1. NAME OF THE MEDICINAL PRODUCT

Bixodalan 250 mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg of abiraterone acetate.

Excipient with known effect
Each film-coated tablet contains 32.3 mg of lactose (34 mg as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White to off-white, oval-shaped film-coated tablets, debossed with "250" on one side, with dimensions of 14.2 mm x 7.2 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Nationally completed name] is indicated with prednisone or prednisolone for:

- the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see section 5.1)
- the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1)
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

4.2 Posology and method of administration

This medicinal product should be prescribed by an appropriate healthcare professional.

Posology
The recommended dose is 1,000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food (see "Method of administration" below). Taking the tablets with food increases systemic exposure to abiraterone (see sections 4.5 and 5.2).

Dosage of prednisone or *prednisolone*
For mHSPC, abiraterone is used with 5 mg prednisone or prednisolone daily.

For mCRPC, abiraterone is used with 10 mg prednisone or prednisolone daily.
Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.

- that (requested addition:)that

Recommended monitoring
Serum transaminases should be measured prior to starting treatment, every two weeks for the firstthree months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly. However, patients with a significant risk for congestive heart failure should be monitored every 2 weeks for the first three months of treatment and monthly thereafter (see section 4.4).

In patients with pre-existing hypokalaemia or those that develop hypokalaemia whilst being treated with abiraterone, consider maintaining the patient's potassium level at ≥ 4.0 mM.
For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema andother non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment with abiraterone should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline.
In the event of a missed daily dose of either [Nationally completed name], prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

Hepatotoxicity
For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]), treatment should be withheld immediately (see section 4.4). Re-treatment following return of liverfunction tests to the patient's baseline may be given at a reduced dose of 500 mg once daily. For patients being re-treated, serum transaminases should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of500 mg daily, treatment should be discontinued.

If patients develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy, treatment should be discontinued and patients should not be re-treated.

Hepatic impairment
No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A.

Moderate hepatic impairment (Child-Pugh Class B) has been shown to increase the systemic exposure to abiraterone by approximately four-fold following single oral doses of abiraterone acetate 1,000 mg(see section 5.2). There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted. The use of abiraterone should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see sections 4.2 and 5.2). Abiraterone should not be used in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Renal impairment
No dose adjustment is necessary for patients with renal impairment (see section 5.2). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients (see section 4.4).

Paediatric population
There is no relevant use of abiraterone in the paediatric population.

Method of administration
[Nationally completed name] is for oral use.
The tablets should be taken at least one hour before or at least two hours after eating. These should be swallowed whole with water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Women who are or may potentially be pregnant (see section 4.6).
- Severe hepatic impairment [Child-Pugh Class C (see sections 4.2, 4.4 and 5.2)].
- Abiraterone with prednisone or prednisolone is contraindicated in combination with Ra-223.

4.4 Special warnings and precautions for use

Hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess
Abiraterone may cause hypertension, hypokalaemia and fluid retention (see section 4.8) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see section 5.1). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in incidence and severity of these adverse reactions. Caution is required intreating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalaemia (e.g., those on cardiac glycosides), or fluid retention (e.g., those with heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia and those with severe renal impairment).

Abiraterone should be used with caution in patients with a history of cardiovascular disease. The Phase 3 studies conducted with abiraterone excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association Class (NYHA) III or IV heart failure (study 301) or Class II to IV heart failure (studies 3011 and 302) or cardiac ejection fraction measurement of < 50%. In studies 3011 and 302, patients with atrial fibrillation, or other cardiac arrhythmia requiring medical therapy were excluded. Safety in patients with left ventricular ejection fraction (LVEF) < 50% or NYHA Class III or IV heart failure (in study 301) or NYHA Class II to IV heart failure (in studies 3011 and 302) was not established (see sections 4.8 and 5.1).

Before treating patients with a significant risk for congestive heart failure (e.g.a history of cardiac failure, uncontrolled hypertension, or cardiac events such as ischaemic heart disease), consider obtaining an assessment of cardiac function (e.g. echocardiogram). Before treatment with abiraterone, cardiac failure should be treated and cardiac function optimised. Hypertension, hypokalaemia and fluid retention should be corrected and controlled. During treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral oedema), and other signs and symptoms of congestive heart failure should be monitored every 2 weeks for 3 months, then monthly thereafter and abnormalities corrected. QT prolongation has been observed in patients experiencing hypokalaemia in association with abiraterone treatment. Assess cardiac function as clinically indicated, institute appropriate management and consider discontinuation of this treatment if there is a clinically significant decrease in cardiac function (see section 4.2).

Hepatotoxicity and hepatic impairment

Marked increases in liver enzymes leading to treatment discontinuation or dose modification occurred in controlled clinical studies (see section 4.8). Serum transaminase levels should be measured prior to starting treatment, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases should be measured immediately. If at any time the ALT or AST rises above 5 times the ULN, treatment should be interrupted immediately and liver function closely monitored. Re-treatment may take place only after return of liver function tests to the patient's baseline and at a reduced dose level (see section 4.2).

If patients develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy, treatment should be discontinued and patients should not be re-treated.

Patients with active or symptomatic viral hepatitis were excluded from clinical trials; thus, there are no data to support the use of abiraterone in this population.

There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). The use of abiraterone should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see sections 4.2 and 5.2). Abiraterone should not be used in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).
There have been rare post-marketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome (see section 4.8).

Corticosteroid withdrawal and coverage of stress situations
Caution is advised and monitoring for adrenocortical insufficiency should occur if patients are withdrawn from prednisone or prednisolone. If abiraterone is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see information above).

In patients on prednisone or prednisolone who are subjected to unusual stress, an increased dose of corticosteroids may be indicated before, during and after the stressful situation.

Bone density
Decreased bone density may occur in men with metastatic advanced prostate cancer. The use of abiraterone in combination with a glucocorticoid could increase this effect.

Prior use of ketoconazole
Lower rates of response might be expected in patients previously treated with ketoconazole for prostate cancer.

Hyperglycaemia
The use of glucocorticoids could increase hyperglycaemia, therefore blood sugar should be measured frequently in patients with diabetes.

Hypoglycaemia
Cases of hypoglycaemia have been reported when abiraterone plus prednisone/prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see section 4.5); therefore, blood sugar should be monitored in patients with diabetes.

Use with chemotherapy

The safety and efficacy of concomitant use of abiraterone with cytotoxic chemotherapy has not been established (see section 5.1).

Intolerance to excipients
This medicinal product contains lactose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

Potential risks
Anaemia and sexual dysfunction may occur in men with metastatic prostate cancer including those undergoing treatment with abiraterone.

Skeletal muscle effects
Cases of myopathy and rhabdomyolysis have been reported in patients treated with abiraterone. Most cases developed within the first 6 months of treatment and recovered after abiraterone withdrawal. Caution is recommended in patients concomitantly treated with medicinal products known to be associated with myopathy/rhabdomyolysis.

Interactions with other medicinal products
Strong inducers of CYP3A4 during treatment are to be avoided unless there is no therapeutic alternative, due to risk of decreased exposure to abiraterone (see section 4.5).

Combination of abiraterone and prednisone/prednisolone with Ra-223
Treatment with abiraterone and prednisone/prednisolone in combination with Ra-223 is contraindicated (see section 4.3) due to an increased risk of fractures and a trend for increased mortality among asymptomatic or mildly symptomatic prostate cancer patients as observed in clinical trials.
It is recommended that subsequent treatment with Ra-223 is not initiated for at least 5 days after the last administration of abiraterone in combination with prednisone/prednisolone.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of food on abiraterone acetate
Administration with food significantly increases the absorption of abiraterone acetate. The efficacy and safety when given with food have not been established therefore this medicinal product must not be taken with food (see sections 4.2 and 5.2).

Interactions with other medicinal products
Potential for other medicinal products to affect abiraterone exposures
In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer rifampicin, 600 mg daily for 6 days followed by a single dose of abiraterone acetate 1,000 mg, the mean plasma AUC_{∞} of abiraterone was decreased by 55%.

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [*Hypericum perforatum*]) during treatment are to be avoided, unless there is no therapeutic alternative.

In a separate clinical pharmacokinetic interaction study of healthy subjects, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Potential to affect exposures to other medicinal products
Abiraterone is an inhibitor of the hepatic drug-metabolising enzymes CYP2D6 and CYP2C8.
In a study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 2.9 fold. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when administering with medicinal products activated by or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised by CYP2D6 should be considered. Examples of medicinal products metabolised by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter three medicinal products requiring CYP2D6 to form their active analgesic metabolites).

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate.
Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Examples of medicinal products metabolised by CYP2C8 include pioglitazone and repaglinide (see section 4.4).

In vitro, the major metabolites abiraterone sulphate and N-oxide abiraterone sulphate were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the concentrations of medicinal products eliminated by OATP1B1. There are no clinical data available to confirm transporter based interaction.

Use with products known to prolong QT interval
Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering abiraterone with medicinal products known to prolong the QT interval or medicinal products able to induce torsades de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc.

Use with Spironolactone
Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with abiraterone is not recommended (see section 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
There are no human data on the use of abiraterone in pregnancy and this medicinal product is not for use in women of childbearing potential.

Contraception in males and females

It is not known whether abiraterone or its metabolites are present in semen. A condom is required ifthe patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of childbearing potential, a condom is required along with another effective contraceptive method. Studies in animals have shown reproductive toxicity (see section 5.3).

Pregnancy
Abiraterone is not for use in women and is contraindicated in women who are or may potentially be pregnant (see section 4.3 and 5.3).

Breast-feeding
Abiraterone is not for use in women.

Fertility
Abiraterone affected fertility in male and female rats, but these effects were fully reversible (see section 5.3).

4.7 Effects on ability to drive and use machines

Abiraterone has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
In an analysis of adverse reactions of composite Phase 3 studies with abiraterone, adverse reactions that were observed in ≥10% of patients were peripheral oedema, hypokalaemia, "hypertension" urinary tract infection, and alanine aminotransferase increased and/or aspartate aminotransferase increased.
Other important adverse reactions include cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis.

Abiraterone may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In Phase 3 studies, anticipated mineralocorticoid adverse reactions were seen more commonly in patients treated with abiraterone acetate than in patients treated with placebo: hypokalaemia 18% vs.8%, hypertension 22% vs. 16% and fluid retention (peripheral oedema) 23% vs. 17%, respectively. In patients treated with abiraterone acetate versus patients treated with placebo: CTCAE(version 4.0) Grades 3 and 4 hypokalaemia were observed in 6% versus 1%. CTCAE (version 4.0) Grades 3 and 4 hypertension were observed in 7% versus 5%, and fluid retention (peripheral oedema) Grades 3 and 4 were observed in 1% versus 1% of patients, respectively. Mineralocorticoid reactions generally were able to be successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions (see section 4.4).

Tabulated list of adverse reactions
In studies of patients with metastatic advanced prostate cancer who were using an LHRH analogue, or were previously treated with orchiectomy, abiraterone was administered at a dose of 1,000 mg daily in combination with low dose prednisone or prednisolone (either 5 or 10 mg daily depending on the indication).

Adverse reactions observed during clinical studies and post-marketing experience 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) and not known (frequency cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

1 **Table 1: Adverse reactions identified in clinical studies and post-marketing**

System Organ Class	Adverse reaction and frequency
Infections and infestations	*very common*: urinary tract infection
	common: sepsis
Immune system disorders	*not known:* anaphylactic reactions
Endocrine disorders	*uncommon*: adrenal insufficiency
Metabolism and nutrition disorders	*very common*: hypokalaemia
	common: hypertriglyceridaemia
Cardiac disorders	*common*: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia
	uncommon: other arrhythmias
	not known: myocardial infarction, QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	*very common*: hypertension
Respiratory, thoracic and mediastinal disorders	*rare:* allergic alveolitis[a]
Gastrointestinal disorders	*very common:* diarrhoea
	common: dyspepsia
Hepatobiliary disorders	*very common:* alanine aminotransferase increased and/or aspartate aminotransferase increased[b]
	rare: hepatitis fulminant, acute hepatic failure
Skin and subcutaneous tissue disorders	*common:* rash
Musculoskeletal and connective tissue disorders	*uncommon:* myopathy, rhabdomyolysis
Renal and urinary disorders	*common:* haematuria
General disorders and administration site conditions	*very common:* oedema peripheral
Injury, poisoning and procedural complications	*common:* fractures**

* Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased

** Fractures includes osteoporosis and all fractures with the exception of pathological fractures

[a] Spontaneous reports from post-marketing experience

[b] Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST increased, and hepatic function abnormal.

The following CTCAE (version 4.0) Grade 3 adverse reactions occurred in patients treated with abiraterone acetate: hypokalaemia 5%; urinary tract infection 2%; alanine aminotransferase increased and/or aspartate aminotransferase increased 4%; hypertension 6%; fractures 2%; peripheral oedema, cardiac failure, and atrial fibrillation 1% each. CTCAE (version 4.0) Grade 3 hypertriglyceridaemia and angina pectoris occurred in < 1% of patients. CTCAE (version 4.0) Grade 4 urinary tract infection, alanine aminotransferase increased and/or aspartate aminotransferase increased, hypokalemia, cardiac failure, atrial fibrillation, and fractures occurred in < 1% of patients.

A higher incidence of hypertension and hypokalemia was observed in the hormone sensitive population (study 3011). Hypertension was reported in 36.7% of patients in the hormone sensitive population (study 3011) compared to 11.8% and 20.2% in studies 301 and 302, respectively.
Hypokalemia was observed in 20.4% of patients in the hormone sensitive population (study 3011) compared to 19.2% and 14.9% in 301 and 302, respectively).

The incidence and severity of adverse events was higher in the subgroup of patients with baseline ECOG2 performance status grade and also in elderly patients (≥75 years).

Description of selected adverse reactions

Cardiovascular reactions
The three Phase 3 studies excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV heart failure (study 301) or Class II to IV heart failure (studies 3011 and 302) or cardiac ejection fraction measurement of < 50%. All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy, predominantly with the use of LHRH analogues, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death. The incidence of cardiovascular adverse reactions in the Phase 3 studies in patients taking abiraterone acetate versus patients taking placebo were as follows: atrial fibrillation 2.6% vs. 2.0%, tachycardia 1.9% vs. 1.0%,angina pectoris 1.7% vs. 0.8%, cardiac failure 0.7% vs. 0.2%, and arrhythmia 0.7% vs. 0.5%.

Hepatotoxicity
Hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with abiraterone acetate. Across Phase 3 clinical studies, hepatotoxicity grades 3 and 4 (e.g., ALT or AST increases of > 5 x ULN or bilirubin increases > 1.5 x ULN) were reported in approximately 6% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment.In Study 3011, grade 3 or 4 hepatotoxicity was observed in 8.4% of patients treated with abiraterone. Ten patients who received abiraterone were discontinued because of hepatotoxicity; two had Grade 2 hepatotoxicity, six had Grade 3 hepatotoxicity, and two had Grade 4 hepatotoxicity. No patient died of hepatotoxicity in Study 3011. In the Phase 3 clinical studies, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5 x ULN, or elevations in bilirubin > 3 x ULN were observed, abiraterone acetate was withheld or discontinued. In two instances marked increases in liver function tests occurred (see section 4.4). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 x ULN and bilirubin elevations 2 to 6 x ULN. Upon discontinuation of treatment, both patients had normalisation of their liver function tests and one patient was re-treated without recurrence of the elevations. In study 302, Grade 3 or 4 ALT or AST elevations were observed in 35 (6.5%) patients treated with abiraterone acetate.

Aminotransferase elevations resolved in all but 3 patients (2 with new multiple liver metastases and 1 with AST elevation approximately 3 weeks after the last dose of abiraterone acetate). In Phase 3 clinical studies, treatment discontinuations due to ALT and AST increases or abnormal hepatic function were reported in 1.1% of patients treated with abiraterone acetate and 0.6% of patients treated with placebo; no deaths were reported due to hepatotoxicity events.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with baseline hepatitis or significant abnormalities of liver function tests. In the 3011 trial, patients with baseline ALT and AST > 2.5 X ULN, bilirubin > 1.5 X ULN or those with active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction were excluded. In the 301 trial, patients with baseline ALT and AST ≥ 2.5 x ULN in the absence of liver metastases and > 5 x ULN in the presence of liver metastases were excluded. In the 302 trial, patients with liver metastases were not eligible and patients with baseline ALT and AST ≥ 2.5 x ULN were excluded. Abnormal liver function tests developing in patients participating in clinical trials were vigorously managed by requiring treatment interruption and permitting re-treatment only after return of liver function tests to the patient's baseline (see section 4.2). Patients with elevations of ALT or AST > 20 x ULN were not re-treated. The safety of re-treatment in such patients is unknown. The mechanism for hepatotoxicity is not understood.

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 national reporting system listed in Appendix V.

4.9 Overdose

Human experience of overdose with abiraterone is limited.

There is no specific antidote. In the event of an overdose, administration should be withheld and general supportive measures undertaken, including monitoring for arrhythmias, hypokalaemia and for signs and symptoms of fluid retention. Liver function also should be assessed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: endocrine therapy, other hormone antagonists and related agents, ATC code: L02BX03

Mechanism of action
Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17).
This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumour tissues. CYP17 catalyses the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17α-hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals (see section 4.4).

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with LHRH analogues or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumour. Treatment with abiraterone decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH analogues (or orchiectomy).

Pharmacodynamic effects
Abiraterone decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH analogues alone or by orchiectomy. This results from the selective inhibition of the CYP17 enzyme required for androgen biosynthesis. PSA serves as a biomarker in patients with prostate cancer. In a Phase 3 clinical study of patients who failed prior chemotherapy with taxanes, 38% of patients treated with abiraterone acetate, versus 10% of patients treated with placebo, had at least a 50% decline from baseline in PSA levels.

Clinical efficacy and safety
Efficacy was established in three randomised placebo-controlled multicentre Phase 3 clinical studies(studies 3011, 302 and 301) of patients with mHSPC and mCRPC. Study 3011 enrolled patients who were newly diagnosed (within 3 months of randomization) mHSPC who had high-risk prognostic factors. High-risk prognosis was defined as having at least 2 of the following 3 risk factors: (1) Gleason score of ≥8; (2) presence of 3 or more lesions on bone scan; (3) presence of measurable visceral (excluding lymph node disease) metastasis. In the active arm, abiraterone was administered at a dose of 1000 mg daily in combination with low dose prednisone 5 mg once daily in addition to ADT (LHRH agonist or orchiectomy), which was the standard of care treatment. Patients in the control arm received ADT and placebos for both abiraterone and prednisone. Study 302 enrolled docetaxel naïve patients; whereas, study 301 enrolled patients who had received prior docetaxel. Patients were using an LHRH analogue or were previously treated with orchiectomy. In the active treatment arm, abiraterone was administered at a dose of 1,000 mg daily in combination with low dose prednisone or prednisolone 5 mg twice daily. Control patients received placebo and low dose prednisone or prednisolone 5 mg twice daily.

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

In all studies spironolactone use was not allowed as spironolactone binds to the androgen receptor and may increase PSA levels.

Study 3011 (patients with newly diagnosed high risk mHSPC)
In Study 3011, (n=1199) the median age of enrolled patients was 67 years. The number of patients treated with abiraterone by racial group was Caucasian 832 (69.4%), Asian 246 (20.5%), Black or African American 25 (2.1%), other 80 (6.7%), unknown/not reported 13 (1.1%), and American Indian or Alaska Native 3 (0.3%). The ECOG performance status was 0

or 1 for 97% of patients. Patients with known brain metastasis, uncontrolled hypertension, significant heart disease, or NYHA Class II-IV heart failure were excluded. Patients that were treated with prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer were excluded with the exception of up to 3 months of ADT or 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease. Co-primary efficacy endpoints were overall survival (OS) and radiographic progression-free survival (rPFS). The median baseline pain score, as measured by the Brief Pain Inventory Short Form (BPI-SF) was 2.0 in both the treatment and Placebo groups. In addition to the co-primary endpoint measures, benefit was also assessed using time to skeletal-related event (SRE),time to subsequent therapy for prostate cancer, time to initiation of chemotherapy, time to pain progression, and time to PSA progression. Treatment continued until disease progression, withdrawal of consent, the occurrence of unacceptable toxicity, or death.

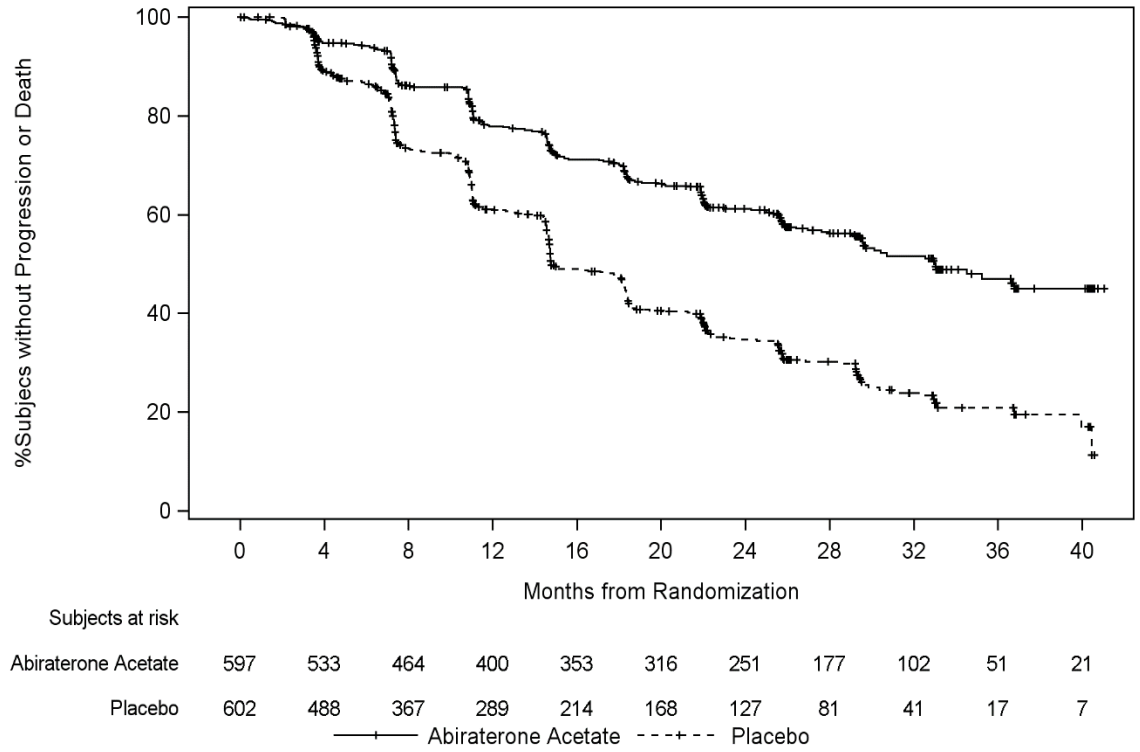
Radiographic progression-free survival was defined as the time from randomization to the occurrence of radiographic progression or death from any cause. Radiographic progression included progression by bone scan (according to modified PCWG2) or progression of soft tissue lesions by CT or MRI(according to RECIST 1.1).
A significant difference in rPFS between treatment groups was observed (see Table 2 and Figure 1).

Table 2: Radiographic Progression-Free Survival - Stratified Analysis; Intent-to-treat Population (Study PCR3011)

	AA-P	Placebo
Subjects randomised	597	602
Event	239 (40.0%)	354 (58.8%)
Censored	358 (60.0%)	248 (41.2%)
Time to Event (months)		
Median (95% CI)	33.02 (29.57, NE)	14.78 (14.69, 18.27)
Range	(0.0+, 41.0+)	(0.0+, 40.6+)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.466 (0.394, 0.550)	

Note: += censored observation, NE=not estimable. The radiographic progression and death are considered in defining the rPFS event. AA-P= subjects who received abiraterone acetate and prednisone.
[a] p value is from a log-rank test stratified by ECOG PS score (0/1 or 2) and visceral lesion (absent or present).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors AA-P.

Figure 1: Kaplan-Meier Plot of Radiographic Progression-free Survival; Intent-to-treat Population
(Study PCR3011)



A statistically significant improvement in OS in favor of AA-P plus ADT was observed with a 34% reduction in the risk of death compared to Placebo plus ADT (HR=0.66; 95% CI: 0.56, 0.78;p<0.0001) (see Table 3 and Figure 2).

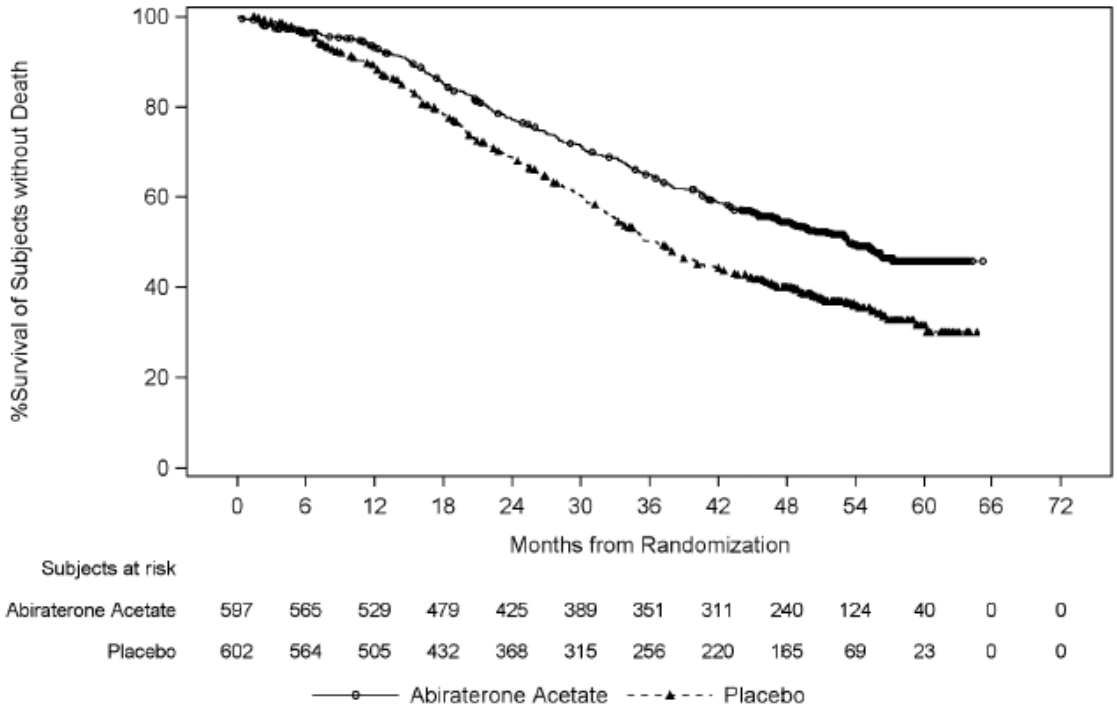
Table 3 Overall Survival of Patients Treated with Either Abiraterone or Placebos in Study PCR3011 (Intent-to-treat Analysis)

Overall Survival	Abiraterone with Prednisone (N=597)	Placebos (N=602)
Deaths (%)	275 (46%)	343 (57%)
Median survival (months)	53.3	36.5
(95% CI)	(48.2, NE)	(33.5, 40.0)
Hazard ratio (95% CI)[1]	0.66 (‘056’, ‘078’)	

NE = Not estimable

[1] Hard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors Abiraterone with prednisone.

Figure 2: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population in Study PCR3011 Analysis



Subgroup analyses consistently favor treatment with abiraterone. The treatment effect of AA-P on rPFS and OS across the pre-specified subgroups was favorable and consistent with the overall study population, except for the subgroup of ECOG score of 2 where no trend towards benefit was observed, however the small sample size (n=40) limits drawing any meaningful conclusion.

In addition to the observed improvements in overall survival and rPFS, benefit was demonstrated for abiraterone vs. placebo treatment in all prospectively-defined secondary endpoints.

Study 302 (chemotherapy naïve patients)
This study enrolled chemotherapy naïve patients who were asymptomatic or mildly symptomatic and for whom chemotherapy was not yet clinically indicated. A score of 0-1 on Brief Pain Inventory-Short Form (BPI-SF) worst pain in last 24 hours was considered asymptomatic, and a score of 2-3 was considered mildly symptomatic.

In study 302, (n = 1,088) the median age of enrolled patients was 71 years for patients treated with abiraterone plus prednisone or prednisolone and 70 years for patients treated with placebo plus prednisone or prednisolone. The number of patients treated with abiraterone by racial group was Caucasian 520 (95.4%), Black 15 (2.8%), Asian 4 (0.7%) and other 6 (1.1%). The Eastern Cooperative Oncology Group (ECOG) performance status was 0 for 76% of patients, and 1 for 24% of patients in both arms. Fifty percent of patients had only bone metastases, an additional 31% of patients had bone and soft tissue or lymph node metastases and 19% of patients had only soft tissue or lymph node metastases. Patients with visceral metastases were excluded. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). In addition to the co-primary endpoint measures, benefit was also assessed using time to opiate use for cancer pain, time to initiation of cytotoxic chemotherapy, time to deterioration in ECOG performance score by ≥ 1 point and time to PSA progression based on Prostate Cancer Working Group-2 (PCWG2) criteria. Study treatments were discontinued at the time of unequivocal clinical progression. Treatments could also be discontinued at the time of confirmed radiographic progression at the discretion of the investigator.

Radiographic progression free survival (rPFS) was assessed with the use of sequential imaging studies as defined by PCWG2 criteria (for bone lesions) and modified Response Evaluation Criteria In SolidTumors (RECIST) criteria (for soft tissue lesions). Analysis of rPFS utilised centrally-reviewed radiographic assessment of progression.

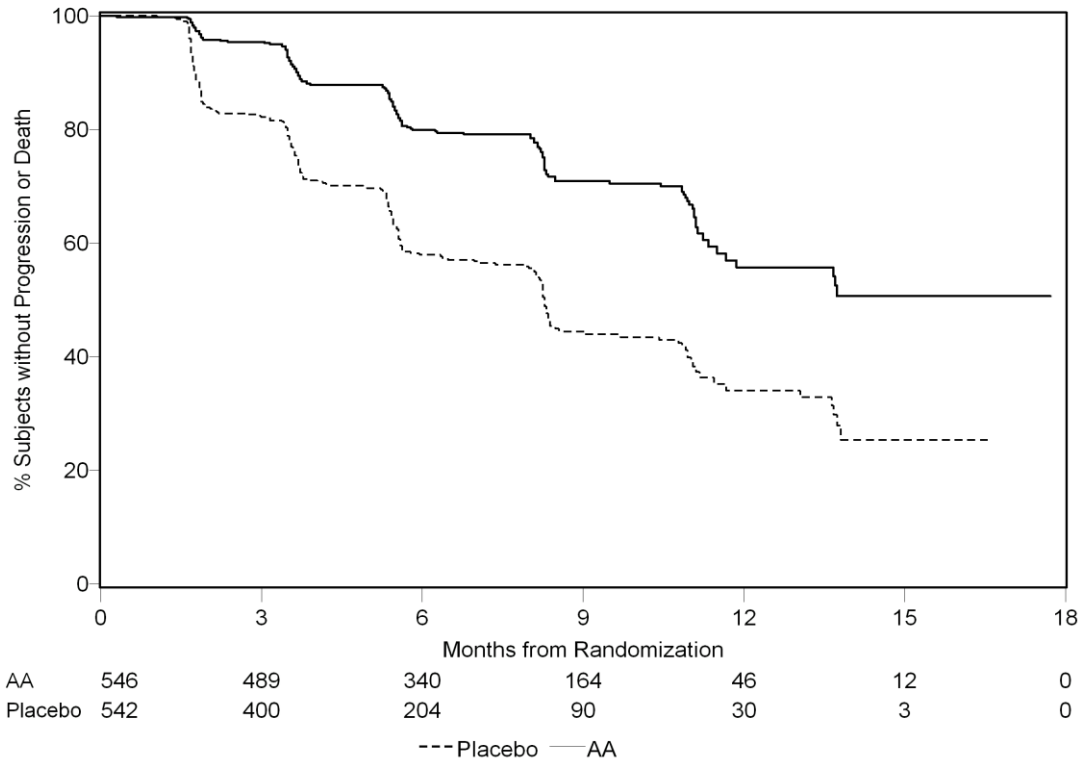
At the planned rPFS analysis there were 401 events, 150 (28%) of patients treated with abiraterone and 251 (46%) of patients treated with placebo had radiographic evidence of progression or had died. A significant difference in rPFS between treatment groups was observed (see Table 4 and Figure 3).

Table 4 Study 302: Radiographic progression-free survival of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

	ABIRATERONE (N = 546)	Placebo (N = 542)
Radiographic Progression-free Survival (rPFS)		
Progression or death	150 (28%)	251 (46%)
Median rPFS in months	Not reached	8.3
(95% CI)	(11.66; NE)	(8.12; 8.54)
p value*	< 0.0001	
Hazard ratio** (95% CI)[b]	0.425 (0.347; 0.522)	

NE=not estimated.
*p value is derived from a log-rank test stratified by baseline ECOG score (0 or 1)
**Hazard ratio <1 favors Abiraterone.

Figure 3: Kaplan Meier curves of radiographic progression-free survival in patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy



AA = Abiraterone

However, subject data continued to be collected through the date of the second interim analysis of Overall survival (OS). The investigator radiographic review of rPFS performed as a follow up sensitivity analysis is presented in Table 5 and Figure 4.

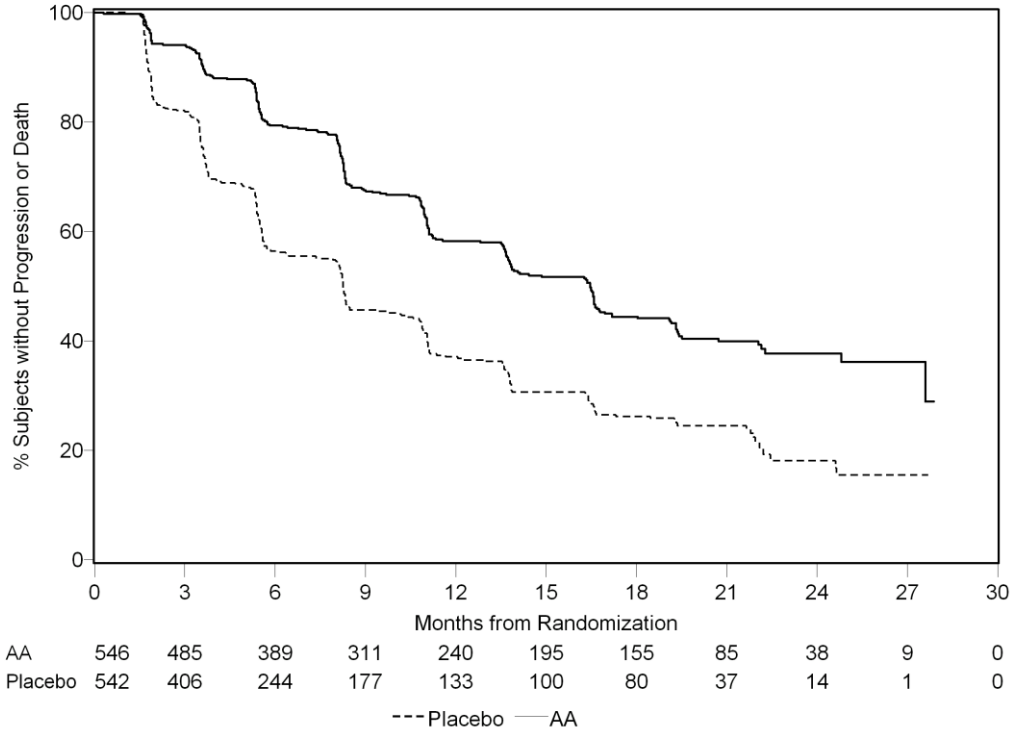
Six hundred and seven (607) subjects had radiographic progression or died: 271 (50%) in the abiraterone acetate group and 336 (62%) in the placebo group. Treatment with abiraterone acetate decreased the risk of radiographic progression or death by 47% compared with placebo (HR = 0.530; 95% CI: [0.451; 0.623], $p < 0.0001$). The median rPFS was 16.5 months in the abiraterone acetate group and 8.3 months in the placebo group.

Table 5 Study 302: Radiographic progression-free survival of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS-Investigator Review)

	ABIRATERONE (N = 546)	Placebo (N = 542)
Radiographic Progression-free Survival (rPFS)		
Progression or death	271 (50%)	336 (62%)
Median rPFS in months	16.5	8.3
(95% CI)	(13.80; 16.79)	(8.05; 9.43)
p value*	< 0.0001	
Hazard ratio** (95% CI)[b]	0.530 (0.451; 0.623)	

*p value is derived from a log-rank test stratified by baseline ECOG score (0 or 1)
**Hazard ratio <1 favors Abiraterone.

Figure 4: Kaplan Meier curves of radiographic progression-free survival in patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS-Investigator Review)



AA = Abiraterone

A planned interim analysis (IA) for OS was conducted after 333 deaths were observed. The study was unblinded based on the magnitude of clinical benefit observed and patients in the placebo group were offered treatment with abiraterone. Overall survival was longer for

abiraterone than placebo with a 25% reduction in risk of death (HR = 0.752; 95% CI: [0.606; 0.934], p = 0.0097), but OS was not mature and interim results did not meet the pre-specified stopping boundary for statistical significance (see Table 4). Survival continued to be followed after this IA.

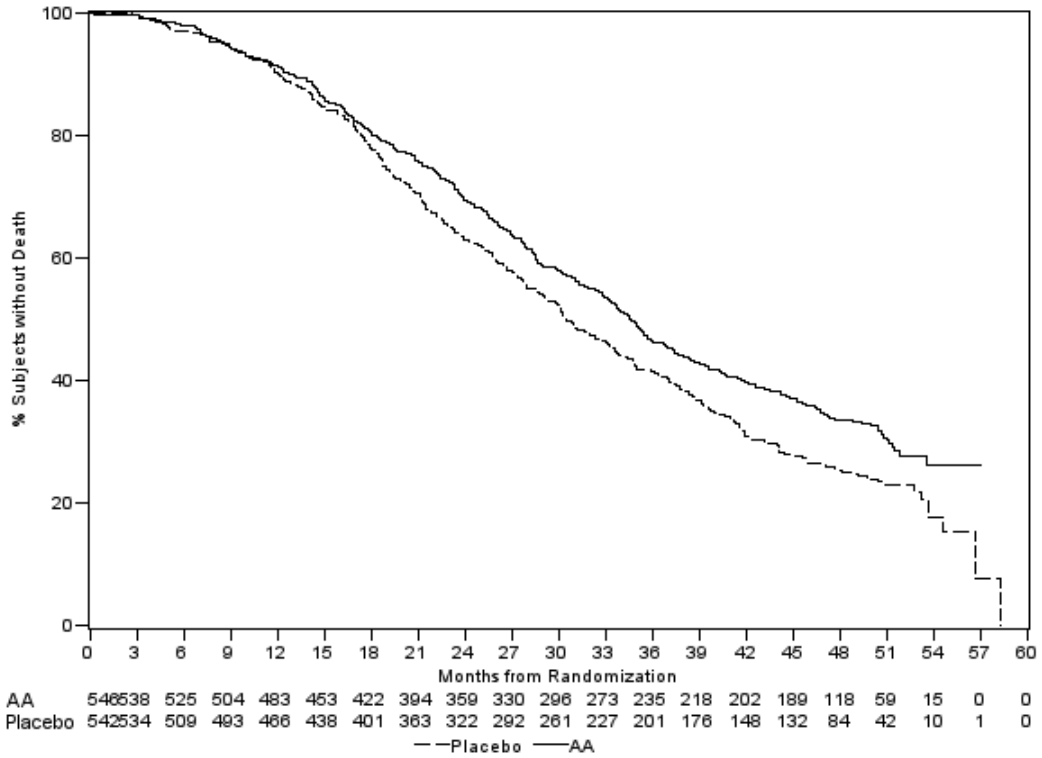
The planned final analysis for OS was conducted after 741 deaths were observed (median follow up of 49 months). Sixty-five percent (354 of 546) of patients treated with abiraterone, compared with 71% (387 of 542) of patients treated with placebo, had died. A statistically significant OS benefit in favour of the abiraterone -treated group was demonstrated with a 19.4% reduction in risk of death (HR = 0.806; 95% CI: [0.697; 0.931], p = 0.0033) and an improvement in median OS of 4.4 months abiraterone 34.7 months, placebo 30.3 months) (see Table 6 and Figure 5). This improvement was demonstrated even though 44% of patients in the placebo arm received abiraterone as subsequent therapy.

Table 6 Study 302: Overall survival of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

	ABIRATERONE (N = 546)	**Placebo (N = 542)**
Interim survival analysis		
Deaths (%)	147 (27%)	186 (34%)
Median survival (months) (95% CI)	Not reached (NE; NE)	27.2 (25.95; NE)
p-value*	0.0097	
Hazard ratio** (95% CI)	0.752 (0.606; 0.934)	
Final survival analysis		
Deaths	354 (65%)	387 (71%)
Median overall survival in months (95% CI)	34.7 (32.7; 36.8)	30.3 (28.7; 33.3)
p-value*	0.0033	
Hazard ratio** (95% CI)	0.806 (0.697; 0.931)	

NE = Not Estimated
*p value is derived from a log-rank test stratified by baseline ECOG score (0 or 1)
**Hazard ratio <1 favors Abiraterone.

Figure 5: Kaplan Meier survival curves of patients treated with either Abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy, final analysis



AA = Abiraterone

In addition to the observed improvements in overall survival and rPFS, benefit was demonstrated for abiraterone vs. placebo treatment in all secondary endpoint measures as follows:

Time to PSA progression based on PCWG2 criteria: The median time to PSA progression was 11.1 months for patients receiving abiraterone and 5.6 months for patients receiving placebo (HR = 0.488; 95% CI: [0.420; 0.568], $p < 0.0001$). The time to PSA progression was approximately doubled with abiraterone treatment (HR = 0.488). The proportion of subjects with a confirmed PSA response was greater in the abiraterone group than in the placebo group (62% vs. 24%; $p < 0.0001$). In subjects with measurable soft tissue disease, significantly increased numbers of complete and partial tumor responses were seen with abiraterone treatment.

Time to opiate use for cancer pain: The median time to opiate use for prostate cancer pain at the time of final analysis was 33.4 months for patients receiving abiraterone and was 23.4 months for patients receiving placebo (HR = 0.721; 95% CI: [0.614; 0.846], $p < 0.0001$).

Time to initiation of cytotoxic chemotherapy: The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients receiving abiraterone and 16.8 months for patients receiving placebo (HR = 0.580; 95% CI: [0.487; 0.691], $p < 0.0001$).

Time to deterioration in ECOG performance score by ≥ 1 point: The median time to deterioration in ECOG performance score by ≥ 1 point was 12.3 months for patients receiving abiraterone and 10.9 months for patients receiving placebo (HR = 0.821; 95% CI: [0.714; 0.943], p = 0.0053).

The following study endpoints demonstrated a statistically significant advantage in favour of abiraterone treatment:

Objective response**:** Objective response was defined as the proportion of subjects with measurable disease achieving a complete or partial response according to RECIST criteria (baseline lymph node size was required to be ≥ 2 cm to be considered a target lesion). The proportion of subjects with measurable disease at baseline who had an objective response was 36% in the abiraterone group and16% in the placebo group (p < 0.0001).

Pain**:** Treatment with abiraterone significantly reduced the risk of average pain intensity progression by 18% compared with placebo (p = 0.0490). The median time to progression was 26.7 months in the abiraterone group and 18.4 months in the placebo group.

Time to degradation in the FACT-P (Total Score): Treatment with abiraterone decreased the risk of FACT-P (Total Score) degradation by 22% compared with placebo (p = 0.0028). The median time to degradation in FACT-P (Total Score) was 12.7 months in the abiraterone group and 8.3 months in the placebo group.

Study 301 (patients who had received prior chemotherapy)
Study 301 enrolled patients who had received prior docetaxel. Patients were not required to show disease progression on docetaxel, as toxicity from this chemotherapy may have led to discontinuation. Patients were maintained on study treatments until there was PSA progression (confirmed 25% increase over the patient's baseline/nadir) together with protocol-defined radiographic progression and symptomatic or clinical progression. Patients with prior ketoconazole treatment for prostate cancer were excluded from this study. The primary efficacy endpoint was overall survival.

The median age of enrolled patients was 69 years (range 39-95). The number of patients treated with abiraterone by racial group was Caucasian 737 (93.2%), Black 28 (3.5%), Asian 11 (1.4%) and other 14 (1.8%). Eleven percent of patients enrolled had an ECOG performance score of 2; 70% had radiographic evidence of disease progression with or without PSA progression; 70% had received one prior cytotoxic chemotherapy and 30% received two. Liver metastasis was present in 11% of patients treated with abiraterone.

In a planned analysis conducted after 552 deaths were observed, 42% (333 of 797) of patients treated with abiraterone compared with 55% (219 of 398) of patients treated with placebo, had died. A statistically significant improvement in median overall survival was seen in patients treated with abiraterone (see Table 7).

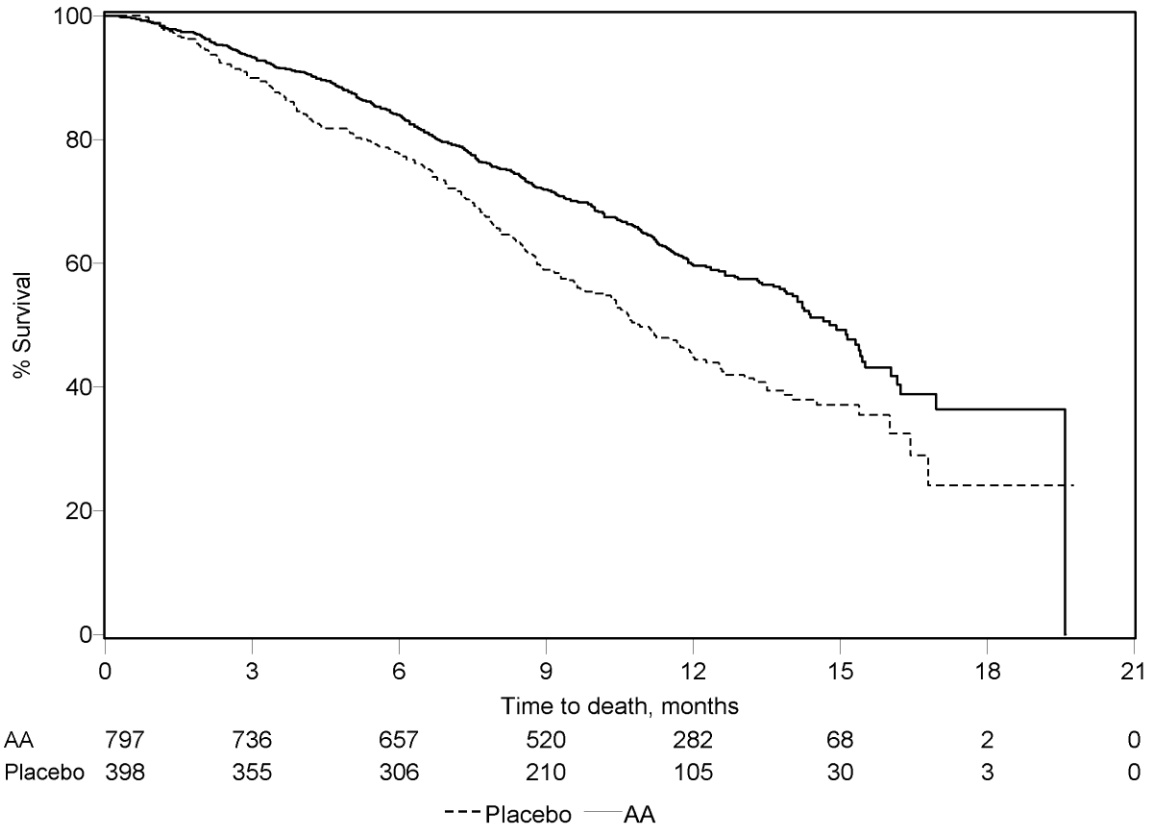
Table 7 Overall survival of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

	ABIRATERONE (N = 797)	Placebo (N = 398)
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1; 15.4)	10.9 (10.2; 12.0)
p-value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.646 (0.543; 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median survival (months) (95% CI)	15.8 (14.8; 17.0)	11.2 (10.4; 13.1)
Hazard ratio (95% CI)[b]	0.740 (0.638; 0.859)	

[a] p value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs. 2), pain score (absent vs. present), number of prior chemotherapy regimens (1 vs. 2), and type of disease progression (PSA only vs. radiographic).
[b] Hazard ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors Abiraterone.

At all evaluation time points after the initial few months of treatment, a higher proportion of patients treated with abiraterone remained alive, compared with the proportion of patients treated with placebo (see Figure 6).

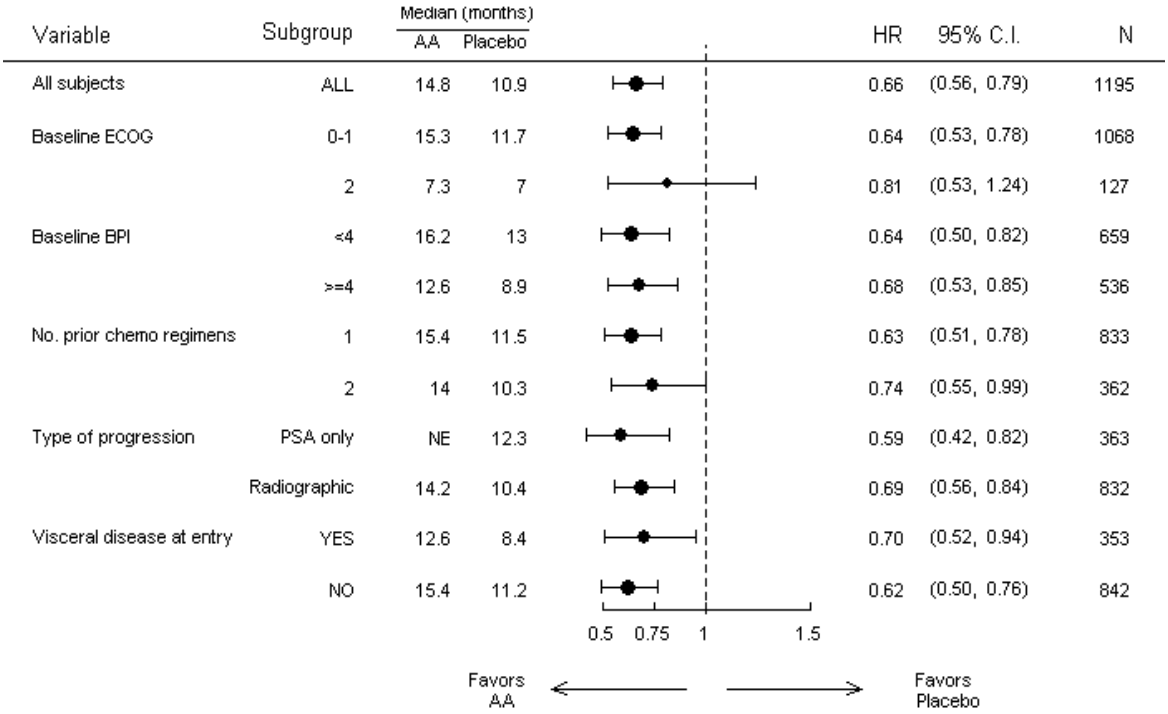
Figure6: Kaplan Meier survival curves of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy



AA = Abiraterone

Subgroup survival analyses showed a consistent survival benefit for treatment with abiraterone (see Figure 7).

Figure 7: Overall survival by subgroup: hazard ratio and 95% confidence interval



AA = Abiraterone; BPI = Brief Pain Inventory; C.I. = confidence interval; ECOG = Eastern Cooperative Oncology Group performance score; HR = hazard ratio; NE = not evaluable

In addition to the observed improvement in overall survival, all secondary study endpoints favoured abiraterone and were statistically significant after adjusting for multiple testing as follows:

Patients receiving abiraterone demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 38% vs. 10%, $p < 0.0001$.

The median time to PSA progression was 10.2 months for patients treated with abiraterone and 6.6 months for patients treated with placebo (HR = 0.580; 95% CI: [0.462; 0.728], $p < 0.0001$).

The median radiographic progression-free survival was 5.6 months for patients treated with abiraterone and 3.6 months for patients who received placebo (HR = 0.673; 95% CI: [0.585; 0.776], $p < 0.0001$).

Pain

The proportion of patients with pain palliation was statistically significantly higher in the abiraterone group than in the placebo group (44% vs. 27%, $p = 0.0002$). A responder for pain palliation was defined as a patient who experienced at least a 30% reduction from baseline in the BPI-SF worst pain intensity score over the last 24 hours without any increase in analgesic usage score observed at two consecutive evaluations four weeks apart. Only patients with a baseline

pain score of ≥ 4 and at least one post-baseline pain score were analysed (N = 512) for pain palliation.

A lower proportion of patients treated with abiraterone had pain progression compared to patientstaking placebo at 6 (22% vs. 28%), 12 (30% vs. 38%) and 18 months (35% vs. 46%). Painprogression was defined as an increase from baseline of ≥ 30% in the BPI-SF worst pain intensity score over the previous 24 hours without a decrease in analgesic usage score observed at two consecutive visits, or an increase of ≥ 30% in analgesic usage score observed at two consecutivevisits. The time to pain progression at the 25th percentile was 7.4 months in the abiraterone group, versus 4.7 months in the placebo group.

Skeletal-related events
A lower proportion of patients in the abiraterone group had skeletal-related events compared with the placebo group at 6 months (18% vs. 28%), 12 months (30% vs. 40%), and 18 months (35% vs. 40%). The time to first skeletal-related event at the 25th percentile in the abiraterone group was twice that ofthe control group at 9.9 months versus 4.9 months. A skeletal-related event was defined as a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing abiraterone in all subsets of the paediatric population in advanced prostate cancer. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects, patients with metastatic advanced prostate cancer and subjects without cancer with hepatic or renal impairment. Abiraterone acetate is rapidly converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor (see section 5.1).

Absorption
Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 hours.

Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 10-fold (AUC) and up to a 17-fold (C_{max}) increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking abiraterone with meals has the potential to result in highly variable exposures. Therefore, Abiraterone must not be taken with food. It should be taken at least one hour before or at least two hours after eating. The tablets should be swallowed whole with water (see section 4.2).

Distribution
The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5,630 l, suggesting that abiraterone extensively distributes to peripheral tissues.

Biotransformation
Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolysed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92%) is found in theform of metabolites of abiraterone. Of 15 detectable metabolites, 2 main metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each represents approximately 43% of total radioactivity.

Elimination
The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects. Following oral administration of ^{14}C-abiraterone acetate 1,000 mg, approximately 88% of the radioactive dose is recovered in faeces and approximately 5% in urine. The major compounds present in faeces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Hepatic impairment
The pharmacokinetics of abiraterone acetate was examined in subjects with pre-existing mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) and in healthy control subjects. Systemic exposure to abiraterone after a single oral 1,000 mg dose increased by approximately 11% and 260% in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with pre-existing severe (n = 8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The AUC to abiraterone increased by approximately 600% and the fraction of freedrug increased by 80% in subjects with severe hepatic impairment compared to subjects with normal hepatic function.

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment.
The use of abiraterone acetate should be cautiously assessed in patients with moderate hepatic impairment in whom the benefit clearly should outweigh the possible risk (see sections 4.2 and 4.4). abiraterone acetate should not be used in patients with severe hepatic impairment (see sections 4.2,4.3 and 4.4).

For patients who develop hepatotoxicity during treatment, suspension of treatment and dose adjustment may be required (see sections 4.2 and 4.4).

Renal impairment
The pharmacokinetics of abiraterone acetate was compared in patients with end-stage renal disease on a stable haemodialysis schedule versus matched control subjects with normal renal function. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stagerenal disease on dialysis. Administration in patients with renal impairment, including severe renal impairment, does not require dose reduction (see section 4.2). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

5.3 Preclinical safety data

In all animal toxicity studies, circulating testosterone levels were significantly reduced. As a result, reduction in organ weights and morphological and/or histopathological changes in the reproductive

organs, and the adrenal, pituitary and mammary glands were observed. All changes showed complete or partial reversibility. The changes in the reproductive organs and androgen-sensitive organs are consistent with the pharmacology of abiraterone. All treatment-related hormonal changes reversed or were shown to be resolving after a 4-week recovery period.

In fertility studies in both male and female rats, abiraterone acetate reduced fertility, which was completely reversible in 4 to 16 weeks after abiraterone acetate was stopped.

In a developmental toxicity study in the rat, abiraterone acetate affected pregnancy including reduced foetal weight and survival. Effects on the external genitalia were observed though abiraterone acetate was not teratogenic.

In these fertility and developmental toxicity studies performed in the rat, all effects were related to the pharmacological activity of abiraterone.

Aside from reproductive organ changes seen in all animal toxicology studies, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse. In a 24-month carcinogenicity study in the rat, abiraterone acetate increased the incidence of interstitial cell neoplasms in the testes. This finding is considered related to the pharmacological action of abiraterone and rat specific. Abiraterone acetate was not carcinogenic in female rats.

The active substance, abiraterone, shows an environmental risk for the aquatic environment, especially to fish.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Croscarmellose sodium
Sodium laurilsulfate
Povidone (E1201)
Cellulose, microcrystalline (E460)
Lactose monohydrate
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)

Coating
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol (E1521)
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters: 3 years
Bottles: 3 years

6.4 Special precautions for storage

This medicinal product does not require special storage conditions.

6.5 Nature and contents of container

The film-coated tablets are provided in:
- Aluminium-OPA/Alu/PVC or Aluminium-PVC/PE/PVDC blisters containing 120 film coated tablets
- Aluminium-OPA/Alu/PVC or Aluminium-PVC/PE/PVDC perforated unit dose blisters containing 120x1 film coated tablets.
- High density polyethylene (HDPE) bottles, with oxygen absorbing canister, closed with a polypropylene (PP) screw cap with child resistant closure containing 120 film coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. This medicinal product may pose a risk to the aquatic environment (see section 5.3).

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Sandoz B.V.
Hospitaaldreef 29
1315 RC Almere
Nederland

8. NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 126069 Bixodalan 250 mg, filmomhulde tabletten

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 1 juli 2021
Datum van laatste verlenging: 21 april 2026

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft rubriek 9: 14 augustus 2025