Darolutamide Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of adult men with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.	C61	00693a	CDS 01/03/2022

*This is for post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Darolutamide is taken twice daily until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Darolutamide	600mg twice daily	PO	Continuous
The tablets should be taken whole with food.			
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.			
Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.			

ELIGIBILITY:

- Indications as above
- Age > 18
- Histologically or cytologically confirmed adenocarcinoma of prostate without neuroendocrine differentiation or small cell features

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- Diagnosis of castration-resistant prostate cancer
- Castrate level of serum testosterone (<1.7 nmol/L [50ng/dL]) on gonadotrophin releasing hormone agonist of antagonist therapy or after bilateral orchiectomy
- Baseline PSA level of at least 2 ng per millilitre
- PSA doubling time of 10 months or less
- ECOG 0-1

CAUTION:

Use in caution in:

- Patients with clinically significant cardiovascular disease within past 6 months

EXCLUSIONS:

- Known hypersensitivity to darolutamide or any of the excipients
- Patients with detectable metastases or a history of metastatic disease
- Prior treatment with second-generation androgen receptor antagonists
- Prior treatment with CYP17 inhibitors
- Prior chemotherapy or immunotherapy for prostate cancer, except adjuvant/neoadjuvant treatment
- Gastrointestinal disorder affecting absorption

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

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TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood pressure
- ECG in patients at risk of QT prolongation

Regular tests:

- FBC, renal and liver profile
- Blood pressure as clinically indicated
- ECG as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

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Renal and Hepatic Impairment:

Table 1: Dose modification of Darolutamide in renal and hepatic impairment

Renal Impairment		**Hepatic Impairment**
CrCl (mL/min)	**Dose**	Child-Pugh A or mild: no dose adjustment is needed Child-Pugh B/C or moderate/severe: 50% of the original dose
≥ 30	No dose adjustment is needed	
< 30	50% of the original dose	
Haemodialysis	50% of the original dose	
Dose modifications from Giraud et al 2023		

Management of adverse events:

Table 2: Dose Modification of Darolutamide for Adverse Events

Adverse Reaction	**Recommended Dose Modification**
Intolerable or ≥ Grade 3 reaction	Withhold or reduce dose to 300mg twice daily until symptoms improve. Treatment may then be resumed at a dose of 600mg twice daily if tolerated. Dose reduction below 300mg twice daily is not recommended because efficacy has not been established.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal (**Refer to local policy)**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE: None specified

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ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **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 darolutamide is prescribed, patients with clinically significant cardiovascular disease should be treated for these conditions according to established guidelines.
- **Hepatic transaminase elevations:** In case of hepatic transaminase elevations suggestive of idiosyncratic drug-induced liver injury related to darolutamide, permanently discontinue treatment with darolutamide.
- **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, physicians should assess the benefit-risk ratio including the potential for Torsade de pointes prior to initiating darolutamide.
- **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. 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.

DRUG INTERACTIONS:

- 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.
- 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.

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- 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.
- 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.

REFERENCES:

1. Fizazi k, et al. Darolutamide in Non-metastatic, Castration-resistant Prostate Cancer. N Engl J Med 2019;380:1235-46
2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available here : https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. Darolutamide (Nubeqa®) Summary of Product Characteristics. Last updated: 20/03/2023. Accessed January 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/nubeqa-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	09/02/2022		Prof Maccon Keane
2	08/02/2024	Reviewed. Updated renal and hepatic information in line with Giraud recommendations, 2023. Added black triangle status. Updated adverse effects.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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