Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2297

darolutamide 300mg film-coated tablets (Nubeqa®)

Bayer plc

9 October 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

darolutamide (Nubeqa®) is accepted for use within NHSScotland.

Indication under review: Darolutamide 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.

In a phase III study in men with high risk nmCRPC, treatment with darolutamide was superior to placebo for metastasis-free survival. High risk was defined as prostate specific antigen (PSA) doubling time ≤10 months and PSA ≥2 nanograms/mL. Both groups received on-going androgen-deprivation therapy or had undergone bilateral orchiectomy.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

Darolutamide 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.[1]

Dosing Information

The recommended dose of darolutamide is 600mg (two whole tablets of 300mg) taken orally, with food, twice daily, equivalent to a total daily dose of 1200mg.

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

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.

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

Please refer to the Summary of product characteristics (SPC) for further information.[1]

Product availability date

15 May 2020

Darolutamide meets SMC orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

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. It competitively inhibits androgen binding, AR nuclear translocation, and AR mediated transcription. Darolutamide treatment decreases prostate tumour cell proliferation leading to potent antitumor activity.[1]

The key evidence supporting the efficacy and safety of darolutamide comes from ARAMIS, a multi-centre, randomised, double-blind, placebo-controlled, phase III study. The study recruited adult males aged ≥18 years with histologically or cytologically confirmed adenocarcinoma of prostate without neuroendocrine differentiation or small cell features. Patients had to have non-metastatic castration resistant prostate cancer (nmCRPC), a prostate-specific antigen (PSA) ≥2 ng/ml, a PSA doubling time (PSADT; estimated time required for the PSA level to double) of ≤10 months at screening, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.[2, 3]

Patients were randomised in a 2:1 ratio to receive darolutamide 600mg orally twice daily (n=955) or placebo (n=554). Treatment was to continue until protocol-defined progression, discontinuation of the regimen because of adverse events, or withdrawal of consent. Patients continued to receive

androgen-deprivation therapy (ADT; luteinizing hormone–releasing hormone agonist or antagonist) throughout the study if they had not undergone bilateral orchiectomy.[2, 3]

The primary outcome was metastasis-free survival (MFS), which was defined as the time from randomisation to confirmed evidence of distant metastasis on imaging or death from any cause, whichever occurred first. The primary outcome was assessed in the intention-to-treat (ITT) population, which included all patients who underwent randomisation. At data cut off 3 September 2018, darolutamide was associated with a statistically significant improvement in MFS compared with placebo (Table 1). The MFS benefit was found to be consistent across all subgroups, including patients at relatively lower risk of metastasis.[2, 3]

Table 1: Metastasis free survival results in ITT population of study ARAMIS (data cut off 3 September 2018). [2, 3]

	Darolutamide (n=955)	**Placebo (n=554)**
Median duration of follow-up (months)	17.9	
Patients with event (%)	221 (23%)	216 (39%)
Median MFS (months)	40.4	18.4
HR (95% CI)	0.41 (0.34 to 0.50)	
p-value	p<0.001	

CI = confidence interval; HR = hazard ratio; MFS = metastasis-free survival

A hierarchical statistical testing strategy was applied for the secondary outcomes in the following order: overall survival, time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, and time to first symptomatic skeletal event. No formal testing of outcomes was performed after the first non-significant outcome. The secondary outcome results were supportive of the primary efficacy outcome. See Table 2 for details.[2-4]

Table 2: Secondary outcome results in ITT population of study ARAMIS. [2-4]

	Darolutamide group (n=955)	**Placebo group (n=554)**	**Darolutamide group (n=955)**	**Placebo group (n=554)**
Data cut-off date	3 September 2018 (primary MFS analysis)		15 November 2019 (final analysis)	
Median duration of follow-up (months)	17.9		NR	
Overall survival				
Patients with event	78	58	148	106
Median overall survival (months)	NE	NE	NE	NE
HR (95% CI)	0.71 (0.50 to 0.99)		0.69 (0.53 to 0.88)	
p-value	0.045[a]		0.003	
Time to pain progression				
Patients with event (%)	251 (26%)	178 (32%)	NR	NR
Median (months)	40.3	25.4	40.3	25.4
HR (95% CI)	0.65 (0.53 to 0.79)		0.65 (0.53 to 0.79)	

p-value	-		<0.001	
Time to first use of cytotoxic chemotherapy				
Patients with event (%)	73 (7.6%)	79 (14%)	NR	NR
Median (months)	NE	38.2	NR	NR
HR (95% CI)	0.43 (0.31 to 0.60)		0.58 (0.44 to 0.76)	
p-value	-		<0.001	
Time to first symptomatic skeletal event				
Patients with event (%)	16 (1.7%)	18 (3.2%)	NR	NR
Median (months)	NE	NE	NR	NR
HR (95% CI)	0.43 (0.22 to 0.84)		0.48 (0.29 to 0.82)	
p-value	-		0.005	

CI = confidence interval; HR = hazard ratio; MFS = metastasis-free survival; NE = not estimable; NR = not reported. a= not statistically significant.

Quality of life (QoL) was assessed using the following questionnaires: the disease-specific Functional Assessment of Cancer Therapy – Prostate (FACT-P questionnaire), the FACT-P prostate cancer-score subscale (PCS subscale of FACT-P), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate cancer module (EORTC-QLQ-PR25), the generic European Quality of Life 5-Domain Scale, 3 Level (EQ-5D-3L questionnaire), and the Brief Pain Inventory Short-Form (BPI-SF questionnaire). Overall, QoL was similar in the darolutamide group and placebo group. Differences in least-squares mean time-adjusted AUC scores favoured darolutamide, however the clinically meaningful thresholds were not reached. The European Medicines Agency (EMA) noted that QoL was not impaired.[2, 3]

Summary of evidence on comparative safety

In the ARAMIS study at data cut-off 03 September 2018, the median duration of treatment in the darolutamide group was 14.8 months and in the placebo group was 11 months. Any treatment-emergent adverse event (AE) was reported by 83% (794/955) of patients in the darolutamide group and 77% (426/554) in the placebo group and these were considered treatment-related in 27% and 20% respectively. In the darolutamide and placebo groups respectively, patients reporting a grade 3 or 4 AE were 25% versus 20%, patients reporting a grade 5 AE were 3.9% versus 3.2%, patients with a reported serious AE were 25% versus 20%, patients with a dose modification due to treatment related AEs were 5.1% versus 2.5%, the proportion of AEs that led to dose interruptions were 12% versus 8.8% and patients discontinuing therapy due to an AE were 8.9% versus 8.7%.[2]

The most frequently reported treatment-related AEs of any grade with an incidence >2% in the darolutamide group versus the placebo group were: fatigue (7.1% vs. 4.3%), hot flush (3.8% vs. 2.7%) and nausea (2.5% vs. 3.1%).[2]

Overall, the EMA considered that darolutamide appeared to be well tolerated with a low overall incidence of treatment-emergent AEs. The toxicity profile of darolutamide appeared to be consistent with other medicines in the androgen receptor antagonist class.[2]

Summary of clinical effectiveness issues

Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses despite castrate levels of testosterone while on treatment with a luteinising hormone-releasing hormone analogue or following bilateral orchiectomy. PSADT is considered to be a useful prognostic factor in identifying patients with nmCRPC at a high risk of developing metastases. Patients with nmCRPC and with PSADT ≤10 months have a high risk of developing metastases.[2] There are limited treatment options available for patients with nmCRPC. In most patients, ADT will be continued, and in some cases off-label bicalutamide or dexamethasone may be concomitantly prescribed despite a lack of evidence to support their use. Watchful waiting is also an option. Androgen receptor inhibitors, enzalutamide and apalutamide, are licensed for nmCRPC at high risk of metastases, however they are not recommended for use within NHSScotland by SMC. Clinical experts consulted by SMC considered that darolutamide fills an unmet need.

Darolutamide meets SMC orphan equivalent criteria for this indication.

Darolutamide was associated with statistically significant prolonged MFS in the double-blind, randomised, placebo-controlled phase III study (ARAMIS). The median MFS was 40.4 months in the darolutamide group compared to 18.4 months in the placebo group (difference of approximately 22 months), a result which can be considered clinically meaningful. Secondary outcomes, subgroup and sensitivity analyses, and QoL data were all supportive of the primary findings. At the final overall survival analysis, data were immature and medians were not reached but statistical difference was shown.

Patients in the placebo group were allowed to crossover and receive darolutamide during the open-label phase of the ARAMIS study (after the primary MFS analysis). This and subsequent treatment lines may have confounded final overall survival (and other secondary outcomes). [2]

The number of protocol deviations in ARAMIS was high, however these were evenly distributed between the two treatment groups. A violation of protocol duration was noted as a number of patients (168 in the darolutamide group and 188 in the placebo group) continued to receive treatment beyond metastasis until metastasis was confirmed by the central review. [2]

During the central efficacy imaging review, 89 patients (5.2% [n=50] in the darolutamide group and 7.0% [n=39] in the placebo group) were retrospectively classified as having metastases at baseline. Sensitivity analyses were performed for MFS with baseline metastasis censored at randomisation date, the results of which were consistent with the primary findings.[2]

ARAMIS only recruited patients with a high risk for developing metastases as defined by PSADT ≤10 months and PSA levels ≥2ng/mL. Therefore it is not known if the study results would apply to patients with PSADT>10 months and with other high risk characteristics (PSA levels >20ng/mL, high Gleason score or clinical stage ≥T2c disease), however it is not clear how many patients could fit these criteria. ARAMIS also excluded patients with Eastern Cooperative Oncology Group (ECOG)

performance status ≥2 and it is therefore unclear if the results are generalisable to patients with poorer ECOG performance status (≥2) in clinical practice. Given the median age (74 years) of the study population, the number of patients having received curative radiotherapy at baseline (18.5 % in darolutamide plus ADT group vs 16.1% in placebo group) may be lower than that seen in practice.

In the ARAMIS study, darolutamide in addition to ADT was compared with placebo plus ADT, which is a relevant comparator. Treatment options also include bicalutamide plus ADT or dexamethasone plus ADT although there is a lack of robust evidence in this patient group and these may be less relevant comparators. Uncertainty remains around the relative efficacy and safety versus all relevant comparators.

Clinical experts consulted by SMC considered that darolutamide is a therapeutic advancement as it significantly delay the development of metastasis with potential survival benefit. They considered that the place in therapy of darolutamide is for patients with non-metastatic castration resistant prostate cancer who are at high risk of developing metastatic disease. There may be service implications associated with the introduction of darolutamide due to monitoring requirements.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating darolutamide within its full marketing authorisation, plus ADT, versus ADT alone.

A three-state partitioned survival modelling approach was used, representing non-metastatic castration resistant prostate cancer (nmCRPC), metastatic castration resistant prostate cancer (mCRPC), and death. The nmCRPC state was further divided into ‘on treatment’ and ‘off treatment’ for darolutamide. The mCRPC state was further subdivided by three active treatment lines followed by best-supportive care, to more adequately reflect the disease course in the metastatic setting. A 27 year time horizon was chosen, and a 28 day cycle length used to match the pack size of darolutamide. The perspective for costs was that of NHSScotland and social services.

Clinical effectiveness data were derived from the ARAMIS study: metastasis-free survival (MFS) data were used to model the transition from nmCRPC state to mCRPC and overall survival (OS) data used to model transition to the death state from anywhere in the model. Parametric curves were fitted to the separate functions on the assumption of non-proportional hazards, with Weibull chosen for both OS and MFS. These were primarily selected based on clinical expert opinion received by the company; other functions were observed to have better statistical goodness-of-fit.

Utility values were derived from the ARAMIS study using EQ-5D-3L for the nmCRPC setting, and valued using UK preference weights. A weighted mean utility value for mCRPC was estimated by multiplying utility values reported in previous SMC Detailed Advice Documents by an estimated

duration within each treatment line. This resulted in utility values of 0.813 for nmCRPC and 0.704 for mCRPC. Disutility due to adverse events and symptomatic spinal events was also included.

Medicines costs included the acquisition cost for darolutamide and a weighted ADT comparator. The dose of darolutamide was based on the licensed indication, while time-on-treatment curves were used to estimate duration of treatment. A Gompertz distribution was selected to estimate duration of treatment; this represents the function with best statistical fit. ADT was assumed to continue across the time horizon for both treatment arms. Costs of subsequent treatments were estimated as a one-off cost, with weighted costs for treatment lines based on expert input regarding the distribution across several treatments (abiraterone, enzalutamide, docetaxel, radium-223, cabazitaxel, bicalutamide and no treatment), with time spent on treatment based on median estimates from corresponding NICE appraisals. Health state resource use was estimated based on a retrospective analysis of electronic health records from Leeds Teaching Hospitals NHS Trust.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price of darolutamide.

A PAS discount is also in place for abiraterone, enzalutamide and radium-223, and these were included in the results used for decision-making by using estimates of the PAS prices for subsequent treatments.

The results presented do not take account of the PAS for abiraterone, enzalutamide and radium-223 or the PAS for darolutamide but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for abiraterone and enzalutamide due to commercial confidentiality and competition law issues. Results at list prices are also unable to be presented due to commercial confidentiality and as such, SMC is unable to present any cost-effectiveness ratios.

Darolutamide acquisition in the nmCRPC state are the major driver of increased costs, while the costs of subsequent medicines acquisition and administration are estimated to be the biggest saving. The QALY gains are predominantly driven by an increase in the duration of time spent in the nmCRPC state, with a small offset against the mCRPC state. Sensitivity analysis was provided which showed that the results were most sensitive to alternative distributions being used for the extrapolation of overall survival and time on treatment.

The submission was associated with a number of limitations:

- A key limitation is that the ARAMIS study included relatively low usage of abiraterone and enzalutamide as post-progression therapies for the comparator arm, whereas these treatments are in established use within NHSScotland. The overall survival trajectory modelled for the comparator population has the potential to underestimate the survival benefit of these treatments in the metastatic setting, and hence overestimate the incremental benefit of darolutamide. As noted above, sensitivity analysis was provided to

show that the results were sensitive to extrapolation approaches that resulted in more conservative estimates of incremental survival.

- Separate approaches to applying mCRPC utilities and costs within the structure have been applied. Again, this may overestimate the cost of post-progression treatment while underestimating utility, with a slight bias towards darolutamide.
- The extrapolation of clinical trial data is based primarily on expert opinion, which in some cases results in significantly different choices than the parametric functions with best statistical fit. Using this approach, the curves selected are favourable towards darolutamide. Combined scenarios were provided to test more conservative approaches to extrapolating the survival curves based on best statistical fit, and suggest the ICER is relatively stable to use of these distributions.
- A plausible combination of scenarios was provided and included a correction to the calculation of subsequent treatment costs, which was deemed appropriate.

Despite the limitations described above, the economic case has been demonstrated.

*Other data were also assessed but remain confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Prostate Cancer UK, Prostate Scotland and Tackle Prostate Cancer. All three organisations are registered charities.
- Prostate Cancer UK has received 0.07% pharmaceutical company funding in the past two years, with none from the submitting company. Prostate Scotland has not received any pharmaceutical company funding in the past two years. Tackle Prostate Cancer has received 46% pharmaceutical company funding in the past two years, including from the submitting company.
- For men with high risk non-metastatic prostate cancer there are currently few treatment options to help stop the prostate cancer spreading where hormone treatment has stopped working. The lack of treatment options for men with either non-detected disseminated disease or no metastases who are no longer responding to hormone therapy can cause great anxiety, because they have evidence of biochemical relapse. These men are left waiting for their cancer to progress before being able to receive treatment.
- Current approaches to the treatment pathway are inconsistent and not well understood by patients or clinicians.
- Darolutamide could lead to increased time before metastases become apparent, and potential increase in life-span. It could also reduce the anxiety experienced by men who are unable to access treatment until progression occurs. Bone metastases are frequently extremely painful, produce an increased risk of bone fractures and lead to the need for complex orthopaedic surgery. The increased time to progression of such adverse events that darolutamide could bring would be an advantage.

- Darolutamide is taken orally twice daily which is very manageable for patients. No patient expects 'miracles' at this stage of disease. However, treatment that can extend life with a good quality would bring enormous benefits both physiologically and psychologically to patients and their families/carers.

Additional information: guidelines and protocols

The European Association of Urology published in 2019 an updated version of their 'Prostate Cancer Guidelines'. For patients with non-metastatic castration resistant prostate cancer at high risk of developing metastasis, these guidelines recommend apalutamide, darolutamide or enzalutamide in order to prolong time to metastases.[5]

The National Institute for Health and Care Excellence (NICE) published in 2019 'Prostate cancer: diagnosis and management (NG131)'. The guidance does not make any specific recommendations on the treatment of patients with high-risk non-metastatic CRPC.[6]

An update of the ESMO Clinical Practice Guidelines on prostate cancer was published in 2020. It recommends the use of apalutamide, darolutamide or enzalutamide for men with nmCRPC and a high risk of disease progression.[7]

Additional information: comparators

Continued androgen-deprivation therapy (ADT) alone, bicalutamide added to ADT or dexamethasone added to ADT.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
darolutamide 300mg film-coated tablets	600mg orally twice daily	52,520

Costs from BNF online on 03 August 2020. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated that the population treated with darolutamide would be 10 patients in year 1, rising to 50 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

References

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3. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, *et al.* Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019;380(13):1235-46. Epub 2019/02/15.
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5. Mottet N, van den Bergh RCN, Briers E, et al. European Association of Urology prostate cancer guideline, 2019. Available at: https://uroweb.org/guideline/prostate-cancer/ (Accessed 14/05/19).
6. National Insitute for Health and Care Excellence. Prostate cancer: diagnosis and management (NG131), 2019. Available at: https://www.nice.org.uk/guidance/ng131 (Accessed 14/05/19).
7. Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, *et al.* Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. ANNONC Annals of Oncology. 2020.

This assessment is based on data submitted by the applicant company up to and including 10 September 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the

operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.