potential) of male patients receiving ENLUTOZA should be advised to use highly effective contraception, during treatment and for 6 months after the last dose of ENLUTOZA.

Men should be advised not to father a child while receiving treatment and advise males with female partners of reproductive potential to use effective contraception during treatment with ENLUTOZA and for 3 months after the last dose of ENLUTOZA.

#### **Excipients**

ENLUTOZA contains 51,2 mg sorbitol per soft capsule. The content of sorbitol in medicines for oral use may affect the bioavailability of other medicines for oral use administered concomitantly.

Sorbitol is a source of fructose. Patients who have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, should not take ENLUTOZA.

Sorbitol may cause gastrointestinal discomfort and have a mild laxative effect.

#### **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  $C_{max}$  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 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*

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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  $C_{max}$  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 ENLUTOZA 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 ENLUTOZA is coadministered with inducers of CYP2C8 or CYP3A4.

**Potential for enzalutamide 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 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-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 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. In a clinical study in patients with metastatic CRPC, ENLUTOZA (160 mg once daily) had no clinically relevant effect on

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the pharmacokinetics of intravenously administered docetaxel (75 mg/m<sup>2</sup> 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<sub>max</sub> 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 medicines (e.g., cabazitaxel)
- Antiepileptics (e.g., 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, 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)

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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 or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicine may be necessary when stopping enzalutamide treatment.

*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 ENLUTOZA.

*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 ENLUTOZA 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

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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 ENLUTOZA.

*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 treatment may prolong the QT interval, the concomitant use of ENLUTOZA 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 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. In clinical studies, ENLUTOZA was administered without regard to food.

#### **4.6 Fertility, pregnancy and lactation**

##### **Women of childbearing potential/Contraception in males and females**

ENLUTOZA is contraindicated for use by women.

Female sexual partners (of childbearing potential) of male patients receiving ENLUTOZA must use highly effective contraception during and for at least 6 months after the final dose of ENLUTOZA.

It is not known whether ENLUTOZA or its metabolites are present in semen. A condom is required during and for 3 months after treatment with ENLUTOZA 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 signalling inhibition, maternal use of

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ENLUTOZA is expected to produce changes in hormone levels that could affect development of the foetus.

**Breastfeeding**

ENLUTOZA is not for use in women. It is unknown whether ENLUTOZA 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 ENLUTOZA.

**4.7 Effects on ability to drive and use machines**

ENLUTOZA 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 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, hypertension, fractures and fall. Other important adverse reactions include cognitive disorder and neutropenia.

Seizure occurred in 0,5 % of enzalutamide-treated patients, 0,1 % of placebo-treated patients and 0,3 % in bicalutamide-treated patients.

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

*Tabulated list of adverse reactions*

Adverse reactions listed below are classified according to frequency and system organ class (SOC).

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Frequency categories are defined according to the following convention:

<b>System Organ Class</b>	<b>Frequent</b>	<b>Less frequent</b>	<b>Frequency unknown</b>
<b>Blood and lymphatic system disorders</b>		leucopenia, neutropenia	thrombocytopenia
<b>Immune system disorders</b>			face oedema, tongue oedema, lip oedema, pharyngeal oedema
<b>Psychiatric disorders</b>	anxiety	visual hallucination	
<b>Nervous system disorders</b>	headache, memory impairment, amnesia, disturbance in attention, dysgeusia, restless legs syndrome	cognitive disorder, seizure <sup>‡</sup>	posterior reversible encephalopathy syndrome
<b>Cardiac disorders</b>	ischemic heart diseases <sup>†</sup>		QT-prolongation (see sections 4.4 and 4.5)
<b>Vascular disorders</b>	hot flushes, hypertension		
<b>Gastrointestinal disorders</b>			nausea, vomiting, diarrhoea
<b>Skin and subcutaneous tissue disorders</b>	dry skin, pruritus		erythema multiforme, rash
<b>Musculoskeletal and connective tissue disorders</b>	fractures <sup>‡</sup>		myalgia, muscle spasms, muscular weakness, back pain
<b>Reproductive system</b>	gynaecomastia		

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<b>and breast disorder</b>			
<b>General disorders and administration site conditions</b>	asthenia, fatigue		
<b>Injury, poisoning and procedural complications</b>	fall		

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

† As evaluated by narrow SMQs of 'Myocardial Infraction' 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.

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 requested to report any suspected adverse drug reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

For any information about this medicine, please contact the local representative of the Holder of Certificate of Registration: Dr. Reddy's Laboratories (Pty) Ltd. Tel: +27 11 324 2100

**4.9 Overdose**

In the event of an overdosage, stop treatment with ENLUTOZA and initiate general supportive measures taking into consideration the half-life of 5,8 days. Patients may be at increased risk of seizure following an overdosage.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacological classification: A 26 Cytostatic medicines.

Pharmacotherapeutic group: hormone antagonists and related medicines, anti-androgens, 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 ( $t_{1/2}$ ) 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 ( $C_m$ ) 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  $C_m$  values for enzalutamide and its active metabolite are 16,6 g/m (I23 % CV) and 12,7 g/m (I30 43 %CV), respectively.

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Food has no clinically significant effect on the extent of absorption. In studies, 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 section 4.4), 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 CYP2E1.

*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 of CYP2C9 and CYP2C19 and has no clinically relevant effect on CYP2C8 (see section 4.4).

*Elimination*

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

Following oral administration of <sup>14</sup>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**

#### *Renally impaired patients*

No formal renal impairment study for enzalutamide has been completed. Patients with serum creatinine > 177  $\mu\text{mol/L}$  (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 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.

#### *Hepatically impaired patients*

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  $C_{\text{max}}$  of enzalutamide in subjects with moderate impairment increased by 29 % and decreased by 11 % and the AUC and  $C_{\text{max}}$  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  $C_{\text{max}}$  in subjects with mild impairment increased by 14 % and 19 %, respectively, the AUC and  $C_{\text{max}}$  in subjects with moderate impairment increased by 14 % and decreased by 17 %, respectively, and the AUC and  $C_{\text{max}}$  in subjects with severe hepatic impairment increased by 34 % and decreased by 27 %, respectively, compared to healthy control subjects.

#### *Elderly*

Of the 4168 patients in the controlled clinical trials who received enzalutamide, 3265 patients (78 %) were 65 years and over and 1469 patients (35 %) were 75 years and over. No overall differences in safety or

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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**

*Blend*

Butylated Hydroxy Anisole

Butylated Hydroxy Toluene

Caprylocaproyl polyoxyl-8 glycerides (Labrasol ALF)

*Gelatin mass*

Gelatin 160 bloom RXL

Glycerin

Purified water

Sorbitol Special

Titanium Dioxide

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

24 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.

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**6.5 Nature and contents of container**

ENLUTOZA is presented as clear PVC/ACLAR foil containing blisters of 28's count wallet pack (4 wallets pack in each carton, 112 capsules in a carton).

**6.6 Special precautions for disposal and other handling**

ENLUTOZA 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, ENLUTOZA may harm a developing foetus.

Women who are or may become pregnant should not handle damaged or opened ENLUTOZA without protection, e.g., gloves.

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

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

Dr. Reddy's Laboratories (Pty) Ltd.  
Block C, Woodmead North Office Park,  
54 Maxwell Drive, Woodmead,  
Sandton,  
Gauteng,  
2191  
South Africa

**8. REGISTRATION NUMBER**

58/26/0123

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

28 October 2025

**10. DATE OF REVISION OF TEXT**

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Not applicable.