L), suggesting extensive extravascular distribution of the drug. Studies in rodents indicate that enzalutamide and its active metabolite can cross the blood brain barrier.
Enzalutamide is highly bound (97 to 98%) to plasma proteins, primarily albumin. The active metabolite is about 95% plasma proteins bound. There was no protein binding displacement between enzalutamide and other highly bound drugs (warfarin, ibuprofen and salicylic acid) in vitro.

Biotransformation

As confirmed in a drug interaction study, in vitro studies indicated that enzalutamide is mainly metabolized by CYP2C8, with minor CYP3A4/5 involvement. In a 14C-enzalutamide mass balance study, a total of seven metabolites were identified. The two main metabolites in circulation are the active N-desmethyl enzalutamide (M2), which in vitro is equally active as enzalutamide, and the inactive carboxylic acid metabolite (M1). The mean steady-state Ctrough concentrations are similar for enzalutamide and its active metabolite N-desmethyl enzalutamide, and therefore both substances contribute to pharmacological activity. The inactive carboxylic metabolite accounts for approximately 75 % of the exposure. N-desmethyl enzalutamide (M2) is metabolized by carboxylesterase 1 to the carboxyl metabolite (M1). No CYP enzymes involved in further metabolism were identified.

Elimination

The mean apparent clearance (CL/F) of enzalutamide in patients ranges from 0.520 and 0.564 L/h. In feces, 0.39 % of the dose was recovered as unchanged parent enzalutamide. Given that overall recovery in excreta was 84.6 % of the 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 at least 84.2 % of the dose was absorbed.

Linearity

The steady-state C_{trough} values for enzalutamide and *N*-desmethyl enzalutamide in individual patients remained constant during more than 1 year of long-term therapy, demonstrating time-linear pharmacokinetics once steady state was achieved. At steady state, enzalutamide showed no major deviations from dose proportionality over the daily dose range of 30–360 mg. In patients, %CV for AUC_t, C_{trough}, and C_{max} was ≤30 %, demonstrating low inter-subject variability.

Renal impairment

Renal excretion was an insignificant elimination pathway for enzalutamide and *N*-desmethyl enzalutamide. Patient with severe renal impairment and end-stage renal disease have not been assessed and hence caution is advised.

Hepatic impairment

Enzalutamide was primarily eliminated by hepatic metabolism.
In a reported study, the pharmacokinetic data were obtained from two non-randomized, open label, single-dose, phase 1 studies conducted in patients with mild (Child-Pugh class A, n = 6) or moderate (Child-Pugh class B, n = 8) hepatic impairment or severe (Child-Pugh class C, n = 8) hepatic impairment and their corresponding matched healthy controls; Subjects with hepatic impairment had liver cirrhosis (n = 19) or chronic hepatitis (n = 3). All subjects received a single oral dose of 160 mg enzalutamide under fasting conditions, with blood samples collected pre-dose and up to 49 days post-dose.

Hepatic impairment did not have a significant effect on the total exposure to enzalutamide or its active metabolite. However t1/2 was 2x in patients with severe hepatic impairment compared to healthy controls (10.4 days compared to 4.7 days), this could be attributed possibly to an increased tissue distribution. It is reported that following a single oral 160 mg dose of enzalutamide, the AUC and C_{max} for enzalutamide in subjects with mild impairment increased by 5% and 24%, respectively, the AUC and C_{max} of enzalutamide in subjects with moderate impairment increased by 29% and decreased by 11%, respectively, 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.

Race

Most patients in the reported clinical trials (>84%) were Caucasian. Based on pharmacokinetic data from a study in Japanese patients with prostate cancer, there were no clinically relevant differences in exposure between Japanese and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

Older people

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

STORAGE
Store below 30°C. Keep the medicine out of reach of children.

SHELF LIFE
Please see manufacturing date and expiry date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

PACKAGING
Blister of 28 capsules.

Manufactured in India by:
BDR Pharmaceuticals Int'l Pvt. Ltd.
R. S. No. 578, Near Effluent Channel Road,
Vill. Luna, Tal. Padra, Dist. Vadodara-391440. Gujarat.

Marketed by :
APRAZER
Aprazer Healthcare Pvt. Ltd.
B-256, 2nd Floor, Naraina Phase-1,
New Delhi, India-110028.
Web.: www.aprazerhealthcare.com

Only for the use of a Registered Specialist or a Hospital or a Laboratory.

Enzalutamide Capsules 40 mg

INDENZA®

COMPOSITION
Each hard Gelatin capsule Contains:
Enzalutamide… 40 mg
Excipients……..... q.s.
Approved colours used in Capsule shell

DOSAGE FORM
Hard Gelatin Capsule

INDICATION
For the treatment adults with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on or after Docetaxel therapy.

DOSAGE AND ADMINISTRATION
The recommended dose is 160 mg of enzalutamide (four 40 mg capsules) as a single oral daily dose.
Medical castration with LHRH analogue should be continued during treatment in patients not surgically castrated.
If a patient misses taking Enzalutamide Capsule at the usual time, take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose. Do not take a double dose to make up for the missed dose.
If more than one daily dose is missed, talk to your doctor.

If a patient has 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 the same or a reduced dose (3 capsules of 40 mg, 120 mg or 2 capsules of 40 mg, 80 mg) if warranted.
Concomitant use with strong CYP2C8 inhibitors

If a patient requires administration of a strong CYP2C8 inhibitor with enzalutamide, then the enzalutamide dose should be reduced to 80 mg/day. It is recommended to avoid concomitant use of enzalutamide with narrow therapeutic index drugs metabolized by CYP2C9, CYP2C19, or CYP3A4, as enzalutamide may decrease their exposure.When simultaneous use 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.

USE IN SPECIAL POPULATION

Hepatic Impairment
No major differences in single-dose pharmacokinetics were observed in subjects with hepatic impairment vs. matched healthy controls. Therefore, no initial dose adjustment is necessary when administering enzalutamide to patients with mild, moderate or severe hepatic impairment. However, an increased half-life of the drug has been observed in patients with severe hepatic impairment and hence caution is advised.

Renal impairment
No significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment compared to patients and volunteers with baseline normal renal function. No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Patient with severe renal impairment and end-stage renal disease have not been assessed and caution is advised.

Older people
No dose adjustment is necessary for older people.
Paediatric population
Enzalutamide is not meant for use in the paediatric population.

METHOD OF ADMINISTRATION

Enzalutamide is for oral use. The capsules should be swallowed whole without opening and are not to be chewed or dissolved or opened.

CONTRAINDICATIONS

Individual hypersensitivity to the active substance or excipients of the product.
Enzalutamide is not indicated for use by women.

WARNINGS AND PRECAUTIONS

Risk of seizures

Enzalutamide belongs to a class of antiandrogens that carry a risk of seizures. Caution should be used in administering Enzalutamide Capsule to patients with a history of seizures or other predisposing factors like brain metastases, brain atrophy associated with alcohol use, brain tumor, or patient on lidocaine therapy or any other drugs which can lower the seizure threshold.

Posterior reversible encephalopathy syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) is a clinical/radiological syndrome characterized by symptoms that can include seizure, headache, impaired vision and hypertension, and can be confirmed by magnetic resonance imaging. The list of medications linked to PRES can include traditional cytotoxic chemotherapeutics (e.g., cisplatin, cyclophosphamide, and high-dose corticosteroids), newer agents that target the vascular endothelial growth factor pathway (e.g., bevacizumab, sunitinib, and pazopanib), and supportive care mediations (e.g., granulocyte colony stimulating factors and erythropoietin). Patients treated with enzalutamide could potentially be at risk for PRES. If symptoms suggestive of PRES arise in patients receiving enzalutamide, the drug should be discontinued immediately and the diagnostic process should be initiated.

Concomitant use with other medicinal products

Enzalutamide is extensively metabolized by CYP2C8. Enzalutamide is a moderate inducer of CYP2C9 and CYP2C19 and a strong inducer of CYP3A4. If a patient requires coadministration of a strong CYP2C8 inhibitor with enzalutamide, then the enzalutamide dose should be reduced to 80 mg/day. It is recommended to avoid concomitant use of enzalutamide with narrow therapeutic index drugs metabolized by CYP2C9, CYP2C19, or CYP3A4, as enzalutamide may decrease their exposure. The effect on CYP3A4 may be clinically relevant as up to 60% of all drugs are metabolized via CYP3A4, and hence additional International Normalized Ratio (INR) monitoring is warranted.
If coadministered with strong CYP2C8 inhibitors such as montelukast, trimethoprim, gemfibrozil, or pioglitazone, plasma levels are likely to be raised. Strong inducers of CYP2C8 may reduce the effectiveness of enzalutamide and hence should be avoided.

200 x 280 mm, 60 gsm Maplitho paper, folding pattern : 1H, 2 V, folding size : 100 x 70 mm

Renal impairment
Patient with severe renal impairment and end-stage renal disease have not been assessed and caution is advised.
Severe Hepatic impairment
Enzalutamide is primarily hepatically eliminated, an increased drug half-life has been observed in patients with severe hepatic impairment and hence caution is advised.

Recent cardiovascular disease
A significant increase in the incidence and relative risk (RR) of cardiovascular toxicity in mCRPC treated with new hormonal agents as opposed to a placebo, has been observed, even though the occurrence of all- and grade 3–4 events rose only 14% and 4%, respectively. Follow-ups for the onset of treatment-related cardiovascular events should, therefore, be considered in these patients.

Androgen deprivation therapy may prolong the QT interval
In patients with a history or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval, physicians should assess the benefit-risk ratio before prescribing Enzalutamide Capsule.

Use with chemotherapy
The safety and efficacy of concomitant use of Enzalutamide Capsule with cytotoxic chemotherapy has not been established. The combination of docetaxel and enzalutamide is feasible, although higher rates of neutropenia and neutropenic fever, than anticipated, were observed. Reductions in docetaxel exposure with enzalutamide coadministration were not considered clinically meaningful.

Hypersensitivity reactions
Hypersensitivity reactions manifested by symptoms including, but not limited to, tongue oedema, lip oedema and pharyngeal oedema have been reported with enzalutamide.

Excipients
Enzalutamide contains a type of sugar called lactose. If you have an intolerance to some sugars, contact your doctor before taking this medicine.

DRUG INTERACTIONS

In the drug interaction study with CYP2C8 and CYP3A4 inhibitors, coadministration of gemfibrozil (strong CYP2C8 inhibitor) increased the composite AUC∞ of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold, and coadministration of itraconazole (strong CYP3A4 inhibitor) increased the composite AUC∞ by 1.3-fold. Based on these findings, it is recommended to avoid CYP2C8 inhibitor, however if a patient requires coadministration of a strong CYP2C8 inhibitor with enzalutamide, then the enzalutamide dose should be reduced to 80 mg once daily.

Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) with Enzalutamide should be avoided if possible. St John's wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with Enzalutamide cannot be avoided, increase the dose of Enzalutamide from 160 mg to 240 mg once daily, Enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer.

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, it reduces the plasma exposure to CYP3A4 substrate like midazolam, CYP2C9 substrate like warfarin, and CYP2C19 substrate like omeprazole. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

P-gp substrates
In in vitro experiments, enzalutamide and N-desmethyl enzalutamide were shown to be inhibitors of P-gp. 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 Enzalutamide Capsule and may require dose adjustment.

BCRP, MRP2, OAT3 and OCT1 substrates
Enzalutamide is not a substrate of P-gp or the breast cancer resistance protein (BCRP). Inhibition of multidrug resistance-associated protein 2 (MRP2), BCRP and OATP1B1 could not be excluded based on in vitro data. Theoretically, induction of these transporters is also possible, and the net clinical effect is presently unidentified.

Medicinal products which prolong the QT interval
Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Enzalutamide Capsule with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA i.e. Fast sodium (Na) channel blockers like Quinidine, procainamide, disopyramide or class III i.e. Potassium (K) channel blockers like amiodarone, sotalol, dofetilide, ibutilide, other antiarrhythmic medicinal products, and methadone, moxifloxacin, antipsychotics, etc., should, therefore, be carefully evaluated.

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)
· Anticoagulants (e.g. acenocoumarol, 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)
· Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin)
· Thyroid agents (e.g. levothyroxine)

Effect of food on enzalutamide exposures
Food has no clinically significant effect on the extent of exposure to enzalutamide. In clinical trials, Enzalutamide Capsule was administered without food.

Fertility, pregnancy and lactation

Women of childbearing potential
Enzalutamide is not indicated for use by women.
Contraception in males and females
It is not known whether enzalutamide or its metabolites are present in semen. A condom is recommended 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. Studies in animals have shown reproductive toxicity.

Pregnancy & Breast-feeding
Enzalutamide is not indicated for use by women.

Fertility
Animal studies suggest that enzalutamide could affect the reproductive system in male rats and dogs.

Effects on ability to drive and use machines
No studies on the effects of Enzalutamide on the ability to drive or use machines have been performed. It is anticipated that Enzalutamide may have a moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizure have been reported. Patients with a history of seizures or other predisposing factors should be advised of the risk of driving or operating machines.

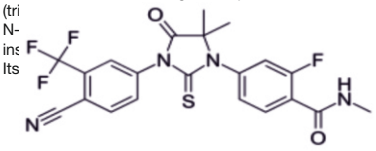
SIDE EFFECTS
Summary of adverse reactions
Adverse reactions observed during clinical studies are listed below by frequency category.

very common	10.0 %	asthenia/fatigue, headache, hot flushes, hypertension,
Common	1.0 % to 10.0 %	Anxiety, memory impairment, amnesia, disturbance in attention, restless legs syndrome, gynaecomastia, dry skin, pruritus, fractures, falls
uncommon	0.1 % to 1.0%	Leucopenia, Neutropenia, visual hallucinations, cognitive disorder, seizure,

Also, some other not known adverse reactions identified are as below:
thrombocytopenia, tongue oedema, lip oedema, pharyngeal oedema, posterior reversible encephalopathy syndrome, QT-prolongation, nausea, vomiting, diarrhea, rash, myalgia, muscle spasms, muscular weakness and back pain,.

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.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTY:
DESCRIPTION:
Enzalutamide is an androgen receptor inhibitor. The chemical name is 4-{3-[4-cyano-3-(tri lideneimidazolidin-1-yl}-2-fluoro-N- line non-hygroscopic solid. It is practically ins Its



Chemical formula:$C_{21}H_{16}F_4N_4O_2S$
Molecular weight: 464.44 g/mol
ATC code: L02BB04
Pharmacotherapeutic group: Anti Neoplastic
Pharmacodynamics
Enzalutamide is a rationally-designed androgen receptor antagonist that blocks androgen receptor (AR) binding, nuclear translocation, and co-activator recruitment more effectively than the androgen receptor antagonists currently in use. Enzalutamide is also unique in that it prevents DNA binding, induces apoptosis, and has no agonist activity when AR is overexpressed

Pharmacokinetics
Enzalutamide is poorly water soluble. The pharmacokinetics of enzalutamide have been evaluated in prostate cancer patients and in healthy male subjects. In a reported dose-escalation study, enzalutamide half-life was 5.8 days, steady state was achieved by day 28, accumulation was 8.3-fold, exposure was approximately dose proportional from 30–360 mg/day, and inter-subject variability was ≤30 %. In the multiple-dose period, enzalutamide was absorbed rapidly on day 84, with the median tmax ranging from 0.00 to 2.07 h, which was similar to the median tmax in the single-dose period. The mean CL/F was 0.61 L/h, also similar to the CL/F during the single-dose period. In general, dosing for 1 month was required to reach steady state, and the daily fluctuations in plasma concentrations were low (mean peak-to-trough ratio, 1.25). Clearance of enzalutamide is primarily via hepatic metabolism, producing an active metabolite, N-desmethylenzalutamide that is equally as active as enzalutamide and circulates at approximately the same plasma concentration as enzalutamide.

Absorption
Absorption after single- and multiple-dose oral administration, the tmax generally occurred around 1 h post dose, showing that enzalutamide is rapidly absorbed. Based on excretion of metabolites in urine and feces in the mass balance and biotransformation study, the extent of absorption of enzalutamide after oral administration is at least 84.2 %.
Maximum plasma concentrations (Cmax) 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 Cmax 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 Vz/F of enzalutamide in patients (110 L) was approximately 2.6 times greater than the volume of total body water (42 L), and approximately 37 times greater than the plasma volume (3