Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

ENZACARE 40

(Enzalutamide Capsules 40 mg)

Brand name: ENZACARE 40. Generic name: Enzalutamide Capsules 40 mg.

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:

Enzalutamide ..... 40 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Hard capsule.

Yellow/yellow size "0" hard gelatin capsule containing a white free-flowing powder.

4. Clinical particulars

4.1 Therapeutic indications

ENZACARE 40 is indicated for:

- the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy;
- 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.

4.2 Posology and method of administration

Treatment with enzalutamide should be initiated and supervised by specialist physicians experienced in the medical treatment of prostate cancer.

Posology

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

Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.

If a patient misses taking ENZACARE 40 at the usual time, the prescribed dose should be taken as close as possible to the usual time. If a patient misses a dose for a whole day, treatment should be resumed the following day with the usual daily dose.

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at 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.

Special populations

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 half-life of enzalutamide 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 adult men with CRPC and mHSPC.

Method of administration

ENZACARE 40 is for oral use. The capsules should not be cut, crushed or chewed but should be swallowed whole with water, and can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Women who are or may become pregnant.

4.4 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 seizures should be taken on a case-by-case basis.

Posterior reversible encephalopathy syndrome

There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving ENZACARE 40. PRES is a rare, reversible neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, blindness and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of ENZACARE 40 in patients who develop PRES is recommended.

Second primary malignancies

Cases of second primary malignancies have been reported in patients treated with enzalutamide in clinical studies. In phase 3 clinical studies, the most frequently reported events in enzalutamide-treated patients, and greater than placebo, were bladder cancer (0.3 %), adenocarcinoma of the colon (0.2 %), transitional cell carcinoma (0.2 %) and 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 during treatment with enzalutamide.

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 ENZACARE 40 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 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 may be increased.

4.5 Interaction with other medicinal products and other forms of interaction

Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products. 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)
- Beta-blockers (e.g. bisoprolol, propranolol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin)
- Corticosteroids (e.g. dexamethasone, prednisolone)
- HIV antivirals (e.g. indinavir, ritonavir)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressants (e.g. tacrolimus)
- Proton pump inhibitors (e.g. omeprazole)
- Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

Medicinal products that prolong the QT interval

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of enzalutamide with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes – such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin and antipsychotics – should be carefully evaluated.

Effect of food on enzalutamide exposure

Food has no clinically significant effect on the extent of exposure to enzalutamide. In clinical trials, ENZACARE 40 was administered without regard to food.

4.6 Pregnancy and Lactation

Women of childbearing potential

There are no human data on the use of ENZACARE 40 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 activity with a woman of childbearing potential, a condom together with another form of effective contraception is required during and for 3 months after treatment.

Pregnancy

Enzalutamide is not for use in women. Enzalutamide is contraindicated in women who are or may become pregnant (see sections 4.3 and 5.3).

Breast-feeding

Enzalutamide is not for use in women. It is not known whether enzalutamide is present in human milk. Enzalutamide and/or its metabolites are secreted in rat milk (see section 5.3).

Fertility

Animal studies showed that enzalutamide affected the reproductive system in male rats and dogs (see section 5.3).

4.7 Effects on ability to drive and use machines

ENZACARE 40 may have moderate influence on the ability to drive and use machines, as psychiatric and neurological 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 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 ischaemic heart disease and seizure.

Seizure occurred in 0.5 % of enzalutamide-treated patients, 0.2 % of placebo-treated patients and 0.3 % of bicalutamide-treated patients.

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

Tabulated list of adverse reactions

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

Table 1: Adverse reactions identified in controlled clinical trials and post-marketing

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

* Spontaneous reports from post-marketing experience.

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

† As evaluated by narrow SMQs of "Myocardial Infarction" and "Other Ischemic Heart Disease" including the following preferred terms observed in at least two patients in randomised placebo-controlled phase 3 studies: angina pectoris, coronary artery disease, myocardial infarction, 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

In controlled clinical studies, 24 patients (0.5 %) experienced a seizure out of 4,403 patients treated with a daily dose of 160 mg enzalutamide, whereas four patients (0.2 %) receiving placebo and one patient (0.3 %) receiving bicalutamide experienced a seizure. Dose appears to be an important predictor of the risk of seizure, as reflected by preclinical data and data from a dose-escalation study. In the controlled clinical studies, patients with prior seizure or risk factors for seizure were excluded.

In the 9785-CL-0403 (UPWARD) single-arm trial to assess incidence of seizure in patients with predisposing factors for seizure (of whom 1.6 % had a history of seizures), 8 of 366 (2.2 %) patients treated with enzalutamide experienced a seizure. The median duration of treatment was 9.3 months.

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

Ischaemic heart disease

In randomised placebo-controlled clinical studies, ischaemic heart disease occurred in 3.9 % of patients treated with enzalutamide plus ADT compared with 1.5 % of patients treated with placebo plus ADT. Fifteen (0.4 %) patients treated with enzalutamide and 2 (0.1 %) patients treated with placebo had an ischaemic heart disease event that led to death.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS): https://pv.pharmacyboardkenya.org

4.9 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: endocrine therapy, 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 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.

Pharmacodynamic effects

In a phase 3 clinical trial (AFFIRM) of patients who failed prior chemotherapy with docetaxel, 54 % of patients treated with enzalutamide, versus 1.5 % of patients who received placebo, had at least a 50 % decline from baseline in PSA levels.

In another phase 3 clinical trial (PREVAIL) in chemotherapy-naive patients, patients receiving enzalutamide demonstrated a significantly higher total PSA response rate (defined as a ≥ 50 % reduction from baseline) compared with patients receiving placebo, 78.0 % versus 3.5 % (difference = 74.5 %, $p < 0.0001$).

In a phase 2 clinical trial (TERRAIN) in chemotherapy-naive patients, patients receiving enzalutamide demonstrated a significantly higher total PSA response rate compared with patients receiving bicalutamide, 82.1 % versus 20.9 % (difference = 61.2 %, $p < 0.0001$).

In a single-arm trial (9785-CL-0410) of patients previously treated with at least 24 weeks of abiraterone (plus prednisone), 22.4 % had a ≥ 50 % decrease from baseline in PSA levels. According to prior chemotherapy history, the proportions of patients with a ≥ 50 % decrease in PSA levels were 22.1 % and 23.2 % for the no prior chemotherapy and prior chemotherapy patient groups, respectively.

In the MDV3100-09 clinical trial (STRIVE) of non-metastatic and metastatic CRPC, patients receiving enzalutamide demonstrated a significantly higher total confirmed PSA response rate compared with patients receiving bicalutamide, 81.3 % versus 31.3 % (difference = 50.0 %, $p < 0.0001$).

In the MDV3100-14 clinical trial (PROSPER) of non-metastatic CRPC, patients receiving enzalutamide demonstrated a significantly higher confirmed PSA response rate compared with patients receiving placebo, 76.3 % versus 2.4 % (difference = 73.9 %, $p < 0.0001$).

Clinical efficacy and safety

Efficacy of enzalutamide was established in three randomised placebo-controlled multicentre phase 3 clinical studies [MDV3100-14 (PROSPER),

CRPC2 (AFFIRM), MDV3100-03 (PREVAIL)] of patients with progressive prostate cancer who had disease progression on androgen deprivation therapy [LHRH analogue or after bilateral orchiectomy]. The PREVAIL study enrolled metastatic CRPC chemotherapy-naive patients; the AFFIRM study enrolled metastatic CRPC patients who had received prior docetaxel; and the PROSPER study enrolled patients with non-metastatic CRPC. Additionally, efficacy in patients with mHSPC was established in one randomised, placebo-controlled multicentre phase 3 clinical study [9785-CL-0335 (ARCHES)]. All patients were treated with a LHRH analogue or had bilateral orchiectomy.

In the active treatment arm, enzalutamide was administered orally at a dose of 160 mg daily. In the four clinical studies (ARCHES, PROSPER, AFFIRM and PREVAIL), patients received placebo in the control arm and patients were allowed, but not required, to take prednisone (maximum daily dose allowed was 10 mg prednisone or equivalent).

Changes in PSA serum concentration independently do not always predict clinical benefit. Therefore, in the four studies it was recommended that patients be maintained on their study treatments until discontinuation criteria were met.

<u>9785-CL-0335 (ARCHES) study (patients with metastatic HSPC)</u>

The ARCHES study enrolled 1,150 patients with mHSPC randomised 1:1 to receive treatment with enzalutamide plus ADT or placebo plus ADT (ADT defined as LHRH analogue or bilateral orchiectomy). Patients received enzalutamide at 160 mg once daily (N = 574) or placebo (N = 576).

Patients with metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesions on CT or MRI scan (for soft tissue) were eligible. Patients whose disease spread was limited to regional pelvic lymph nodes were not eligible. Patients were allowed to receive up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of day 1 and no evidence of disease progression during or after the completion of docetaxel therapy. Excluded were patients with known or suspected brain metastasis or active leptomeningeal disease, or with a history of seizure or any condition that may predispose to seizure.

The demographic and baseline characteristics were well balanced between the two treatment groups. The median age at randomisation was 70 years in both treatment groups. Most patients in the total population were Caucasian (80.5 %); 13.5 % were Asian and 1.4 % were Black. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score was 0 for 78 % of patients and 1 for 22 % of patients at study entry.

Patients were stratified by low versus high volume of disease and prior docetaxel therapy for prostate cancer. Thirty-seven percent of patients had a low volume of disease and 63 % had a high volume of disease. Eighty-two percent of patients had not received prior docetaxel therapy,

2 % received 1-5 cycles and 16 % received 6 prior cycles. Treatment with concurrent docetaxel was not allowed.

Radiographic progression-free survival (rPFS), based on independent central review, was the primary endpoint, defined as the time from randomisation to the first objective evidence of radiographic disease progression or death (due to any cause from time of randomisation up until 24 weeks from study drug discontinuation), whichever occurred first.

Enzalutamide demonstrated a statistically significant 61 % reduction in the risk of an rPFS event compared to placebo [HR = 0.39 (95 % CI: 0.30, 0.50); p < 0.0001]. Consistent rPFS results were observed in patients with high or low volume of disease and patients with and without prior docetaxel therapy. The median time to an rPFS event was not reached in the enzalutamide arm and was 19.0 months (95 % CI: 16.6, 22.2) in the placebo arm.

Table 2: Summary of efficacy in patients treated with either enzalutamide or placebo in the ARCHES study (intent-to-treat analysis)

	Enzalutamide plus ADT (N = 574)	**Placebo plus ADT (N = 576)**
Radiographic progression-free survival		
Number of events (%)	91 (15.9)	201 (34.9)
Median, months (95% CI)[1]	NR	19.0 (16.6, 22.2)
Hazard ratio (95% CI)[2]	0.39 (0.30, 0.50)	
P-value[2]	p < 0.0001	

NR = not reached. [1] Calculated using the Brookmeyer and Crowley method. [2] Stratified by volume of disease (low vs high) and prior docetaxel use (yes or no).

At the pre-specified final analysis for overall survival, conducted when 356 deaths were observed, a statistically significant 34 % reduction in the risk of death was demonstrated in the group randomised to receive enzalutamide compared with the group randomised to receive placebo [HR = 0.66 (95 % CI: 0.53, 0.81), p < 0.0001]. The median time for overall survival was not reached in either treatment group. The estimated median follow-up time for all patients was 44.6 months.

Key secondary efficacy endpoints assessed in the study included time to PSA progression, time to start of new antineoplastic therapy, PSA undetectable rate (decline to < 0.2 µg/L) and objective response rate (RECIST 1.1 based on independent review). Statistically significant improvements in patients treated with enzalutamide compared to placebo were demonstrated for all these secondary endpoints.

MDV3100-14 (PROSPER) study (patients with non-metastatic CRPC)

The PROSPER study enrolled 1,401 patients with asymptomatic, high-risk non-metastatic CRPC who continued on androgen deprivation therapy (ADT; defined as LHRH analogue or prior bilateral orchiectomy). Patients were required to have a PSA doubling time ≤ 10 months, PSA ≥

2 ng/mL and confirmation of non-metastatic disease by blinded independent central review (BICR).

Patients with a history of mild to moderate heart failure (NYHA Class I or II) and patients taking medicinal products associated with lowering the seizure threshold were allowed. Patients were excluded with a previous history of seizure, a condition that might predispose them to seizure, or certain prior treatments for prostate cancer (chemotherapy, ketoconazole, abiraterone acetate, aminoglutethimide and/or enzalutamide).

Patients were randomised 2:1 to receive either enzalutamide at a dose of 160 mg once daily (N = 933) or placebo (N = 468). Patients were stratified by Prostate Specific Antigen Doubling Time (PSADT) (< 6 months or ≥ 6 months) and the use of bone-targeting agents (yes or no).

The demographic and baseline characteristics were well balanced between the two treatment arms. The median age at randomisation was 74 years in the enzalutamide arm and 73 years in the placebo arm. Most patients (approximately 71 %) were Caucasian; 16 % were Asian and 2 % were Black. Eighty-one percent of patients had an ECOG performance status score of 0 and 19 % had a score of 1.

Metastasis-free survival (MFS) was the primary endpoint, defined as the time from randomisation to radiographic progression or death within 112 days of treatment discontinuation without evidence of radiographic progression, whichever occurred first. Key secondary endpoints were time to PSA progression, time to first use of new antineoplastic therapy and overall survival.

Enzalutamide demonstrated a statistically significant 71 % reduction in the relative risk of radiographic progression or death compared to placebo [HR = 0.29 (95 % CI: 0.24, 0.35), p < 0.0001]. Median MFS was 36.6 months (95 % CI: 33.1, NR) on the enzalutamide arm versus 14.7 months (95 % CI: 14.2, 15.0) on the placebo arm. Consistent MFS results were observed in all pre-specified patient subgroups.

Table 3: Summary of efficacy results in the PROSPER study (intent-to-treat analysis)

	Enzalutamide (N = 933)	**Placebo (N = 468)**
Primary endpoint – metastasis-free survival		
Number of events (%)	219 (23.5)	228 (48.7)
Median, months (95% CI)[1]	36.6 (33.1, NR)	14.7 (14.2, 15.0)
Hazard ratio (95% CI)[2]	0.29 (0.24, 0.35)	
P-value[3]	p < 0.0001	
Key secondary endpoint – overall survival[4]		
Number of events (%)	288 (30.9)	178 (38.0)
Median, months (95% CI)[1]	67.0 (64.0, NR)	56.3 (54.4, 63.0)
Hazard ratio (95% CI)[2]	0.734 (0.608, 0.885)	
P-value[3]	p = 0.0011	
Time to PSA progression		
Number of events (%)	208 (22.3)	324 (69.2)
Median, months (95% CI)[1]	37.2 (33.1, NR)	3.9 (3.8, 4.0)

	Enzalutamide (N = 933)	Placebo (N = 468)
Hazard ratio (95% CI)[2]	0.07 (0.05, 0.08)	
P-value[3]	p < 0.0001	
Time to first use of new antineoplastic therapy		
Number of events (%)	142 (15.2)	226 (48.3)
Median, months (95% CI)[1]	39.6 (37.7, NR)	17.7 (16.2, 19.7)
Hazard ratio (95% CI)[2]	0.21 (0.17, 0.26)	
P-value[3]	p < 0.0001	

NR = not reached. [1] Based on Kaplan-Meier estimates. [2] HR is based on a Cox regression model (with treatment as the only covariate) stratified by PSA doubling time and prior or concurrent use of a bone-targeting agent; HR is relative to placebo, with < 1 favouring enzalutamide. [3] P-value is based on a stratified log-rank test by PSA doubling time and prior or concurrent use of a bone-targeting agent. [4] Based upon a pre-specified interim analysis with data cut-off date of 15 October 2019.

At the final analysis for overall survival, conducted when 466 deaths were observed, a statistically significant improvement in overall survival was demonstrated with a 26.6 % reduction in risk of death [HR = 0.734 (95 % CI: 0.608, 0.885), p = 0.0011]. The median follow-up time was 48.6 and 47.2 months for the enzalutamide and placebo groups respectively. Thirty-three percent of enzalutamide-treated and 65 % of placebo-treated patients received at least one subsequent antineoplastic therapy that may prolong overall survival.

MDV3100-09 (STRIVE) study (chemotherapy-naive patients with non-metastatic/metastatic CRPC)

The STRIVE study enrolled 396 non-metastatic or metastatic CRPC patients who had serologic or radiographic disease progression despite primary androgen deprivation therapy, randomised to receive either enzalutamide 160 mg once daily (N = 198) or bicalutamide 50 mg once daily (N = 198). PFS was the primary endpoint. Median PFS was 19.4 months (95 % CI: 16.5, not reached) in the enzalutamide group versus 5.7 months (95 % CI: 5.6, 8.1) in the bicalutamide group [HR = 0.24 (95 % CI: 0.18, 0.32), p < 0.0001]. For the non-metastatic subgroup (N = 139), 19 of 70 (27.1 %) patients treated with enzalutamide and 49 of 69 (71.0 %) patients treated with bicalutamide had PFS events; the hazard ratio was 0.24 (95 % CI: 0.14, 0.42) and the median time to a PFS event was not reached in the enzalutamide group versus 8.6 months in the bicalutamide group.

9785-CL-0222 (TERRAIN) study (chemotherapy-naive patients with metastatic CRPC)

The TERRAIN study enrolled 375 chemotherapy- and antiandrogen-therapy-naive patients with metastatic CRPC randomised to receive either enzalutamide 160 mg once daily (N = 184) or bicalutamide 50 mg once daily (N = 191). Median PFS was 15.7 months for patients on enzalutamide versus 5.8 months for patients on bicalutamide [HR = 0.44 (95 % CI: 0.34, 0.57), p < 0.0001]. Consistent PFS benefit was observed across all pre-specified patient subgroups.

MDV3100-03 (PREVAIL) study (chemotherapy-naive patients with metastatic CRPC)

A total of 1,717 asymptomatic or mildly symptomatic chemotherapy-naive patients were randomised 1:1 to receive either enzalutamide orally at a dose of 160 mg once daily (N = 872) or placebo orally once daily (N = 845). Patients with visceral disease, patients with a history of mild to moderate heart failure (NYHA Class I or II) and patients taking medicinal products associated with lowering the seizure threshold were allowed. Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate or severe pain from prostate cancer were excluded.

The median age was 71 years (range 42-93) and the racial distribution was 77 % Caucasian, 10 % Asian, 2 % Black and 11 % other or unknown. Sixty-eight percent of patients had an ECOG performance status score of 0. Approximately 45 % of patients had measurable soft tissue disease at study entry and 12 % had visceral (lung and/or liver) metastases.

Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS).

At the pre-specified interim analysis for overall survival, when 540 deaths were observed, treatment with enzalutamide demonstrated a statistically significant improvement in overall survival compared to placebo, with a 29.4 % reduction in risk of death [HR = 0.706 (95 % CI: 0.60, 0.84), p < 0.0001]. A final analysis of 5-year PREVAIL data showed a statistically significant increase in overall survival was maintained [HR = 0.835 (95 % CI: 0.75, 0.93); p = 0.0008] despite 28 % of patients on placebo crossing over to enzalutamide. The 5-year OS rate was 26 % for the enzalutamide arm compared with 21 % for the placebo arm.

Table 4: Overall survival of patients treated with either enzalutamide or placebo in the PREVAIL study (intent-to-treat analysis)

	Enzalutamide (N = 872)	**Placebo (N = 845)**
Pre-specified interim analysis		
Number of deaths (%)	241 (27.6 %)	299 (35.4 %)
Median survival, months (95% CI)	32.4 (30.1, NR)	30.2 (28.0, NR)
P-value[1]	p < 0.0001	
Hazard ratio (95% CI)[2]	0.71 (0.60, 0.84)	
Updated survival analysis		
Number of deaths (%)	368 (42.2 %)	416 (49.2 %)
Median survival, months (95% CI)	35.3 (32.2, NR)	31.3 (28.8, 34.2)
P-value[1]	p = 0.0002	
Hazard ratio (95% CI)[2]	0.77 (0.67, 0.88)	
5-year survival analysis		
Number of deaths (%)	689 (79 %)	693 (82 %)
Median survival, months (95% CI)	35.5 (33.5, 38.0)	31.4 (28.9, 33.8)
P-value[1]	p = 0.0008	
Hazard ratio (95% CI)[2]	0.835 (0.75, 0.93)	

NR = not reached. [1] P-value derived from an unstratified log-rank test. [2] Hazard ratio derived from an unstratified proportional hazards model; hazard ratio < 1 favours enzalutamide.

At the pre-specified rPFS analysis, a statistically significant improvement was demonstrated between the treatment groups with an 81.4 % reduction in risk of radiographic progression or death [HR = 0.19 (95 % CI: 0.15, 0.23), p < 0.0001]. The median rPFS was not reached (95 % CI: 13.8, not reached) in the enzalutamide-treated group and was 3.9 months (95 % CI: 3.7, 5.4) in the placebo-treated group.

The median time to initiation of cytotoxic chemotherapy was 28.0 months for patients receiving enzalutamide and 10.8 months for patients receiving placebo [HR = 0.35 (95 % CI: 0.30, 0.40), p < 0.0001]. The proportion of enzalutamide-treated patients with measurable disease at baseline who had an objective soft tissue response was 58.8 % (95 % CI: 53.8, 63.7) compared with 5.0 % (95 % CI: 3.0, 7.7) of patients receiving placebo. Enzalutamide significantly decreased the risk of the first skeletal-related event by 28 % [HR = 0.718 (95 % CI: 0.61, 0.84), p < 0.0001]. The median time to PSA progression per PCWG2 criteria was 11.2 months for patients treated with enzalutamide and 2.8 months for patients who received placebo [HR = 0.17 (95 % CI: 0.15, 0.20), p < 0.0001].

CRPC2 (AFFIRM) study (patients with metastatic CRPC who previously received chemotherapy)

A total of 1,199 patients were randomised 2:1 to receive either enzalutamide orally at a dose of 160 mg once daily (N = 800) or placebo once daily (N = 399). The median age was 69 years (range 41-92) and the racial distribution was 93 % Caucasian, 4 % Black, 1 % Asian and 2 % other. Most (91 %) patients had metastases in bone and 23 % had visceral lung and/or liver involvement.

The AFFIRM study excluded patients with medical conditions that may predispose them to seizures and medicinal products known to decrease the seizure threshold, as well as clinically significant cardiovascular disease.

The protocol pre-specified interim analysis after 520 deaths showed a statistically significant superiority in overall survival in patients treated with enzalutamide compared to placebo.

Table 5: Overall survival of patients treated with either enzalutamide or placebo in the AFFIRM study (intent-to-treat analysis)

	Enzalutamide (N = 800)	**Placebo (N = 399)**
Deaths (%)	308 (38.5 %)	212 (53.1 %)
Median survival, months (95% CI)	18.4 (17.3, NR)	13.6 (11.3, 15.8)
P-value[1]	p < 0.0001	
Hazard ratio (95% CI)[2]	0.63 (0.53, 0.75)	

NR = not reached. [1] P-value derived from a log-rank test stratified by ECOG performance status score (0-1 vs 2) and mean pain score (< 4 vs ≥ 4). [2] Hazard ratio derived from a stratified proportional hazards model; hazard ratio < 1 favours enzalutamide.

Radiographic progression-free survival was 8.3 months for patients treated with enzalutamide and 2.9 months for patients who received placebo [HR = 0.40 (95 % CI: 0.35, 0.47), p < 0.0001]. Confirmed PSA declines of 50 % or 90 % were 54.0 % and 24.8 % respectively for patients treated with enzalutamide, and 1.5 % and 0.9 % respectively for patients who received placebo (p < 0.0001). The median time to first skeletal-related event was 16.7 months for patients treated with enzalutamide and 13.3 months for patients who received placebo [HR = 0.69 (95 % CI: 0.57, 0.84), p < 0.0001].

9785-CL-0410 study (enzalutamide post-abiraterone in patients with metastatic CRPC)

This single-arm study in 214 patients with progressing metastatic CRPC who received enzalutamide (160 mg once daily) after at least 24 weeks of treatment with abiraterone acetate plus prednisone gave a median rPFS (the study's primary endpoint) of 8.1 months (95 % CI: 6.1, 8.3). Median OS was not reached. PSA response (defined as ≥ 50 % decrease from baseline) was 22.4 % (95 % CI: 17.0, 28.6). Although there was a limited response in some patients from treatment with enzalutamide after abiraterone, the reason for this finding is currently unknown.

Elderly

Of the 4,403 patients in the controlled clinical trials who received enzalutamide, 3,451 patients (78 %) were 65 years and over and 1,540 patients (35 %) were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

Paediatric population

The licensing authority has waived the obligation to submit the results of studies with enzalutamide in all subsets of the paediatric population in prostate carcinoma.

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 (t½) 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

The median time to reach maximum plasma enzalutamide concentrations (Cmax) is 2 hours (range 0.5 to 6 hours). Following oral administration of

160 mg daily in patients with metastatic CRPC, the steady-state plasma mean Cmax values for enzalutamide and its active metabolite are 16.6 µg/mL (23 % CV) and 12.7 µg/mL (30 % CV) respectively.

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.

Food has no clinically significant effect on the extent of absorption. In clinical trials, ENZACARE 40 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 medicinal products (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 4.5), 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.

Elimination

The mean apparent clearance (CL/F) of enzalutamide in patients ranges from 0.520 to 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).

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

major metabolites do not inhibit OATP1B1, OATP1B3, OCT2 or OAT1 at clinically relevant concentrations.

Linearity

No major deviations from dose proportionality are observed over the dose range 40 to 160 mg. The steady-state Cmin 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 study for enzalutamide has been completed. Patients with serum creatinine > 177 µmol/L (2 mg/dL) were excluded from clinical studies. Based on a population pharmacokinetic analysis, no dose adjustment is necessary for patients with calculated creatinine clearance (CrCL) values ≥ 30 mL/min (estimated by the Cockcroft-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. The half-life of enzalutamide 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.

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, the AUC and Cmax for enzalutamide in subjects with mild impairment increased by 5 % and 24 % respectively; in subjects with moderate impairment the AUC increased by 29 % and Cmax decreased by 11 %; and in subjects with severe impairment the AUC increased by 5 % and Cmax decreased by 41 %, compared to healthy control subjects. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC and Cmax in subjects with mild impairment increased by 14 % and 19 % respectively; in subjects with moderate impairment the AUC increased by 14 % and Cmax decreased by 17 %; and in subjects with severe hepatic impairment the AUC increased by 34 % and Cmax decreased by 27 %, compared to healthy control subjects.

Race

Most patients in the controlled clinical studies (> 75 %) were Caucasian. Based on pharmacokinetic data from studies 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 elderly population pharmacokinetic analysis.

5.3 Preclinical safety data

Enzalutamide treatment of pregnant mice resulted in an increased incidence of embryo-fetal deaths and external and skeletal changes. Fertility studies were not conducted with enzalutamide, but in studies in rats (4 and 26 weeks) and dogs (4, 13 and 39 weeks), atrophy, aspermia/hypospermia and hypertrophy/hyperplasia in the reproductive system were noted, consistent with the pharmacological activity of enzalutamide. In studies in mice (4 weeks), rats (4 and 26 weeks) and dogs (4, 13 and 39 weeks), changes in the reproductive organs associated with enzalutamide were decreases in organ weight with atrophy of the prostate and epididymis. Leydig cell hypertrophy and/or hyperplasia were observed in mice (4 weeks) and dogs (39 weeks). Additional changes to reproductive tissues included hypertrophy/hyperplasia of the pituitary gland and atrophy in seminal vesicles in rats, and testicular hypospermia and seminiferous tubule degeneration in dogs. Gender differences were noted in rat mammary glands (male atrophy and female lobular hyperplasia). Changes in the reproductive organs in both species were consistent with the pharmacological activity of enzalutamide and reversed or partially resolved after an 8-week recovery period. There were no other important changes in clinical pathology or histopathology in any other organ system, including the liver, in either species.

Studies in pregnant rats have shown that enzalutamide and/or its metabolites are transferred to fetuses. After oral administration of radiolabelled 14C-enzalutamide to rats on day 14 of pregnancy at a dose of 30 mg/kg (approximately 1.9 times the maximum dose indicated in humans), the maximum radioactivity in the fetus was reached 4 hours after administration and was lower than that in the maternal plasma, with a tissue/plasma ratio of 0.27. The radioactivity in the fetus decreased to 0.08 times the maximum concentration at 72 hours after administration.

Studies in lactating rats have shown that enzalutamide and/or its metabolites are secreted in rat milk. After oral administration of radiolabelled 14C-enzalutamide to lactating rats at a dose of 30 mg/kg (approximately 1.9 times the maximum dose indicated in humans), the maximum radioactivity in the milk was reached 4 hours after administration and was up to 3.54-fold higher than that in the maternal plasma. Study results also have shown that enzalutamide and/or its metabolites are transferred to infant rat tissues via milk and subsequently eliminated.

Enzalutamide was negative for genotoxicity in a standard battery of in vitro and in vivo tests. In a 6-month study in transgenic rasH2 mice, enzalutamide did not show carcinogenic potential (absence of neoplastic findings) at doses up to 20 mg/kg per day (AUC24h approximately 317 µg·h/mL), which resulted in plasma exposure levels similar to the clinical exposure (AUC24h approximately 322 µg·h/mL) in mCRPC patients receiving 160 mg daily.

Daily dosing of rats for two years with enzalutamide produced an increased incidence of neoplastic findings. These included benign thymoma, fibroadenoma in the mammary glands, benign Leydig cell tumours in the testes and urothelium papilloma and carcinoma of the urinary bladder in males; benign granulosa cell tumour in the ovaries in females; and adenoma in the pars distalis of the pituitary in both sexes. The human relevance of thymoma, pituitary adenoma and mammary fibroadenoma, as well as urothelium papilloma and carcinoma of the urinary bladder, cannot be ruled out. Enzalutamide was not phototoxic in vitro.

6. Pharmaceutical Particulars

6.1 List of Excipients

Capsule contents

- Lactose monohydrate
- Microcrystalline cellulose
- Croscarmellose sodium
- Povidone (PVP K 30)
- Colloidal silicon dioxide (light)
- Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

36 months.

6.4 Special Precautions for storage

Store at controlled room. temperature

6.5 Nature and Content of container

14 capsules in an alu-PVC blister. Four blisters (56 capsules) in a printed duplex board carton together with the package insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

8. Marketing Authorization Number
H2025/CTD10968/23337

9. Date of first authorization/renewal of the authorization
2025 January 23

10. Date of revision of the text
2025 January 23