

Lanzotred soft capsules

Enzalutamide Soft capsules 40 mg

COMPOSITION

Each capsule contains: Enzalutamide-----40 mg

Source of Gelatin: PORCINE

Therapeutic indications

Lanzotred is indicated for:

- the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).
- the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC).
- 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.
- the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

Posology and method of administration

Posology

The recommended dose is 160 mg enzalutamide (four 40 mg capsules) as a single oral daily dose.

Medical castration with an LHRH analogue should be continued during treatment of patients not surgically castrated.

If a patient misses taking Lanzotred 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 $\geq$ 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 the same or a reduced dose (120 mg or 80 mg) if warranted.

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 enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is

discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

Elderly

No dose adjustment is necessary for elderly patients.

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.

Renal impairment

No dose adjustment is necessary for patients with mild or moderate renal impairment. Caution is advised in patients with severe renal impairment or end-stage renal disease.

Paediatric population

There is no relevant use of enzalutamide in the paediatric population in the indication of treatment of patients with CRPC and mHSPC.

Method of administration

Lanzotred 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.

Contraindications

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

Women who are or may become pregnant.

Special warnings and precautions for use

Risk of seizure

Use of enzalutamide has been associated with seizure. The decision to continue treatment in patients who develop seizure should be taken case by case.

Posterior Reversible Encephalopathy Syndrome

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

Concomitant use with other medicinal products

Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products. A review of concomitant medicinal products should therefore be conducted when initiating enzalutamide treatment. Concomitant use of enzalutamide with medicinal products 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.

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

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 drug half-life 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 may be increased.

Recent cardiovascular disease

There are no data of its 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) $\geq 45\%$, bradycardia or uncontrolled hypertension. This should be taken into account if Lanzotred is prescribed in these patients.

Use with chemotherapy

The safety and efficacy of concomitant use of Lanzotred with cytotoxic chemotherapy has not been established. Co-administration of enzalutamide has no clinically relevant effect on the pharmacokinetics of intravenous docetaxel; however, an increase in the occurrence of docetaxel-induced neutropenia cannot be excluded.

Excipients

Lanzotred contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

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.

Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products 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), the AUC of enzalutamide increased while C_{max} of enzalutamide decreased. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased while C_{max} decreased. 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.

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), the AUC of enzalutamide increased while C_{max} was unchanged. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased while C_{max} was again unchanged. No dose adjustment is necessary when Lanzotred 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), the AUC of enzalutamide plus the active metabolite decreased while

C_{max} remained unchanged. No dose adjustment is necessary when Lanzotred is co-administered with inducers of CYP2C8 or CYP3A4.

Potential for enzalutamide to affect exposures to other medicinal products

Enzyme induction

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

It is 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 a decrease in the AUC of midazolam (CYP3A4 substrate), a decrease in the AUC of S-warfarin (CYP2C9 substrate), and a decrease in the AUC of omeprazole (CYP2C19 substrate). UGT1A1 may have been induced as well. In patients with metastatic CRPC, Enzalutamide (160 mg once daily) had no clinically relevant effect on the pharmacokinetics of intravenously administered docetaxel (75 mg/m² by infusion every 3 weeks). The AUC of docetaxel decreased while C_{max} decreased.

Interactions with certain medicinal products 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 medicinal products 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 medicinal products 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)
- 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 metabolized by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment, when steady-state plasma concentrations of enzalutamide are reached, although some induction effects may be apparent earlier. Patients taking medicinal products 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), effects on enzymes may persist for one month or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicinal product 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 while C_{max} decreased. The AUC and C_{max} of caffeine decreased. No dose adjustment is indicated when a CYP1A2 or CYP2C8 is co-administered with Lanzotred.

P-gp substrates

It is indicated that enzalutamide may be an inhibitor of the efflux transporter P-gp. The effect of enzalutamide on P-gp substrates has not been evaluated; however, under conditions of clinical use, enzalutamide may be an inducer of P-gp via activation of the nuclear pregnane receptor (PXR).

Medicinal products 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 Lanzotred and may require dose adjustment to maintain optimal plasma concentrations.

BCRP, MRP2, OAT3 and OCT1 substrates

Based on 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.

Effect of food on enzalutamide exposures

Food has no clinically significant effect on the extent of exposure to enzalutamide. In current available data, Enzalutamide was administered without regard to food.

Fertility, pregnancy and lactation

Women of childbearing potential

There are no data on the use of Lanzotred in pregnancy and this medicinal product is not for use in women of childbearing potential. This medicine may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant.

Contraception in males and females

It is not known whether enzalutamide or its metabolites are present in semen. A condom is required during and for 3 months after treatment with enzalutamide 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. Data have shown reproductive toxicity

Pregnancy

Enzalutamide is not for use in women. Enzalutamide is contraindicated in women who are or may become pregnant

Breast-feeding

Enzalutamide is not for use in women. It is not known if enzalutamide is present in human milk. Enzalutamide and/or its metabolites are secreted in rat milk

Fertility

Data showed that enzalutamide affected the reproductive system in male rats and dogs

Effects on ability to drive and use machines

Enzalutamide may have moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizure have been reported. Patients should be advised of the potential risk of experiencing a psychiatric or neurological event while driving or operating machines. No studies to establish the effects of enzalutamide on the ability to drive and use machines have been conducted.

Undesirable effects

Summary of the safety profile

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

Seizure occurred in enzalutamide-treated patients.

Rare cases of posterior reversible encephalopathy syndrome have been reported in enzalutamide treated patients.

Tabulated summary of adverse reactions

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common; common; uncommon; rare; very rare; not known. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System organ class	Frequency
Blood and lymphatic system disorders	Uncommon: leucopenia, neutropenia
Immune system disorders	Not known*: face oedema, tongue oedema, lip oedema, pharyngeal oedema
Psychiatric disorders	Common: anxiety Uncommon: visual hallucinations
Nervous system disorders	Common: headache, memory impairment, amnesia, disturbance in attention, restless legs syndrome Uncommon: cognitive disorder, seizure [‡] Not known*: posterior reversible encephalopathy syndrome
Cardiac disorders	Common: ischemic heart disease [†]
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*: 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
General disorders and administration site conditions	Very common: asthenia, fatigue
Injury, poisoning and procedural complications	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: angina pectoris, coronary artery disease, myocardial infarctions, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischaemia, and arteriosclerosis coronary artery.

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

Description of selected adverse reactions

Seizure

Dose appears to be an important predictor of the risk of seizure, as reflected by available data. In the available data, patients with prior seizure or risk factors for seizure were excluded.

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

Ischemic Heart Disease

Ischemic heart disease occurred in patients treated with enzalutamide plus ADT.

Overdose

There is no antidote for enzalutamide. In the event of an overdose, treatment with enzalutamide should be stopped and general supportive measures initiated taking into consideration the half-life of 5.8 days. Patients may be at increased risk of seizures following an overdose.

Pharmacological properties**Pharmacodynamic properties**

ATC: 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 localization and DNA binding. Enzalutamide is a potent 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. In preclinical studies enzalutamide lacks androgen receptor agonist activity.

Pharmacokinetic properties

Enzalutamide is poorly water soluble. In this product, the solubility of enzalutamide is increased by caprylocaproyl macrogolglycerides as emulsifier/surfactant. In preclinical studies, the absorption of enzalutamide was increased when dissolved in caprylocaproyl macrogolglycerides.

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, enzalutamide accumulates approximately 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 plasma concentrations (C_{max}) of enzalutamide in patients 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 $\mu\text{g/mL}$. Food has no

clinically significant effect on the extent of absorption. In available data, 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. Data 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 (N-desmethyl enzalutamide) is 95% bound to plasma proteins. There is no protein binding displacement between enzalutamide and other highly bound medicinal products (warfarin, ibuprofen and salicylic acid).

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, both of which play a role in the formation of the active metabolite. 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.

Enzalutamide is a strong inducer of CYP3A4, a moderate inducer of CYP2C9 and CYP2C19, and has no clinically relevant effect on CYP2C8.

Elimination

The mean apparent clearance (CL/F) of enzalutamide in patients ranges from 0.520 and 0.564 L/h.

Following oral administration of ¹⁴C-enzalutamide, 84.6% of the radioactivity is recovered by 77 days post dose: 71.0% is recovered in urine (primarily as the inactive metabolite, with trace amounts of enzalutamide and the active metabolite), and 13.6% is recovered in faeces (0.39% of dose as unchanged enzalutamide).

Data indicates that enzalutamide is not a substrate for OATP1B1, OATP1B3, or OCT1; and N-desmethyl enzalutamide is not a substrate for P-gp or BCRP.

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 observed over the dose range 40 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.

Renal impairment

No formal renal impairment data for enzalutamide is available. Patients with serum creatinine > 177 µmol/L (2 mg/dL) were excluded from available data. 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 caution is advised when treating these 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. Drug half-life was however doubled in patients with severe hepatic impairment compared with healthy controls (10.4 days compared to 4.7 days), possibly related to an increased tissue distribution.

Following a single oral 160 mg dose of enzalutamide, the AUC and C_{max} for enzalutamide in subjects with mild impairment increased, the AUC and C_{max} of enzalutamide in subjects with moderate impairment increased, and the AUC and C_{max} of enzalutamide in subjects with severe impairment increased and decreased, respectively. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC and C_{max} in subjects with mild impairment increased, the AUC and C_{max} in subjects with moderate impairment increased and decreased, respectively, and the AUC and C_{max} in subjects with severe hepatic impairment increased and decreased, respectively.

Race

Most patients in the available data (>74%) were Caucasian. Based on pharmacokinetic data from data in Japanese and Chinese patients with prostate cancer, there were no clinically relevant differences in exposure among the populations. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

Elderly

No clinically relevant effect of age on enzalutamide pharmacokinetics was seen in the population pharmacokinetic analysis.

Pharmaceutical information

Product Description

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

Shelf Life

36 Months

Precautions for Storage

Store below 30°C

Nature and contents of container

PVC/ACLAR-Aluminium blisters of 4 soft capsules

28 blisters are placed in a carton along with the Pack Insert (112 Soft Capsules).

Manufacturer

Lotus Pharmaceutical Co., Ltd.,
Nantou Plant No. 30,
Chenggong 1st Rd., Sinsing Village, Nantou City,
Nantou County 54066, Taiwan.

Product Registration Holder

Dr. Reddy's Laboratories Malaysia Sdn. Bhd.
UNIT NO. SO-29-07 AND SO-29-08, MENARA 1, STRATA OFFICE, NO. 3, JALAN
BANGSAR, KL ECO CITY, 59200 KUALA LUMPUR MALAYSIA

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