1. NAME OF THE MEDICINAL PRODUCT

NUBEQA 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated oral tablet contains 300 mg of darolutamide.

Excipient with known effect

Each film-coated tablet contains 186 mg of lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

White to off-white, oval tablets with a length of 16 mm and a width of 8 mm, marked with "300" on one side, and "BAYER" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- NUBEQA ,in combination with ADT is indicated for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease (see section 5.1).
- NUBEQA is indicated for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated and supervised by a specialist physician experienced in treatment of prostate cancer.

Posology

The recommended dose is 600 mg darolutamide (two tablets of 300 mg) taken twice daily, equivalent to a total daily dose of 1200 mg (see section 5.2).

Darolutamide should be continued until disease progression or unacceptable toxicity.

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

metastatic hormone-sensitive prostate cancer (mHSPC)
mHSPC patients should start darolutamide in combination with docetaxel (see section 5.1). The first of 6 cycles of docetaxel should be administered within 6 weeks after the start of darolutamide treatment. The recommendation in the product information of docetaxel should be followed. Treatment with darolutamide should be continued until disease progression or unacceptable toxicity even if a cycle of docetaxel is delayed, interrupted, or discontinued.

Missed dose
If a dose is missed, the dose should be taken as soon as the patient remembers prior to the next scheduled dose. The patient should not take two doses together to make up for a missed dose.

Dose modification
If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction related to darolutamide (see sections 4.4 and 4.8), dosing should be withheld or reduced to 300 mg twice daily until symptoms improve. Treatment may then be resumed at a dose of 600 mg twice daily.

Dose reduction below 300 mg twice daily is not recommended, because efficacy has not been established.

Special populations

Elderly
No dose adjustment is necessary in elderly patients (see section 5.2).

Renal impairment
No dose adjustment is necessary for patients with mild or moderate renal impairment.
For patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) not receiving haemodialysis, the recommended starting dose is 300 mg twice daily (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment.
The available data on darolutamide pharmacokinetics in moderate hepatic impairment is limited.
Darolutamide has not been studied in patients with severe hepatic impairment.
For patients with moderate and severe hepatic impairment (Child-Pugh Classes B and C), the recommended starting dose is 300 mg twice daily (see sections 4.4 and 5.2.).

Paediatric population
There is no relevant use of darolutamide in the paediatric population

Method of administration

NUBEQA is for oral use.

The tablets should be taken whole with food (see section 5.2).

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 (see section 4.6).

4.4 Special warnings and precautions for use

Renal impairment

The available data in patients with severe renal impairment are limited.
As exposure might be increased those patients should be closely monitored for adverse reactions (see sections 4.2 and 5.2).

Hepatic impairment

The available data in patients with moderate hepatic impairment are limited, and darolutamide has not been studied in patients with severe hepatic impairment.
As exposure might be increased those patients should be closely monitored for adverse reactions (see sections 4.2 and 5.2).

Recent cardiovascular disease

Patients with clinically significant cardiovascular disease in the past 6 months including stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, and symptomatic congestive heart failure were excluded from the clinical studies. Therefore, the safety of darolutamide in these patients has not been established.
If NUBEQA is prescribed, patients with clinically significant cardiovascular disease should be treated for these conditions according to established guidelines.

Hepatotoxicity

In case of liver function test abnormalities suggestive of idiosyncratic drug-induced liver injury, permanently discontinue treatment with darolutamide (see section 4.8).

Concomitant use with other medicinal products

Use of strong CYP3A4 and P-gp inducers during treatment with darolutamide may decrease the plasma concentration of darolutamide and is not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product with less potential to induce CYP3A4 or P-gp should be considered (see section 4.5).

Patients should be monitored for adverse reactions of BCRP, OATP1B1 and OATP1B3 substrates as co-administration with darolutamide may increase the plasma concentrations of these substrates. Co-administration with rosuvastatin should be avoided unless there is no therapeutic alternative (see section 4.5).

Androgen deprivation therapy may prolong the QT interval

In patients with a history of risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5), physicians should assess the benefit-risk ratio including the potential for Torsade de pointes prior to initiating NUBEQA.

Information about excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on darolutamide

CYP3A4 and P-gp inducers
Darolutamide is a substrate of CYP3A4 and P-glycoprotein (P-gp).
Use of strong and moderate CYP3A4 inducers and P-gp inducers (e.g. carbamazepine, phenobarbital, St. John's Wort, phenytoin, and rifampicin) during treatment with darolutamide is not recommended, unless there is no therapeutic alternative. Selection of an alternate concomitant medicinal product, with no or weak potential to induce CYP3A4 or P-gp should be considered.
Repeated administration of rifampicin (600 mg), a strong CYP3A4 and a P-gp inducer, with a single dose of darolutamide (600 mg) together with food, resulted in a decrease of 72% in mean exposure (AUC_{0-72}) and a decrease of 52% in C_{max} of darolutamide.

CYP3A4, P-gp and BCRP inhibitors
Darolutamide is a substrate of CYP3A4, P-gp and breast cancer resistance protein (BCRP).
No clinically relevant drug-drug interaction is expected in case of CYP3A4, P-gp or BCRP inhibitor administration. Darolutamide may be given concomitantly with CYP3A4, P-gp or BCRP inhibitors.
Concomitant use of darolutamide with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure which may increase the risk of darolutamide adverse reactions. It is recommended to monitor patients more frequently for darolutamide adverse reactions and modify darolutamide dose as needed.
Administration of itraconazole (200 mg twice daily on day 1 and once daily on the following 7 days), a strong CYP3A4, P-gp and BCRP inhibitor, with a single dose of darolutamide (600 mg on day 5 together with food) resulted in a 1.7-fold increase in mean exposure (AUC_{0-72}) and a 1.4-fold increase of C_{max} of darolutamide.

UGT1A9 inhibitors
Darolutamide is a substrate of UGT1A9.
No clinically relevant drug-drug interaction is expected in case of UGT1A9 inhibitor administration. Darolutamide may be given concomitantly with UGT1A9 inhibitors.
A population pharmacokinetic analysis showed that co-administration of UGT1A9 inhibitors with darolutamide resulted in a 1.2-fold increase in exposure (AUC_{0-72}) of darolutamide.

Docetaxel
Administration of darolutamide in combination with docetaxel resulted in no clinically relevant changes in the pharmacokinetics of darolutamide in mHSPC patients (see section 5.1).

Effects of darolutamide on other medicinal products

BCRP, OATP1B1 and OATP1B3 substrates
Darolutamide is an inhibitor of breast cancer resistance protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3.
Co-administration of rosuvastatin should be avoided unless there is no therapeutic alternative. Selection of an alternative concomitant medicinal product with less potential to inhibit BCRP, OATP1B1 and OATP1B3 should be considered.
Administration of darolutamide (600 mg twice daily for 5 days) prior to co-administration of a single dose of rosuvastatin (5 mg) together with food resulted in approximately 5-fold increase in mean exposure (AUC) and C_{max} of rosuvastatin.
Co-administration of darolutamide with other BCRP substrates should be avoided where possible. Co-administration of darolutamide may increase the plasma concentrations of other concomitant BCRP, OATP1B1 and OATP1B3 substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin, pitavastatin). Therefore, it is recommended to monitor patients for adverse reactions of BCRP, OATP1B1 and OATP1B3 substrates. In addition, the related recommendation in the product information of these substrates should be followed when co-administered with darolutamide.

P-gp substrates
No clinically relevant drug-drug interaction is expected in case of P-gp substrate administration. Darolutamide may be given concomitantly with P-gp substrates (e.g. digoxin, verapamil or nifedipine). Co-administration of darolutamide together with the sensitive P-gp substrate dabigatran etexilate did not reveal any increase in exposure (AUC and C_{max}) of dabigatran.

CYP3A4 substrates
Darolutamide is a mild inducer of CYP3A4.
No clinically relevant drug-drug interaction is expected in case of CYP substrate administration. Darolutamide may be given concomitantly with CYP substrates (e.g. warfarin, L-thyroxine, omeprazole).
Administration of darolutamide (600 mg twice daily for 9 days) prior to co-administration of a single dose of the sensitive CYP3A4 substrate midazolam (1 mg) together with food, decreased the mean exposure (AUC) and C_{max} of midazolam by 29% and 32%, respectively.
Darolutamide did not inhibit the metabolism of selected CYP substrates *in vitro* at clinically relevant concentrations.

Docetaxel
Administration of darolutamide in combination with docetaxel resulted in no clinically relevant changes in the pharmacokinetics of docetaxel in mHSPC patients (see section 5.1).

Medicinal products that prolong the QT interval

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

4.6 Fertility, pregnancy and lactation

This medicinal product is not indicated in women of childbearing potential. It is not to be used in women who are, or may be, pregnant or breast-feeding (see sections 4.1 and 4.3).

Women of childbearing potential / contraception in males and females

It is not known whether darolutamide or its metabolites are present in semen. If the patient is engaged in sexual activity with a woman of childbearing potential, a highly effective contraceptive method (<1% failure rate per year) should be used during and for 1 week after completion of treatment with NUBEQA to prevent pregnancy.

Pregnancy

Based on its mechanism of action, darolutamide may cause foetal harm. No non-clinical reproductive toxicity studies have been conducted (see section 5.3).
It is not known whether darolutamide or its metabolites are present in semen. If the patient is engaged in sexual activity with a pregnant woman, a condom should be used during and for 1 week after completion of treatment with NUBEQA. Exposure of the foetus to an androgen receptor inhibitor through seminal transfer to the pregnant woman has to be avoided, as this could affect development of the foetus.

Breast-feeding

It is unknown whether darolutamide or its metabolites are excreted in human milk. No studies in animals have been conducted to evaluate the excretion of darolutamide or its metabolites into milk (see section 5.3). A risk to the breast-fed child cannot be excluded.

Fertility

There are no human data on the effect of darolutamide on fertility.
Based on animal studies, NUBEQA may impair fertility in males of reproductive potential (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse reactions in patients with
- nmCRPC receiving darolutamide are fatigue/asthenic conditions (15.8%).
- mHSPC receiving darolutamide in combination with docetaxel are rash (16.6%) and hypertension (13.8%).

For additional safety information when darolutamide is administered in combination, refer to the product information of the individual medicinal products.

Tabulated list of adverse reactions

The adverse reactions observed in patients with nmCRPC treated with darolutamide are listed in Table 1. The adverse reactions observed in patients with mHSPC treated with darolutamide in combination with docetaxel are listed in Table 2.
Adverse reactions are classified according to System Organ Class.They are grouped according to their frequencies. Frequency groups are defined by the following convention: 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 group, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported in the ARAMIS study[a]

System organ class (MedDRA)	**Very common**	**Common**
Cardiac disorders		Ischaemic heart disease[b] Heart failure[c]
Skin and subcutaneous tissue disorders		Rash[d]
Musculoskeletal and connective tissue disorders		Pain in extremity Musculoskeletal pain Fractures
General disorders and administration site conditions	Fatigue/asthenic conditions[e]	
Investigations[f]	Neutrophil count decreased Blood bilirubin increased AST increased	

[a] The median duration of exposure was 14.8 months (range: 0.0 to 44.3 months) in patients treated with darolutamide and 11.0 months (range: 0.1 to 40.5 months) in patients treated with placebo.
[b] Includes arteriosclerosis coronary artery, coronary artery disease, coronary artery occlusion, coronary artery stenosis, acute coronary syndrome, acute myocardial infarction, angina pectoris, angina unstable, myocardial infarction, myocardial ischaemia.
[c] Includes cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiogenic shock.
[d] Includes rash, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, dermatitis.
[e] Includes fatigue and asthenia, lethargy and malaise.

[f] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The incidence is based on values reported as laboratory abnormalities.

Table 2: Adverse reactions reported in mHSPC patients treated with darolutamide in combination with docetaxel in the ARASENS study[a, b]

System organ class (MedDRA)	Very common	Common
Vascular disorders	Hypertension[c]	
Skin and subcutaneous tissue disorders	Rash[d, e]	
Musculoskeletal and connective tissue disorders		Fractures
Reproductive system and breast disorders		Gynaecomastia
Investigations[f]	Neutrophil count decreased Blood bilirubin increased ALT increased AST increased	

[a] The median duration of exposure was 41.0 months (range: 0.1 to 56.5 months) in patients treated with darolutamide+docetaxel and 16.7 months (range: 0.3 to 55.8 months) in patients treated with placebo+docetaxel.

[b] Adverse reactions incidences may not be attributable to darolutamide alone but may contain contributions from other medicinal products used in combination.

[c] Includes hypertension, blood pressure increased, hypertensive emergency.

[d] Includes rash, drug eruption, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, erythema, dermatitis.

[e] The incidence was highest during the first 6 months of treatment.

[f] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The incidence is based on values reported as laboratory abnormalities.

Description of selected adverse reactions

Liver function tests

Cases of idiosyncratic drug-induced liver injury with grade 3 and 4 increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) to ≥ 5 and ≥ 20 x upper limit of normal (ULN) have been reported with darolutamide treatment including increased transaminases along with a simultaneous increase in total bilirubin to ≥ 2 x ULN. Time to onset ranged from 1 month to 12 months after initiation of darolutamide. In many cases the ALT and AST elevations were reversible upon darolutamide discontinuation. For specific recommendations, see section 4.4.

non-metastatic castration resistant prostate cancer (nmCRPC)

Fatigue

Fatigue/asthenic conditions were reported in 15.8% of patients treated with darolutamide and in 11.4% of patients treated with placebo. Events with worst grade of 3 were reported in 0.6% of patients treated with darolutamide and in 1.1% of patients treated with placebo. Fatigue (not including asthenia, lethargy or malaise) occurred in the majority of patients (12.1% of patients treated with darolutamide and 8.7% of patients treated with placebo).

Fractures

Fractures occurred in 4.2% of patients treated with darolutamide and in 3.6% of patients treated with placebo.

Ischaemic heart disease and heart failure

Ischaemic heart disease occurred in 3.2% of patients treated with darolutamide and in 2.5% of patients treated with placebo. Grade 5 events occurred in 0.3% of patients treated with darolutamide and 0.2% of patients treated with placebo. Heart failure occurred in 1.9% of patients treated with darolutamide and in 0.9% of patients treated with placebo.

Neutrophil count decreased
Neutrophil count decreased was reported as a laboratory abnormality in 19.6% of patients treated with darolutamide and in 9.4% of patients treated with placebo. The median time to nadir was 256 days. The laboratory tests abnormalities manifested predominantly as grade 1 or 2 intensity. Neutrophil count decreased of grade 3 and 4 was reported in 3.5% and 0.5% of patients, respectively. Only one patient permanently discontinued darolutamide due to neutropenia. Neutropenia was either transient or reversible (88% of patients) and were not associated with any clinically relevant signs or symptoms.

Blood bilirubin increased
Bilirubin increased was reported as a laboratory abnormality in 16.4% of patients treated with darolutamide and in 6.9% of patients treated with placebo. The episodes were predominantly of grade 1 or 2 intensity, not associated with any clinically relevant signs or symptoms, and reversible after darolutamide was discontinued. Bilirubin increased of grade 3 was reported in 0.1% of patients treated with darolutamide and in 0% of patients treated with placebo. In the darolutamide arm, the mean time to first onset of increased bilirubin was 153 days, and the mean duration of the first episode was 182 days. No patients were discontinued from treatment due to increase in bilirubin.

AST increased
AST increased was reported as a laboratory abnormality in 22.5% of patients treated with darolutamide and in 13.6% of patients treated with placebo. The episodes were predominantly of grade 1 or 2 intensity, not associated with any clinically relevant signs or symptoms, and reversible after darolutamide was discontinued. AST increased of grade 3 was reported in 0.5% of patients treated with darolutamide and in 0.2% of patients treated with placebo. In the darolutamide arm, the mean time to first onset of increased AST was 258 days, and the mean duration of the first episode was 118 days. No patients were discontinued from treatment due to increase in AST.

metastatic hormone-sensitive prostate cancer (mHSPC)
Hypertension
In the ARASENS study hypertension was reported in 13.8% of patients treated with darolutamide+docetaxel and 9.4% of patients treated with placebo+docetaxel.
Grade 3 hypertension was reported in 6.4% of patients treated with darolutamide+docetaxel compared to 3.5% of patients treated with placebo+docetaxel. One patient had grade 4 hypertension in each treatment arm.
One case was reported as grade 5 hypertension with grade 5 arteriosclerosis in the darolutamide+docetaxel arm. This patient had a long-standing history of hypertension and smoking and the case occurred more than 3 years after starting darolutamide treatment. Events of hypertension were reported more commonly in patients with no medical history of hypertension in both treatment arms.

Fractures
Fractures occurred in 7.5% of patients treated with darolutamide+docetaxel and in 5.1% of patients treated with placebo+docetaxel.

Neutrophil count decreased
Neutrophil count decreased was reported as a laboratory abnormality in 50.6% of patients treated with darolutamide+docetaxel and in 45.5% of patients treated with placebo+docetaxel. Grade 3 and 4 neutrophil count decreased was reported in 34.4% of patients treated with darolutamide+docetaxel and in 31.4% of patients treated with placebo+docetaxel. In both treatment arms, the incidences of neutrophil count decreased and neutropenia were highest during the first months of treatment, after which the incidence and severity of the events decreased.

Blood bilirubin increased
Bilirubin increased was reported as a laboratory abnormality in 19.6% of patients treated with darolutamide+docetaxel and in 10.0% of patients treated with placebo+docetaxel. The events were predominantly of grade 1 or 2 intensity. Grade 3 and 4 bilirubin increased was reported in 0.5% of patients treated with darolutamide+docetaxel and in 0.3% of patients treated with placebo+docetaxel.

ALT and AST increased
Alanine aminotransferase (ALT) increased was reported as a laboratory abnormality in 42.3% of patients treated with darolutamide+docetaxel and in 38.0% of patients treated with placebo+docetaxel. Aspartate aminotransferase (AST) increased was reported as a laboratory abnormality in 43.9% of patients treated with darolutamide+docetaxel and in 39.3% of patients treated with placebo+docetaxel. ALT and AST elevations were predominantly of grade 1 intensity. Grade 3 and 4 ALT increased was reported in 3.7% of patients treated with darolutamide+docetaxel and in 3.0% of patients treated with placebo+docetaxel. Grade 3 and 4 AST increased was reported in 3.6% of patients treated with darolutamide+docetaxel and in 2.3% of patients treated with placebo+docetaxel.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

The highest dose of darolutamide studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.
Considering the saturable absorption (see section 5.2) and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to toxicity.
In the event of intake of a higher than recommended dose, treatment with darolutamide can be continued with the next dose as scheduled.
There is no specific antidote for darolutamide and symptoms of overdose are not established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, anti-androgens; ATC code: L02BB06

Mechanism of action

Darolutamide is an androgen receptor (AR) inhibitor with a flexible polar-substituted pyrazole structure that binds with high affinity directly to the receptor ligand binding domain.
Darolutamide competitively inhibits androgen binding, AR nuclear translocation, and AR mediated transcription. A major metabolite, keto-darolutamide, exhibited similar *in vitro* activity to darolutamide. Darolutamide treatment decreases prostate tumour cell proliferation leading to potent antitumour activity.

Pharmacodynamic effects

No prolongation of the mean QTcF interval (i.e., greater than 10 ms) was observed after oral administration of 600 mg darolutamide twice daily compared to placebo.

Clinical efficacy and safety

Efficacy and safety were established in two randomised placebo-controlled multicentre phase III studies in patients with nmCRPC (ARAMIS) and mHSPC (ARASENS). All patients received a luteinising hormone-releasing hormone (LHRH) analogue concurrently or had a bilateral orchiectomy.

non-metastatic castration resistant prostate cancer (nmCRPC)
The efficacy and safety of darolutamide was assessed in a randomised, double-blind, placebo-controlled multicentre phase III study (ARAMIS) in patients with non-metastatic (as assessed by conventional imaging CT, bone scan, MRI) castration resistant prostate cancer with a prostate-specific antigen doubling time (PSADT) of ≤ 10 months.
Patients were included in the trial if they had 3 rising prostate-specific antigen (PSA) levels after the nadir taken at least 1 week apart during androgen deprivation therapy, PSA ≥ 2 ng/mL at screening and castrate level of serum testosterone < 1.7 nmol/L.
Patients with a medical history of seizure were allowed to enter the study. There were 12 patients (0.21%) enrolled on the darolutamide arm with a history of seizure.
Patients with uncontrolled hypertension or recent (in the past 6 months) stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, congestive heart failure New York Heart Association (NYHA) Class III or IV were excluded from the study.
Patients with prior treatment with second generation AR inhibitors such as enzalutamide, apalutamide and darolutamide, or CYP17 enzyme inhibitors such as abiraterone acetate as well as patients receiving systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/day within 28 days before randomisation were excluded from the study.
In total, 1509 patients were randomized 2:1 to receive either 600 mg darolutamide orally twice daily (n=955) or matching placebo (n=554).
Patients with presence of pelvic lymph nodes < 2 cm in short axis below the aortic bifurcation were allowed to enter the study. Absence or presence of metastasis was assessed by independent central radiological review. Included in these analyses were 89 patients that were retrospectively identified with metastasis at baseline. Randomization was stratified by PSADT (≤ 6 months or > 6 months) and use of osteoclast-targeted therapy at study entry (yes or no).

The following patient demographics and disease characteristics were balanced between treatment arms. The median age was 74 years (range 48-95) and 9% of patients were 85 years of age or older. The racial distribution was 79% White, 13% Asian, and 3% Black. A majority of patients had a Gleason score of 7 or higher at diagnosis (73%). The median PSADT was 4.5 months. Nine percent (9%) of patients had prior orchiectomy, 25% of patients had prior prostatectomy and 50% of patients had at least one prior radiotherapy. Seventy-six percent (76%) of patients received more than one prior anti-hormonal treatment. Patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 (69%) or 1 (31%) at study entry.

Treatment with darolutamide continued until radiographic disease progression as assessed by conventional imaging (CT, bone scan, MRI) by blinded central review, unacceptable toxicity or withdrawal.
The primary efficacy endpoint was metastasis free survival (MFS). Secondary endpoints were overall survival (OS), time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, and time to first symptomatic skeletal events (defined as occurrence of any of the following: external beam radiotherapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, spinal cord compression, or tumour-related orthopaedic surgical intervention).

Treatment with darolutamide resulted in an improvement in MFS compared to placebo (see Table 3 and Figure 1).
MFS results were consistent across patient subgroups regardless of PSADT, prior use of bone-targeting agents or loco-regional disease. Additional subgroups with consistent MFS results included PSA at baseline, Gleason score at diagnosis, age, geographical region, ECOG PS at baseline, race, and number of prior hormonal therapies.
After the primary analysis of MFS, once the study was unblinded, patients receiving placebo were offered treatment with open-label darolutamide (cross-over option). Among the 554 patients

randomised to placebo, 170 (31%) crossed over to receive darolutamide treatment. The OS analysis was not adjusted for confounding effects of cross-over.

At the time of the final analysis, treatment with darolutamide resulted in a statistically significant improvement in overall survival compared to placebo (median was not reached in either arm, see Table 3 and Figure 2).
Treatment with darolutamide also resulted in statistically significant delays in time to pain progression, time to initiation of first cytotoxic chemotherapy and time to first symptomatic skeletal event compared to placebo (see Table 3).

At the time of final analysis, the median duration of treatment in patients treated with darolutamide was 33.3 months (range: 0.0 to 74.0 months) during combined double-blind and open-label period.

All analyses were performed in the full analysis set.

Table 3: Efficacy results from the ARAMIS study

Efficacy parameter	**Number (%) of patient with events**		**Median (months) (95% CI)**		**Hazard Ratio[b] (95% Confidence Interval [CI]) p-value (two-sided)**
	Darolutamide (N=955)	**Placebo[a] (N=554)**	**Darolutamide (N=955)**	**Placebo[a] (N=554)**	
Metastasis free survival[c]	221 (23.1%)	216 (39.0%)	40.4 (34.3, NR)	18.4 (15.5, 22.3)	0.413 (0.341, 0.500) <0.000001
Overall survival	148 (15.5%)	106 (19.1%)	NR (56.1, NR)	NR (46.9, NR)	0.685 (0.533, 0.881) 0.003048
Time to pain progression[c, d]	251 (26.3%)	178 (32.1%)	40.3 (33.2, 41.2)	25.4 (19.1, 29.6)	0.647 (0.533, 0.785) 0.000008
Time to initiation of first cytotoxic chemotherapy	127 (13.3%)	98 (17.7%)	NR (NR, NR)	NR (NR, NR)	0.579 (0.444, 0.755) 0.000044
Time to first symptomatic skeletal event	29 (3.0%)	28 (5.1%)	NR (NR, NR)	NR (NR, NR)	0.484 (0.287, 0.815) 0.005294

[a] including 170 patients who crossed over to open-label darolutamide
[b] Hazard ratio < 1 favours darolutamide
[c] for MFS and time to pain progression, the analysis performed at the time of primary completion is considered as the final analysis
[d] Patient reported outcome as evaluated by Brief Pain Inventory-Short Form questionnaire
NR: Not reached.

Treatment with darolutamide resulted in a longer progression free survival (PFS, median 36.8 vs 14.8 months, HR=0.380, nominal p<0.000001) and time to PSA progression (median 29.5 vs 7.2 months, HR=0.164, nominal p<0.000001). Consistency of effect was observed across all measures of survival (MFS, OS and PFS).

Figure 1: Kaplan-Meier curves of metastasis free survival (ARAMIS)

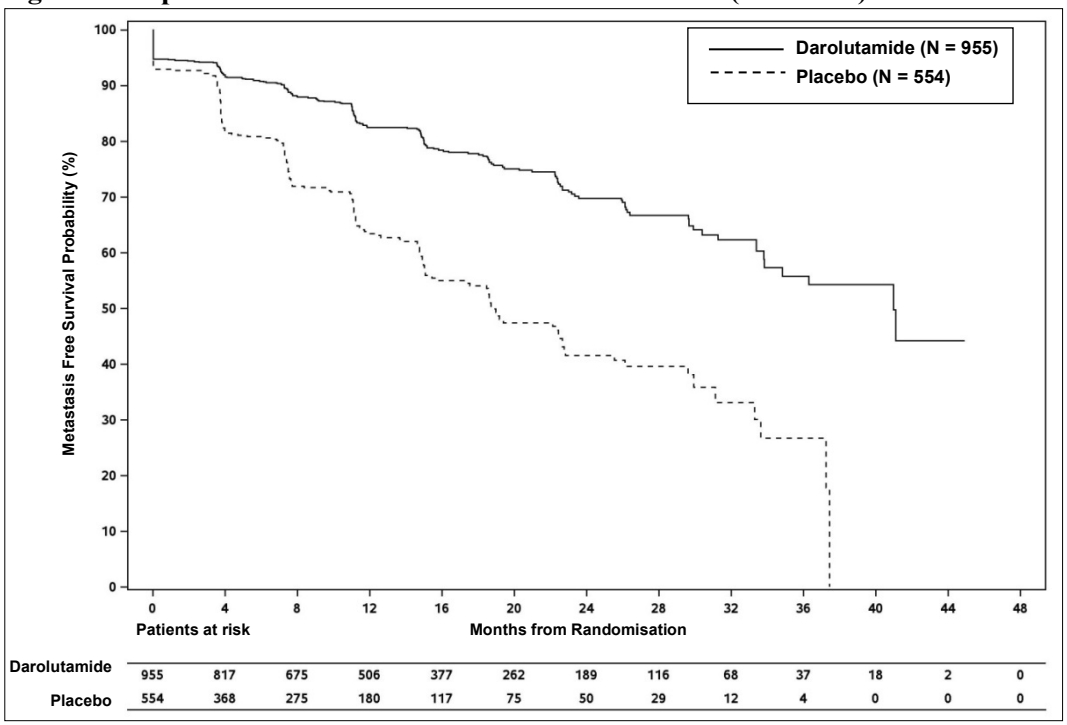
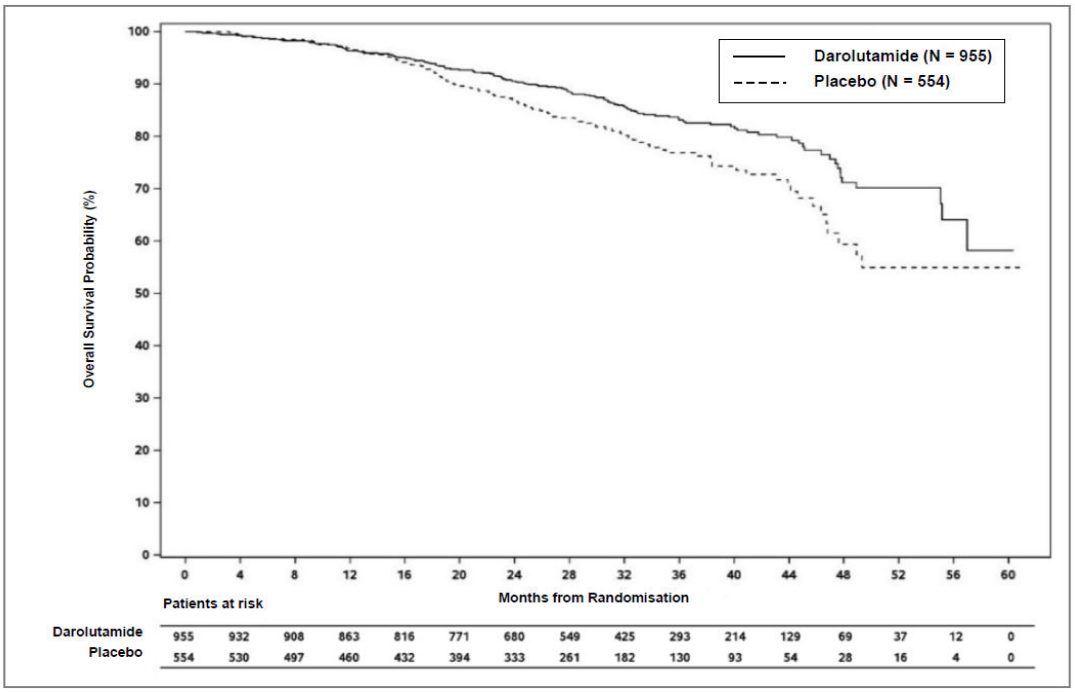


Figure 2: Kaplan-Meier curves of overall survival (ARAMIS)



Patients receiving darolutamide in the ARAMIS study (double-blind period) demonstrated a significantly higher confirmed PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 84.0% vs 7.9% (difference = 76.1%, p<0.000001 (nominal p-value, for information only)).

metastatic hormone-sensitive prostate cancer (mHSPC)
The efficacy and safety of darolutamide in combination with docetaxel was assessed in a multicentre, double-blind, placebo-controlled phase III study (ARASENS) in patients with mHSPC. In total, 1306 patients were randomised 1:1 to receive 600 mg darolutamide orally twice daily (n=651) or matching placebo (n=655), concomitantly with 75 mg/m^2 of docetaxel for 6 cycles. Treatment with darolutamide or placebo continued until symptomatic progressive disease, change of antineoplastic therapy, unacceptable toxicity, death, or withdrawal.

Presence of metastasis was assessed by independent central radiological review. Patients with regional lymph node involvement only (M0) were excluded from the study. Randomisation was stratified by extent of disease (non-regional lymph nodes metastases only (M1a), bone metastases with or without lymph node metastases (M1b) or visceral metastases with or without lymph node metastases or with or without bone metastases (M1c)) and by alkaline phosphatase level (< or ≥ upper limit of normal) at study entry. Patients with brain metastases were allowed to enter the study but there were no patients with brain metastasis enrolled.

The following patient demographics and disease characteristics were balanced between treatment arms. The median age was 67 years (range 41-89) and 0.5% of patients were 85 years of age or older. The racial distribution was 52% White, 36% Asian, and 4% Black. A majority of patients had a Gleason score of 8 or higher at diagnosis (78%). 71% of patients had an ECOG PS score of 0 and 29% of patients had an ECOG PS score of 1. There were 86.1% of patients with *de novo* and 12.9% of patients with recurrent disease. At study entry 3% of patients had M1a, 79.5% had M1b and 17.5% had M1c; alkaline phosphatase was < ULN in 44.5% of patients and ≥ ULN in 55.5% of patients; median PSA level at baseline was 30.3 µg/L and 24.2 µg/L for darolutamide vs the placebo group, respectively. Patients with a medical history of seizure were allowed to enter the study, and 4 patients (0.6%) were enrolled in the darolutamide+docetaxel arm.

77.0% of patients had high-volume disease and 23.0% had low-volume disease. High-volume disease was defined as presence of visceral metastases or 4 or more bone lesions, with at least 1 metastasis beyond the vertebral column and pelvic bones. Around 25% of patients received concomitant treatment with bisphosphonates or denosumab.

The primary efficacy endpoint was overall survival (OS). Secondary endpoints were time to castration-resistant prostate cancer, time to pain progression, symptomatic skeletal event free survival (SSE-FS), time to first symptomatic skeletal event (SSE), time to initiation of subsequent antineoplastic therapy, time to worsening of disease-related physical symptoms, and time to initiation of opioid use for ≥ 7 consecutive days. Pain progression was assessed using the patient-reported outcome (PROs) Brief Pain Inventory-Short Form (BPI-SF), defined as at least a 2-point worsening from nadir, and initiation of short- or long-acting opioid use for pain for ≥7 consecutive days.

The median duration of treatment was 41.0 months (range: 0.1 to 56.5 months) in patients treated with darolutamide+docetaxel and 16.7 months (range: 0.3 to 55.8 months) in patients treated with placebo+docetaxel. 87.6% and 85.5% of patients received full 6 cycles of docetaxel and 1.5% and 2.0% of patients did not receive docetaxel in darolutamide+docetaxel and placebo+docetaxel arm, respectively.

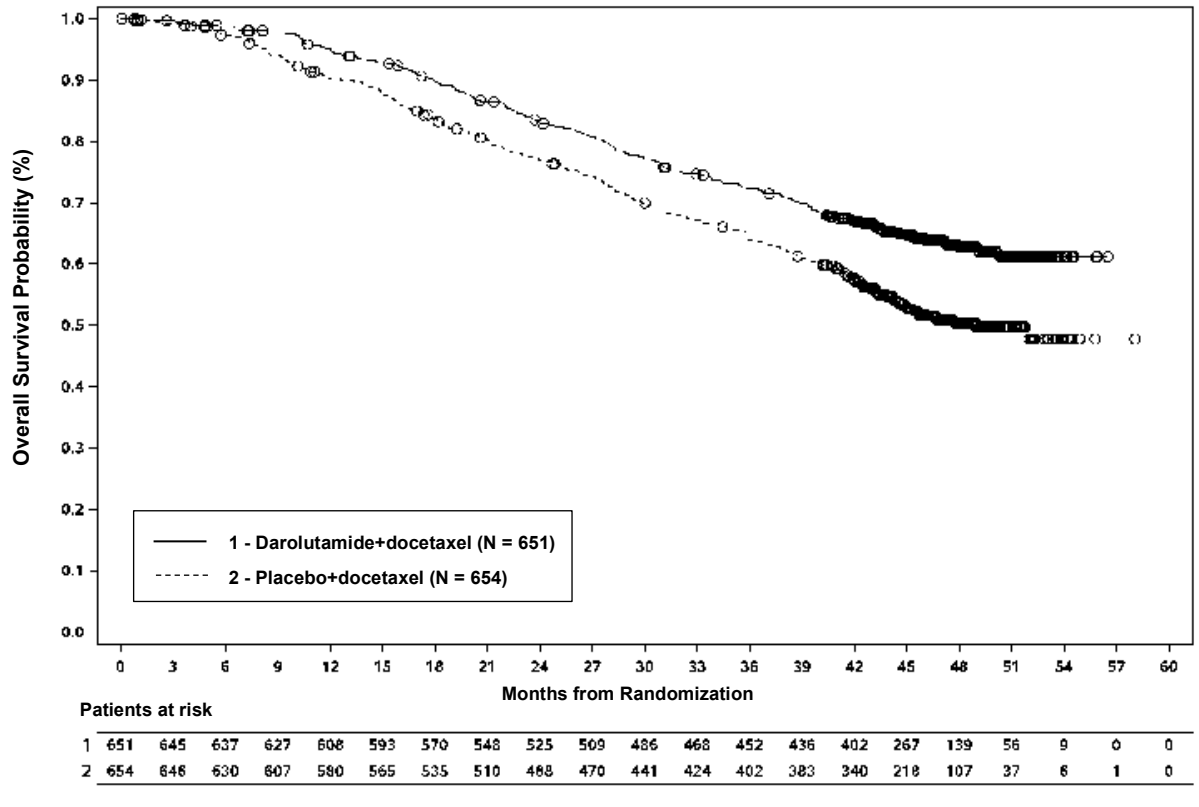
Table 4: Efficacy results from the ARASENS study

Efficacy parameter	Number (%) of patients with events		Median (months) (95% CI)		Hazard Ratio[b] (95% Confidence Interval [CI]) p-value (one-sided)[c]
	Darolutamide + docetaxel (N=651)	Placebo + docetaxel (N=654)[a]	Darolutamide + docetaxel (N=651)	Placebo + docetaxel (N=654)[a]	
Overall survival[d]	229 (35.2%)	304 (46.5%)	NR (NR, NR)	48.9 (44.4, NR)	0.675 (0.568, 0.801) <0.0001

[a] one patient in placebo arm was excluded from all analyses
[b] Hazard ratio < 1 favours darolutamide
[c] based on stratified log-rank test
[d] OS results were consistent across patient subgroups, including extent of disease and alkaline phosphatase levels
NR: not reached

The following secondary efficacy endpoints showed a statistically significant advantage in favour of the patients in the darolutamide+docetaxel arm compared to patients in the placebo+docetaxel arm: time to castration-resistant prostate cancer (median NR vs 19.1 months; HR=0.357, p<0.0001); time to first symptomatic skeletal event (median NR vs NR months; HR=0.712, p=0.0081); time to initiation of subsequent antineoplastic chemotherapy (median NR vs 25.3 months; HR=0.388, p<0.0001); time to pain progression (median NR vs 27.5 months; HR=0.792, p=0.0058); symptomatic skeletal event free survival time (median 51.2 vs 39.7 months; HR=0.609, p<0.0001).

Figure 3: Kaplan-Meier curves of overall survival (ARASENS)[a]



[a] OS rate at 36 months was 72.3% (95% CI, 68.8 to 75.8) in the darolutamide+docetaxel arm vs 63.8% (95% CI, 60.1 to 67.6) in the placebo+docetaxel arm.
OS rate at 48 months was 62.7% (95% CI, 58.7 to 66.7) in the darolutamide+docetaxel arm vs 50.4% (95% CI, 46.3 to 54.6) in the placebo+docetaxel arm.

5.2 Pharmacokinetic properties

General introduction

Darolutamide consists of two diastereomers [(*S*,*R*)-darolutamide and (*S*,*S*)-darolutamide] which interconvert via the main circulating metabolite called keto-darolutamide. *In vitro*, all three substances show similar pharmacological activity. Darolutamide is poorly soluble in aqueous solvents over a large pH range and generally more soluble in organic solvents.

Absorption

Following oral administration of 600 mg (2 tablets of 300 mg) twice daily, peak plasma concentrations of darolutamide at steady state were 4.79 mg/L (coefficient of variation: 30.9%) in nmCRPC patients in the ARAMIS study and 3.84 mg/L (coefficient of variation: 35.6%) in mHSPC patients in the ARASENS study. Median time to achieve peak plasma concentrations was 3 to 4 hours. The ratio of the two diastereomers, (*S*,*R*)-darolutamide to (*S*,*S*)-darolutamide, changed from a 1:1 ratio in the tablet to an approximately 1:9 ratio in plasma based on AUC_{0-12} data at steady-state. Following oral administration together with food, steady-state is reached after 2-5 days of repeated twice-daily dosing.
The absolute bioavailability compared to an intravenous injection is approximately 30% following oral administration of a NUBEQA tablet containing 300 mg darolutamide under fasted conditions. Bioavailability of darolutamide was enhanced by 2.0- to 2.5-fold when administered with food. A similar increase of exposure was observed for the major metabolite keto-darolutamide.

Distribution

The apparent volume of distribution of darolutamide after intravenous administration is 119 L indicating that darolutamide is widely distributed throughout the body to both intracellular and extracellular fluid spaces.
Darolutamide is moderately (92%) bound to human plasma proteins without any difference between the two diastereomers. The major metabolite of darolutamide, keto-darolutamide, is highly (99.8%) bound to plasma proteins.
Passage of darolutamide across the blood-brain barrier has not been studied clinically. However, brain exposures to darolutamide in terms of AUC_{0-24} are very low with 4.5% of plasma exposure after single dose in rats and 1.9-3.9% after repeated dose in mice. This indicates low passage of darolutamide across the intact blood-brain barrier in rats and mice and a low likelihood that darolutamide crosses the intact blood-brain barrier in humans to a clinically relevant extent.

Biotransformation

The diastereomers (*S*,*R*)-darolutamide and (*S*,*S*)-darolutamide are able to interconvert via the metabolite keto-darolutamide with a preference for (*S*,*S*)-darolutamide.
Following single oral administration of 300 mg ^{14}C-darolutamide given as an oral solution, keto-darolutamide is the only major metabolite with about 2-fold higher total exposure in plasma compared to darolutamide. Darolutamide and keto-darolutamide accounted together for 87.4% of the ^{14}C-radioactivity in plasma indicating that all other metabolites are of minor importance.
Darolutamide is metabolised primarily by oxidative metabolism mediated mainly by CYP3A4, as well as by direct glucuronidation mediated preferentially by UGT1A9 and UGT1A1. In addition, mainly the AKR1C isoforms were shown to catalyse the reduction of keto-darolutamide to the substance diastereomers.

Elimination

The effective half-life of darolutamide and keto-darolutamide in plasma of patients is approximately 18 to 20 hours. Of the two diastereomers comprising darolutamide, (*S*,*R*)-darolutamide has a shorter effective half-life of 9 hours compared to (*S*,*S*)-darolutamide with an effective half-life of 22 hours. The clearance of darolutamide following intravenous administration was 116 mL/min (CV: 39.7%). A total of 63.4% of substance-related material is excreted in the urine (approximately 7% unchanged), 32.4% is excreted in the faeces. More than 95% of the dose was recovered within 7 days after administration.

Linearity / Non-linearity

In the dose range of 100 to 700 mg (after single dose and at steady state), the exposure to the two diastereomers and the major metabolite keto-darolutamide increases linearly in a nearly dose-related manner. Based on a saturated absorption, no further increase in exposure to darolutamide was observed at 900 mg twice daily.

Special populations

Elderly
No clinically relevant differences in the pharmacokinetics of darolutamide were observed (65-95 years).

Renal impairment
In a clinical pharmacokinetic study, AUC and C_{max} for darolutamide were 2.5 and 1.6-fold higher in patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] 15 to 29 mL/min/1.73 m^2) compared to healthy volunteers.
A population pharmacokinetic analysis indicates a 1.1-, 1.3- and an approximately 1.5-fold higher exposure (AUC) of darolutamide in patients with mild, moderate and severe renal impairment (eGFR 15 to 89 mL/min/1.73 m^2) compared to patients with normal renal function.
The pharmacokinetics of darolutamide has not been studied in patients with end-stage renal disease receiving dialysis (eGFR < 15 mL/min/1.73 m^2).

Hepatic impairment
In a clinical pharmacokinetic study, C_{max} and AUC for darolutamide were 1.5 and 1.9-fold higher in patients with moderate hepatic impairment (Child-Pugh B) compared to healthy volunteers. There are no data for patients with severe hepatic impairment (Child-Pugh C).

Ethnic differences
No clinically relevant differences in the pharmacokinetics of darolutamide were observed based on ethnicity (White, Japanese, non-Japanese Asian, Black or African American). A population pharmacokinetic analysis indicated a geometric mean increase in exposure (AUC) of up to 1.56-fold (90% CI: 1.43 to 1.70) in Japanese patients compared to patients from all other regions in both the ARAMIS and ARASENS studies.

5.3 Preclinical safety data

Systemic toxicity

In repeated dose toxicity studies in rats and dogs, the main findings were changes in the male reproductive organs (decreases in organ weight with atrophy of the prostate and epididymides). These effects occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison). Additional changes to reproductive tissues included minimal increase in vacuolation of the pituitary gland, atrophy and secretory reduction in seminal vesicles and mammary glands in rats as well as testicular hypospermia, seminiferous tubule dilatation and degeneration in dogs. Changes in the male reproductive organs in both species were consistent with the pharmacological activity of darolutamide and reversed or partially resolved after 4- to 8-week recovery periods.

Embryotoxicity / teratogenicity

Studies on developmental toxicity have not been performed.

Reproduction toxicity

Studies on reproductive toxicity have not been performed. However, male fertility is likely to be impaired based on the findings in repeat-dose toxicity studies in rats and dogs, which are consistent with the pharmacological activity of darolutamide.

Genotoxicity and carcinogenicity

Darolutamide did not induce mutations in the microbial mutagenesis (Ames) assay. At high concentrations, darolutamide did induce structural chromosome aberrations *in vitro* in cultured human lymphocytes. However, in the *in vivo* combined bone marrow micronucleus test and the Comet assay in the liver and duodenum of the rat, no genotoxicity was observed at exposures in excess of the maximum human exposure.
Oral administration of darolutamide to male rasH2 transgenic mice for 6 months did not show carcinogenic potential at doses up to 1000 mg/kg/day, which is 0.9-1.3 times for darolutamide and 2.1-2.3 times for keto-darolutamide the clinical exposure (AUC) at the recommended clinical daily dose of 1200 mg/day. Based on this study carcinogenic risk of darolutamide cannot be completely excluded.

Safety pharmacology

In vitro, darolutamide weakly inhibited the hERG potassium current and the L-type calcium channel. *In vivo*, in anaesthetised dogs, darolutamide slightly decreased the QT interval duration, but this effect was not found in conscious dogs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Calcium hydrogen phosphate
Croscarmellose sodium
Povidone K 30
Magnesium stearate

Film-coating
Hypromellose
Lactose monohydrate
Macrogol
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions, it is recommended to store at room temperature.

6.5 Nature and contents of container

PVC/Aluminium foil blisters containing 16 film-coated tablets.
Each pack contains 112 film-coated tablets.

6.6 Special precautions for disposal

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

7. Manufacturer:
Orion Corporation, Orion Pharma, Salo, Joensuunkatu 7, 24100 Salo, Finland,
8. Registration holder
Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 4527702.

Revised in June 2024 according to the MoHs Guidelines.