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SMC2604

darolutamide 300mg film-coated tablets (Nubeqa®)

Bayer plc

08 September 2023

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

ADVICE: following a resubmission assessed under the orphan medicine process

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

Indication under review: treatment of adults with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel.

Darolutamide plus androgen deprivation therapy (ADT) and docetaxel significantly improved overall survival compared with placebo plus ADT and docetaxel in adults with mHSPC.

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.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Darolutamide is an androgen receptor inhibitor that binds with high affinity to the receptor ligand domain of the androgen receptor. By antagonising androgen receptor signalling processes, darolutamide reduces the growth of prostate cancer cells and induces cell death.[1, 2] Darolutamide has already been accepted for use by SMC for the treatment of adults with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease (SMC2297). The recommended dose of darolutamide for metastatic hormone-sensitive prostate cancer (mHSPC) is 600mg twice daily administered orally, in combination with docetaxel chemotherapy and androgen deprivation therapy (ADT); continued until disease progression or unacceptable toxicity. Please see the summary of product characteristics (link is available in section 9.3 of the DAD) for further information.

1.2. Disease background

In Scotland, prostate cancer is the most common cancer in males with around 3,394 new cases diagnosed in 2020; it is estimated that approximately 15% to 30% of these cases will have been a mHSPC.[2-4] mHSPC is dependent on androgen to grow and survive; therefore, ADT is a key component of treatment, especially early on in the disease. For some, ADT can result in a median overall survival of 3 to 4 years, but in most cases treatment can become less effective over time as prostate cancer cells become less responsive; resulting in patients with mHSPC progressing to a hormone-resistant form of prostate cancer and dying within a median of approximately one year.[2]

1.3. Treatment pathway and relevant comparators

Clinical experts consulted by SMC advised that for the treatment of mHSPC, ADT can be used alone or be combined with other systemic treatments that have been shown to improve overall survival including: apalutamide, docetaxel (with or without prednisolone), enzalutamide, and abiraterone acetate (with prednisolone) which is indicated only for newly diagnosed high-risk mHSPC.[2, 5, 6] In September 2022, SMC issued advice (SMC2472) that apalutamide is accepted for use in adults with mHSPC. However, due to the timing of this advice, comparisons versus apalutamide were not required.

1.4 Category for decision-making process

Eligibility for interim acceptance decision option

Darolutamide received an Innovation Passport allowing entry into the Medicines and Healthcare Products Regulatory Agency Innovative Licensing and Access Pathway (ILAP).

Eligibility for a PACE meeting

Darolutamide meets SMC orphan equivalent criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of darolutamide for the indication under review comes from ARASENS. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	ARASENS study[7, 8]
Study Design	Phase III, international, randomised, double-blind, placebo-controlled study.
Eligible Patients	• Patients aged ≥18 years of age with an ECOG PS score of 0 or 1. • Histologically or cytologically confirmed adenocarcinoma of prostate. • Metastatic disease documented either by a positive bone scan, or for soft tissue or visceral metastases, by an abdominal/pelvic/chest CT or MRI scan. • Commenced ADT (LHRH agonist or LHRH antagonist or orchidectomy) with or without first generation anti-androgen therapy ≤12 weeks before randomisation. First generation antiandrogen therapy had to be stopped prior to randomisation.[9] • No prior: second-generation AR inhibitor therapy (including enzalutamide, apalutamide, and darolutamide); cytochrome P17 inhibitor such as abiraterone acetate or oral ketoconazole as antineoplastic treatment for prostate cancer; chemotherapy or immunotherapy for prostate cancer prior to randomisation; or radiotherapy ≤2 weeks before randomisation.[9]
Treatments	Oral darolutamide 600mg (two 300mg tablets) twice daily with food (n=651) or matching placebo (n=655), given concomitantly with ADT (LHRH agonist or LHRH antagonist or orchidectomy) plus IV docetaxel 75mg/m^2 on day 1 and every 3 weeks for six cycles (with oral prednisone or prednisolone at the investigator's discretion). Permitted concomitant medicines included: analgesia, GCSF or GM-CSF for docetaxel-related toxicity, bisphosphonates and denosumab. Switching ADT to an LHRH antagonist was permitted during the study. The study drug could be interrupted, or dose reduced, to manage clinically significant toxicities. Darolutamide or placebo continued until symptomatic disease progression, a change in anticancer therapy, unacceptable toxicity, non-adherence, death or patient or physician decision.
Randomisation	Patients were randomised equally to receive either darolutamide or placebo. Randomisation was stratified by the extent of disease according to the tumour–node–metastasis system (non-regional lymph-node metastases only [M1a], bone metastases with or without lymph-node metastases [M1b], or visceral metastases with or without lymph-node or bone metastases [M1c]), and by alkaline phosphatase level (< or ≥ the upper limit of the normal range) at study entry.
Primary outcome	The primary outcome was overall survival, assessed in the FAS[a]. For the analysis of overall survival, data on patients in whom death had not been confirmed were censored as of the last known date the patients were alive.
Secondary outcomes	Time to castration-resistant prostate cancer (CRPC); time to pain progression; symptomatic skeletal event-free survival; time to first symptomatic skeletal event; time to initiation of subsequent systemic antineoplastic therapy; time to worsening of disease-related physical symptoms; time to initiation of opioid use for ≥7 consecutive days.
Statistical analysis	A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported). The order of the hierarchical statistical testing analysis was overall survival, then the secondary outcomes as outlined above.

Abbreviations: ADT = androgen deprivation therapy; AR = androgen receptor; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FAS = full analysis set; GCSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IV = intravenous; LHRH = luteinising hormone releasing hormone; MRI = magnetic resonance imaging.

[a] The FAS population included all randomised patients except for one patient in the placebo group who was excluded for a Good Clinical Practice violation.

At the primary analysis of overall survival (data cut-off 25 October 2021), darolutamide plus ADT and docetaxel significantly improved overall survival, as well as several secondary outcomes (see Table 2.2), when compared with placebo plus ADT and docetaxel. The secondary outcomes time to worsening of disease-related symptoms and time to initiation of opioid use for ≥7 consecutive days both numerically favoured the darolutamide treatment, but were not statistically significant. Detailed results are presented in Table 2.2.[7, 8]

Table 2.2 Primary and selected secondary outcomes from the ARASENS study (data cut-off 25 October 2021).[7, 8]

	Darolutamide plus ADT and docetaxel (n=651)[a]	**Placebo plus ADT and docetaxel (n=654)[a]**
Median follow-up	43.7 months	42.4 months
Primary outcome: overall survival		
Deaths, n	229	304
HR (95% CI), p-value	0.68 (0.57 to 0.80), p<0.001	
Median overall survival (months)	NR	48.9
KM estimated overall survival at 48 months	63%	50%
Secondary outcome: time to CRPC[b]		
Events, n	225	391
HR (95% CI), p-value	0.36 (0.30 to 0.42), p<0.001	
Median (months)	NR	19.1
Secondary outcome: time to pain progression[b]		
Events, n	222	248
HR (95% CI), p-value	0.79 (0.66 to 0.95), p=0.01	
Median (months)	NR	27.5
Secondary outcome: symptomatic skeletal event-free survival[b]		
Events, n	257	329
HR (95% CI), p-value	0.61 (0.52 to 0.72), p<0.001	
Median (months)	51.2	39.7
Secondary outcome: time to first symptomatic skeletal event[b]		
Events, n	95	108
HR (95% CI), p-value	0.71 (0.54 to 0.94), p=0.02	
Median (months)	NR	NR
Secondary outcome: time to initiation of subsequent systemic antineoplastic therapy[b]		
Events, n	219	395
HR (95% CI), p-value	0.39 (0.33 to 0.46), p<0.001	
Median (months)	NR	25.3

ADT = androgen deprivation therapy; CI = confidence interval, CRPC = castration-resistant prostate cancer; HR = hazard ratio; KM = Kaplan-Meier; NR = not reached.

[a] one patient who was randomly assigned to the placebo group but received darolutamide was included in the placebo group in the full analysis set.

[b] KM estimates from relevant time points were not reported for this outcome.

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Prostate Symptom Index-17 (assessed disease-related physical symptoms) and the Brief Pain Inventory Short-Form (assessed pain and question 3 partly informed the analysis of the secondary outcome time to pain progression) questionnaires.[7] HRQoL was maintained for patients on both treatment arms.[1]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing darolutamide plus ADT and docetaxel with abiraterone plus prednisolone with ADT, and enzalutamide plus ADT the submitting company presented a Bayesian network meta-analysis (NMA) which was conducted in patients with mHSPC as described in table 2.3.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian NMA.
Population	Adult patients with mHSPC [also referred to as castration-sensitive (LATITUDE), non-castrate (GETUG-AFG 15), and hormone-naïve (STAMPEDE-2, -3, -4)].
Comparators	ADT alone, abiraterone plus prednisolone with ADT, enzalutamide plus ADT, and docetaxel plus ADT.
Studies included	ARASENS[7]; ARCHES[10]; LATITUDE[11]; CHAARTED[12]; GETUG-AFG 15[13]; and STAMPEDE-2, -3, -4 (data from these three studies were combined).[14-16]
Outcomes	Overall survival and PFS. The definition of PFS varied, with studies using outcomes such as time to complete response or death, radiological PFS, clinical PFS or failure free survival as a proxy for PFS.
Results	The results suggest that darolutamide plus ADT and docetaxel is likely to be superior to ADT alone for overall survival and PFS. The company provided updated results with longer follow up that suggested darolutamide plus ADT and docetaxel may be associated with improvements in PFS over enzalutamide plus ADT. However, superiority of darolutamide plus ADT and docetaxel was not demonstrated compared to ADT in combination with either enzalutamide or abiraterone acetate (both plus ADT) for overall survival and abiraterone plus ADT for PFS.

ADT = androgen deprivation therapy; mHSPC= metastatic Hormone Sensitive Prostate Cancer; NMA = network meta-analysis; PFS = progression free survival

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

3. Summary of Safety Evidence

Safety analyses were performed in the safety analysis set, which included all patients who had received at least one dose of study medicine. In the ARASENS study at the data cut-off 25 October 2021, the median duration of treatment in the darolutamide group was 41.0 months (range: 0.1 to 56.5 months) and in the placebo group was 16.7 months (range: 0.3 to 55.8 months). 88% (571/652) of patients in the darolutamide group and 86% (556/650) of patients in the placebo group received the full six cycles of docetaxel.[7]

Any treatment emergent adverse event (AE) was reported by 99.5% of patients in the darolutamide group and 98.9% in the placebo group,[7].

In the darolutamide and placebo groups respectively, the most common treatment emergent AEs (occurring in ≥20% of patients) were: alopecia (41% versus 41%), neutropenia (39% versus 39%), fatigue (33% versus 33%), anaemia (28% versus 25%), arthralgia (27% versus 27%), peripheral oedema (27% versus 26%), diarrhoea (26% versus 24%), and constipation (23% versus 20%).[7]

In the darolutamide and placebo groups respectively, patients reporting a grade ≥3 AE were 70% versus 68%; patients with a reported serious AE were 45% versus 42%; patients with a dose interruption, delay, or reduction, due to treatment emergent AEs were 26% versus 17%; patients discontinuing study treatment due to an AE was 14% versus 11%; and patients discontinuing docetaxel due to an AE was 8.0% and 10%.[7]

The rates of AEs of special interest for patients on androgen receptor pathway inhibitors (including fatigue, falls, fractures, mental impairment, rash, hypertension, and cardiovascular events) were similar between the two treatment groups; except for rash (17% versus 14%) and hypertension (14% versus 9.2%). The study authors concluded that the addition of darolutamide has minimal impact on toxicity, and docetaxel is the dominant treatment that drives toxicity.[7] No additional monitoring is warranted with the addition of darolutamide to docetaxel and ADT; however, as per the summary of product characteristics, patients on docetaxel should be monitored for AEs such as neutropenia, gastrointestinal toxicity, worsening pulmonary symptoms and tumour lysis syndrome.[17]

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

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the ARASENS study, darolutamide plus ADT and docetaxel resulted in a significant improvement in overall survival, when compared with placebo plus ADT and docetaxel.[7]
- When compared with placebo plus ADT and docetaxel, darolutamide plus ADT and docetaxel resulted in a significant improvement in two clinically important outcomes, time to castration-resistant prostate cancer and time to initiation of subsequent systemic antineoplastic therapy.[7]
- Despite having a longer median duration of treatment, patients in the darolutamide group had similar rates of AEs to the placebo group; indicating that the addition of darolutamide to docetaxel and ADT is unlikely to result in increased toxicity.[7]

4.2. Key uncertainties

- The medians were not reached in the darolutamide plus ADT and docetaxel group for overall survival and all secondary outcomes (except for symptomatic skeletal event-free survival).[7] The submitting company have advised that the ARASENS study is complete, and that there are no further data cuts planned.
- By the data cut-off 25 October 2021, 28% (179/651) of patients in the darolutamide plus ADT and docetaxel group and 57% (374/654) of patients in the placebo plus ADT and docetaxel group received subsequent therapy; 48% (315/651) and 76% (495/654) entered active or survival follow-up. Of the patients who entered for active or survival follow-up: 36% (112/315)

and 47% (232/495) received subsequent abiraterone; 15% and 28% received subsequent enzalutamide; 15% and 18% received subsequent docetaxel; and 0.6% and 0.4% received subsequent apalutamide, within the respective groups. These subsequent treatments received by patients in ARASENS may not accurately reflect the subsequent treatments used for metastatic prostate cancer patients in Scottish clinical practice. Additionally, imbalances in the proportion of these subsequent treatments and follow-up may confound the assessment of overall survival.[7]

- The ARASENS study was placebo-controlled and there are no direct comparative data with the following relevant comparators in Scottish practice: ADT alone, enzalutamide plus ADT, and in patients with newly diagnosed high-risk disease, abiraterone plus ADT. In addition, ARASENS only provided results for darolutamide in combination with ADT and docetaxel, but there is no data supporting the effectiveness of darolutamide with ADT (without docetaxel).[7]
- There were limitations with the NMA, which included: credible intervals around the hazard ratios (HRs) were wide (and in some instances crossed 1); there was inconsistent reporting of, and missing data across, the studies; and the company did not include any safety or quality of life outcomes. In addition, there were several methodological and clinical differences between the studies including: study design (for example different treatments and dosing schedules for the ADT arms); eligibility criteria (for example LATITUDE only included newly diagnosed high-risk mHSPC patients); baseline characteristics (for example patients had received prior chemotherapy in some studies however, the company noted that the number of prior chemotherapies allowed were minimal and unlikely to influence the overall results); the definition for PFS (see Table 2.3). Overall, it was felt the NMA was broadly suitable to inform decision-making but there was some uncertainty regarding the submitting company's conclusions, especially any regarding the superiority of darolutamide plus ADT and docetaxel over abiraterone or enzalutamide, in combination with ADT.
- There is some uncertainty about the generalisability of the study results to the population that may receive darolutamide triplet therapy in clinical practice in Scotland. The ARASENS study enrolled patients with an ECOG PS of 0 or 1 who had mHSPC with either bone or visceral metastases, or both, at the time of their initial diagnosis. Therefore, there is uncertainty about the generalisability of the results to patients with mHSPC and a better prognosis; including those with node-only metastases, recurrent metastases, or both.[7]
- It was noted that the overall survival benefit was consistent across all subgroups, however subgroup analyses were not carried out on high versus low-risk/volume disease.[7] Given that some clinical experts contacted by SMC suggested that the place in therapy for darolutamide will be for patients with higher volume, high-risk disease, the lack of data on response in high volume disease is potentially an issue. However, the submitting company provided post-hoc subgroup analyses in the high-volume and high-risk subgroups from the ARASENS study which are supportive of the results seen in the previous subgroup analyses.

4.3. Innovative Licensing and Access Pathway (ILAP) and ongoing studies

The submitting company have advised that the ARASENS study is complete, and that no other ongoing studies are assessing the use of darolutamide plus docetaxel and ADT in patients with mHSPC.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that darolutamide plus ADT and docetaxel is a therapeutic advancement since it appears to improve overall survival, which is the aim of treatment for this condition.

Clinical experts consulted by SMC considered that the place in therapy of darolutamide plus ADT and docetaxel is for patients with a good ECOG PS and higher volume, high-risk disease.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine may impact on the patient and service delivery as this would result in an increase in the administration of parenteral chemotherapy (docetaxel) that had dropped in use during the COVID-19 pandemic.

5. Patient and carer engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **darolutamide (Nubeqa®),** as an **orphan equivalent** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Prostate cancer is the most common cancer that affects men in Scotland, whilst metastatic prostate cancer is still the second leading cause of cancer deaths in males within the UK.
- The diagnosis, and the incurable nature of the disease, can result in an overarching fear for patients about when their prostate cancer may become hormone-resistant and progress.
- Current treatments can provide many patients and families with a fulfilling lifestyle and some prolonged control. However, the disease burden can still have a significant impact on the psychological and physical wellbeing of those affected. This means that there is a need for a greater choice of treatments that extend good quality life expectancy, and delay treatment progression.
- The results of the ARASENS trial showed that compared to ADT & docetaxel alone, the addition of darolutamide to this regimen could improve life expectancy, delay disease progression, and delay clinical deterioration. Additionally, it could allow those considered fit enough for the treatment combination to remain well and independent for longer despite having an incurable cancer.
- The addition of darolutamide to ADT & docetaxel does not appear to result in increased toxicity; additionally darolutamide may have less potential drug-to-drug interactions compared to other ARTAs used for this indication.

- Darolutamide is administered orally. However, it must be administered with docetaxel, which is not currently the standard of care for patients with newly diagnosed mHSPC; as a result, patients will have to attend hospitals more often for docetaxel administration, monitoring, and reviews.
- This 'triplet combination' is thought to be a welcomed one due to the benefits seen in patients with mHSPC, and would be discussed with patients with a new diagnosis and offered to those deemed fit enough for chemotherapy. This is in spite of the known requirements of docetaxel chemotherapy administration such as travelling to and from hospital, and supporting patients through the administration of the drug.

Additional Patient and Carer Involvement

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 less than 1% pharmaceutical company funding in the past two years, including from the submitting company. Prostate Scotland has not received any pharmaceutical company funding in the past two years. Tackle Prostate Cancer has received 18% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from all three organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	Lifetime (34 years)
Population	Adults with mHSPC
Comparators	Darolutamide plus docetaxel plus ADT was compared with: docetaxel plus ADT, enzalutamide plus ADT, abiraterone plus ADT, and ADT alone.
Model description	The economic analysis was based on a three state partitioned survival model. Patients started in a pre-progressed state, before transitioning into a progressed state or death. Within the context of the model, these pre-progressed and progressed states were labelled as metastatic hormone sensitive prostate cancer (mHSPC) and metastatic castration resistant prostate cancer (mCRPC).
Clinical data	The main source of clinical data was the ARASENS study[7], which compared darolutamide plus docetaxel plus ADT with placebo plus docetaxel plus ADT. Additionally, the company used a Bayesian NMA to generate HRs for progression-free survival and overall survival between docetaxel plus ADT and all other treatments included in the model.
Extrapolation	An independent log-normal curve was fitted to the overall survival data within the placebo plus docetaxel plus ADT arm of the ARASENS study. A generalised gamma function was fitted to the progression-free survival data, again for the placebo plus docetaxel plus ADT arm of the study. Progression-free survival and overall survival curves for all other treatments, including darolutamide plus docetaxel plus ADT, were modelled by applying HRs to the parametric curves for docetaxel plus ADT.
Quality of life	HRQoL data was identified through a systematic search of secondary sources. The central utility values were matched to a previous health technology assessment submission for the treatment

	of metastatic hormone sensitive prostate cancer.[18] Patients in the mHSPC state were assigned a utility value of 0.806. Patients who progressed to hormone resistant cancer had a utility value ranging between 0.723 and 0.530, dependent on line of subsequent treatment. Additional disutilities were included for adverse events.
Costs and resource use	Medicine costs covered acquisition and administration costs, at initial and subsequent lines of treatment, as well as adverse events costs. Wider resource use costs were captured through clinician and nurse consultations, CT scans, MRI scans, bone scans, full blood count, liver function tests, kidney function tests and prostate specific antigen tests. An end of life cost was also included.
PAS (Patient Access Scheme)	A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. A PAS discount is in place for enzalutamide and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

Inclusive of the PAS discount on darolutamide, the incremental cost effectiveness ratios (ICERs) were £7,099 compared to ADT alone and £10,195 compared to docetaxel plus ADT. The SMC did not consider ADT alone or docetaxel plus ADT as the most relevant comparators in Scottish practice. Excluding the PAS discounts on enzalutamide, darolutamide plus docetaxel plus ADT was dominant, meaning it was estimated as resulting in lower costs and better health outcomes for patients. Inclusion of the PAS discount on enzalutamide significantly altered the economic case for that comparator. Using the list price of branded abiraterone, darolutamide plus docetaxel plus ADT was estimated as being dominant, however, generic versions of abiraterone are available. This is discussed further in Section 6.5.

6.3. Sensitivity analyses

Sensitivity analysis suggested that the model was sensitive to changes in the HRs estimated between docetaxel plus ADT and the remaining treatments, the utility values used and the healthcare resource use level in the mHSPC state for patients receiving darolutamide. Results for those analyses cannot be presented as they have been marked commercial in confidence by the submitting company.

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

6.4. Key strengths

- The model structure was reasonable and aligned with previous submissions for the same clinical indication.
- The key clinical study used to inform the economic analysis, ARASENS, was a randomised head-to-head comparison between darolutamide plus docetaxel plus ADT and placebo plus docetaxel plus ADT.

6.5. Key uncertainties

- The list of comparators included in the analysis was comprehensive, but there remained some uncertainty on what medicine would most likely be replaced by darolutamide. The company reported clinical feedback suggesting that enzalutamide plus ADT was the main comparator of interest. Feedback received by SMC from Scottish clinicians suggested that abiraterone plus ADT was also commonly used and so was also a relevant comparator.

- The company's submission used the list price cost of abiraterone, upon which sensitivity analysis was performed altering the confidential PAS discount. Generic versions of abiraterone are available, and clinical advice received by SMC suggested these were commonly used in Scottish practice. The use of generic prices led to a substantial increase in the incremental cost-effectiveness ratio comparing darolutamide to abiraterone.
- The overall survival benefits of darolutamide plus docetaxel plus ADT over comparators was a major driver of economic results, but also an area of uncertainty. While the company had direct-head-to-head evidence comparing darolutamide plus docetaxel plus ADT with docetaxel plus ADT, they also utilized the results from a Bayesian NMA to estimate the survival gains relative to the remaining comparators. That NMA had some weaknesses and generated large credible intervals, some of which crossed 1. Both the company and SMC looked to validate the overall survival projections with clinicians. While the company consulted clinicians agreed that the projections were reasonable, some of the clinicians consulted by SMC felt that the estimated survival benefit of darolutamide over abiraterone may not be seen in practice.
- No suitable health related quality of life data was captured in the ARASENS study, leading to the reliance on externally sourced values. These values did appear reasonable and in alignment with others used within the same indication, but were indicated as a large driver of economic results within the sensitivity analysis.
- The base case approach to modelling the length of time patients received different types of treatment was inconsistent. Patients were assumed to receive darolutamide in line with the duration observed in the ARASENS study. Enzalutamide and abiraterone were modelled by assuming patients would receive treatment up until the point they progressed. Within the ARASENS study, progression typically took place after a patient had discontinued darolutamide. This may have artificially inflated the costs of enzalutamide and abiraterone treatment relative to darolutamide. However, the company provided additional scenario analysis which suggested the implications of this may be small.
- The company included the costs of patients receiving chemotherapy alongside darolutamide within oncology centres. However, some of the experts consulted by SMC noted that COVID-19 had led to a shift towards oral treatment for prostate cancer. It is unclear whether the costs included in the modelling would accurately account for the service implications of returning patients to up to 6 cycles of docetaxel.

7. Conclusion

The Committee considered the benefits of darolutamide in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as darolutamide is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted darolutamide plus ADT and docetaxel for use in NHSScotland.

8. Guidelines and Protocols

Published in May 2019 (updated in December 2021), the National Institute for Health and Care Excellence (NICE) published clinical guideline number 131, Prostate cancer: diagnosis and management. This recommends offering docetaxel chemotherapy to people with newly diagnosed metastatic prostate cancer who do not have significant comorbidities as follows: start treatment within 12 weeks of starting ADT and use six 3-weekly cycles at a dose of 75mg/m^2 (with or without daily prednisolone). Do not offer combined androgen blockade as a first-line treatment for people with metastatic prostate cancer. For people with metastatic prostate cancer who are willing to accept the adverse impact on overall survival and gynaecomastia with the aim of retaining sexual function, offer anti-androgen monotherapy with bicalutamide (150mg). Begin ADT and stop bicalutamide treatment in people with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function.[19]

In June 2020, the European Society of Medical Oncology (ESMO) updated their clinical guideline on prostate cancer. This notes that ADT is recommended as first-line treatment of metastatic hormone naïve prostate cancer (mHNPC) in combination with abiraterone/prednisone or apalutamide or docetaxel or enzalutamide. Radiotherapy to the primary tumour combined with the systemic treatment is recommended for patients with low volume mHNPC. ADT alone is recommended as first-line systemic treatment of mHNPC in men who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel. For men starting on ADT, management to prevent cancer treatment-induced bone loss is recommended.[20]

In 2022, the European Association of Urology (EAU) updated their guideline on prostate cancer. In the first-line treatment of metastatic disease this makes the following recommendations:

- Offer immediate ADT to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease in symptomatic patients.
- Discuss combination therapy including ADT plus systemic therapy with all patients.
- Do not offer ADT monotherapy to patients whose first presentation is metastatic disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy and are willing to accept the increased risk of side effects.
- Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is metastatic disease and who are fit for docetaxel.
- Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is metastatic disease and who are fit enough for the regimen.[21]

9. Additional Information

9.1. Product availability date

27 November 2022.

9.2. Summary of product characteristics

See the SPC for further information including dosing and safety. Available from: Darolutamide 300mg film coated tablets (Nubeqa®).

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
darolutamide	**600mg twice daily until disease progression or unacceptable toxicity**	**52,520**

Costs from BNF online on 28 November 2022. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The company estimated there would be 577 patients eligible for treatment with darolutamide plus ADT and docetaxel in year 1 and 1990 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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This assessment is based on data submitted by the applicant company up to and including 06 July 2023.

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.