Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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# Resubmission

## desmopressin 25 microgram, 50 microgram oral lyophilisate (Noqdirna®)

SMC No. (1218/17)

## Ferring Pharmaceuticals Ltd

07 July 2017

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 NHS Scotland. The advice is summarised as follows:

**ADVICE**: following a resubmission

**desmopressin oral lyophilisate (Noqdirna®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** Symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults.

**SMC restriction:** For use in patients aged 65 years and over.

Two phase III, placebo-controlled studies demonstrated that desmopressin, at licensed doses over three months, significantly reduced the mean number of nocturnal voids and resulted in higher proportions of responders compared with placebo, in patients with nocturia.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

## Indication

Symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults.[1, 2]

## Dosing Information

Women: desmopressin 25 microgram daily, one hour before bedtime, administered sublingually without water.[1]
Men: desmopressin 50 microgram daily, one hour before bedtime, administered sublingually without water. [2]
Food intake may reduce the intensity and duration of the antidiuretic effect at low doses of desmopressin.[1, 2]

## Product availability date

October 2016.

## Summary of evidence on comparative efficacy

Desmopressin acetate is a synthetic analogue of arginine vasopressin and mimics the antidiuretic action. Desmopressin (Noqdirna®) is formulated as an oral lyophilisate (orally disintegrating tablet) which is administered by placing under the tongue without water, one hour before bedtime. The dose is gender specific.[1, 2]

Nocturia has multi-factorial aetiology and pathogenesis, including nocturnal polyuria, and is considered to have a detrimental impact on health when at least two nocturnal voids occur, mainly due to broken sleep. Nocturnal polyuria is associated with decreased secretion of arginine vasopressin and is defined as nocturnal urine output greater than 20% to 33% of 24-hour output, depending on age.[3, 4] The submitting company has requested that SMC considers desmopressin oral lyophilisate (Noqdirna®) in patients aged 65 years and over.

Evidence of efficacy for the oral lyophilisate formulation comes from two pivotal phase III placebo-controlled, three-month studies conducted in females (study CS40) and males (study CS41) aged ≥18 years with nocturia defined as at least two voids per night, determined via a three-day bladder diary. Patients on stable doses of overactive bladder treatments (for at least three months) were permitted to enter the study. Patients were randomised equally to desmopressin 25 microgram or placebo (in study CS40) or desmopressin 50 microgram [licensed dose in males], desmopressin 75 microgram or placebo (in study CS41), stratified by age (<65 years, ≥65 years). Treatments were taken one hour before bedtime and patients were also instructed to empty the bladder before bedtime, drink to satisfy thirst only, and limit evening intake of coffee, tea, caffeinated soft drinks and alcoholic beverages.[3-5]

The co-primary endpoints were change from baseline in mean number of nocturnal voids and 33% responder status during three months of treatment, using a longitudinal analysis. This involved a repeated measures analysis of co-variance (ANCOVA) comparing change from baseline with visits at week 1 and months 1, 2 and 3, adjusted for age, visit and baseline nocturnal voids. A 33% responder was defined as a patient with a decrease of at least 33% in the mean number of nocturnal voids at each visit compared with baseline. Both studies met their co-primary endpoints. In CS41, analyses of desmopressin 75 microgram versus placebo were statistically

significant, therefore testing of the desmopressin 50 microgram proceeded according to a hierarchical step-down approach.[3, 4] Results for the licensed doses of desmopressin only are presented in table 1, below.

**Table 1: results of co-primary endpoints for studies CS40 and CS41 (licensed doses)**

| | **Study CS40** | | **Study CS41** | |
|---|---|---|---|---|
| | **desmopressin 25 microgram** | **placebo** | **desmopressin 50 microgram** | **placebo** |
| N (FAS) | 133 | 128 | 119 | 142 |
| Mean number of nocturnal voids at baseline | 2.84 | 2.88 | 2.88 | 2.90 |
| Change from baseline in mean number of nocturnal voids | -1.46 | -1.24 | -1.25 | -0.88 |
| Treatment difference (95% CI), p-value | -0.22 (95% CI: -0.42 to -0.02), p=0.028 | | -0.37 (95% CI: -0.57 to -0.17), p=0.0003 | |
| 33% responder probability | 0.76 | 0.64 | 0.67 | 0.50 |
| Odds ratio (95% CI), p-value | 1.85 (95% CI: 1.19 to 2.86), p=0.006 | | 1.98 (95% CI: 1.32 to 2.96), p=0.0009 | |

N=number of patients, FAS=full analysis set, CI=confidence interval

Results are available for the subgroups of patients aged ≥65 years (48% of study populations). In CS40 the adjusted mean change in nocturnal voids over three months was -1.31 for desmopressin and -0.96 for placebo; treatment difference -0.35 (95% CI: -0.65 to -0.05) and the proportion of 33% responders over three months was 0.71 for desmopressin and 0.55 for placebo, odds ratio 2.02 (95% CI: 1.11 to 3.69). In CS41, the adjusted mean change in nocturnal voids over three months was -1.06 for desmopressin 50 microgram and -0.63 for placebo; treatment difference -0.43 (95% CI: -0.72 to -0.14) and the proportion of 33% responders over three months was 0.58 for desmopressin 50 microgram and 0.40 for placebo, odds ratio 2.09 (95% CI: 1.19 to 3.69).[5]

Results of the secondary endpoints were supportive of the co-primary endpoints. Selected secondary endpoints are reported in table 2, below.

**Table 2: results of secondary endpoints for studies CS40 and CS41 (licensed doses)**

| | **Study CS40** | | **Study CS41** | |
|---|---|---|---|---|
| | **desmopressin 25 microgram** | **placebo** | **desmopressin 50 microgram** | **placebo** |
| N (FAS) | 133 | 128 | 119 | 142 |
| Mean time to first void at baseline | 147 minutes | 143 minutes | 146 minutes | 147 minutes |
| Change from baseline in mean time to first nocturnal void | 155 minutes | 106 minutes | 112 minutes | 73 minutes |

| | | | | |
|---|---|---|---|---|
| Treatment difference (95% CI), p-value | 49 minutes (95% CI: 16 to 82), p=0.003 | | 39 minutes (95% CI: 11 to 67), p=0.0006. | |
| Mean nocturnal urine volume at baseline | 627mL | 607mL | 607mL | 620mL |
| Change from baseline in nocturnal urine volume | -235mL | -151mL | -209mL | -131mL |
| Treatment difference (95% CI), p-value | -84mL (95% CI: -139 to -28), p=0.003 | | -78mL (95% CI: -136 to -20), p=0.009 | |

N=number of patients; FAS=full analysis set, CI=confidence interval

An exploratory assessment of quality of life included sleep quality ratings and the Nocturia Quality of Life (NQoL) questionnaire. Sleep quality was rated on a scale of 1 (poor) to 10 (excellent) and a mean score over three successive mornings was obtained for three questions. The NQoL questionnaire included one statement on global quality of life and 12 disease specific statements which were rated on a scale of 0 (lowest) to 4 (highest). Scores were transformed into a standardised score out of 100. In both studies, patients treated with desmopressin compared with placebo had their sleep quality improved. Results of the NQoL questionnaire indicated improvements in bother/concern and sleep/energy domains and total score in CS40 and in sleep/energy domain, global quality of life and total score in CS41. [3 4]

Study CS29 was a four-week study conducted in females and males and with similar inclusion criteria to the pivotal studies, where patients were randomised to one of four doses of desmopressin (some not licensed and not discussed further) or placebo.[6] There were significant differences for desmopressin 50 microgram versus placebo for the co-primary endpoint of change from baseline to week 4 in mean number of nocturnal voids. Long-term data are available from study CS31, an optional, open-label extension to study CS29, where patients were treated for up to 96 weeks.[7] A total of 408 patients entered the long-term extension and 248 patients provided data on number of nocturnal voids after 52 weeks of treatment. At week 52, in the desmopressin 25 microgram and 50 microgram groups, respectively, the changes from baseline in mean number of nocturnal voids were -1.4 and -1.8, and these were maintained at week 92: -1.4 and -1.9 respectively. The 33% responder probabilities were 0.74 and 0.73 at week 52 and 0.63 and 0.77 at week 92.[8] Results are available (at week 52) for 40 women and 48 men treated with licensed desmopressin doses. In the desmopressin 25 microgram group, the change from baseline in mean number of nocturnal voids was -1.7 and the 33% responder probability was 0.88. In the desmopressin 50 microgram group, the change from baseline in mean number of nocturnal voids was -1.7 and the 33% responder probability was 0.63.

## Summary of evidence on comparative safety

There are no comparative safety data other than versus placebo. In study CS40, adverse events considered by the investigator to be possibly/probably related to study medicine occurred in 19% (26/135) of desmopressin-treated patients and 12% (15/126) of placebo-treated patients, and those leading to treatment discontinuation occurred in 2.2% (3/135) and 0% of patients,

respectively. There was one severe and no serious adverse events in the desmopressin group compared with three severe and two serious adverse events in the placebo group.[3]

In study CS41, adverse events considered by the investigator to be possibly/probably related to study medicine occurred in 19% (23/119) of desmopressin-treated patients and 15% (22/143) of placebo-treated patients, and those leading to treatment discontinuation occurred in 3.4% (4/119) and 2.8% (4/143) of patients, respectively. There were two severe and four serious adverse events in the desmopressin 50 microgram group compared with two severe and one serious adverse event in the placebo group.[4]

Serum sodium was measured during screening and at all study visits thereafter; any patient with a serum sodium ≤130mmol/L underwent investigation and those with a serum sodium ≤125mmol/L were immediately withdrawn. In study CS40, in the desmopressin and placebo groups respectively, the proportion of patients with serum sodium of 126 to 129mmol/L was 2.2% (3/135) versus no patients. Serum sodium returned to >130mmol/L within two to four days without the need to discontinue treatment in all three patients (two of whom had serum sodium less than 135mmol/L at baseline). In study CS41, no patients had serum sodium of 126 to 129mmol/L. Two patients in the desmopressin 50 microgram group had serum sodium ≤125mmol/L; one patient was taking concomitant medicines (enalapril and lovastatin) which may have contributed to the hyponatraemia. Following treatment discontinuation in these patients serum sodium returned to values >130mmol/L.[3, 4, 9, 10]

In the longer term study desmopressin was well tolerated with similar frequency and type of adverse events to those reported in shorter term studies. [7]

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

## Summary of clinical effectiveness issues

There are no other treatments licensed for symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults aged at least 65 years. Current strategies include lifestyle or behavioural modifications and medicines such as alpha-blockers, antimuscarinics and antidiuretics, and desmopressin is likely to be used in addition to these. Off-label use of other formulations/strengths of desmopressin has been noted.[11]

The submitting company has requested that SMC considers desmopressin when used in patients aged 65 years and over.

Two phase III, placebo-controlled studies (CS40 in females and CS41 in males) demonstrated that desmopressin, at licensed doses over three months, significantly reduced the mean number of nocturnal voids and resulted in higher proportions of 33% responders compared with placebo. A longitudinal analysis was used for the co-primary endpoints as data from the previous CS29 study indicated some variability at each individual time point. It was considered that an average response over a longer treatment period might be more representative of the clinical benefit. Subgroup analyses of the pivotal studies provide evidence of efficacy in patients aged ≥65 years, where similar results to the overall populations were observed. However, there are no efficacy data specifically in patients with idiopathic nocturnal polyuria and aged ≥65 years, the positioning within the licensed indication proposed by the company. Nocturnal polyuria was not a specific inclusion criterion in the pivotal studies. However, at baseline, 89% of women and 87% of men

met the definition of nocturnal polyuria (nocturnal urine output greater than 33% of 24-hour output) and patients with potentially treatable medical underlying causes for nocturia were excluded from the studies. Furthermore, results of the co-primary endpoints in the subgroups of patients (of any age) with nocturnal polyuria were the same as in the total study populations.[3-5]

In the overall populations of the pivotal studies, treatment with desmopressin compared with placebo improved sleep quality and quality of life, assessed using the NQoL questionnaire (where a treatment difference at three months of approximately five points has been suggested as being clinically meaningful). High placebo responses were observed in these studies. All patients were instructed on lifestyle and behavioural modifications, however and this may have contributed to the placebo response. In addition, the completion of diaries may also have raised awareness of these issues. The authors of the study publications noted that high placebo responses have previously been seen in urological studies (e.g. overactive bladder and benign prostatic hyperplasia).[3-5]

There are no comparative data versus desmopressin preparations used off-label. Furthermore there are limited long-term data for desmopressin at licensed doses. In 40 females treated with desmopressin 25 microgram and 48 males treated with desmopressin 50 microgram the change in mean number of nocturnal voids from baseline to week 52 was -1.7.[3, 4, 7]

Data on falls or fractures were not collected in the pivotal studies. Although the submitting company presented an analysis of three studies in support of an increased risk of fracture due to nocturia, one study assessed only falls, not fractures.[12] Another study reported that the significant increase in falls reported by nocturia participants did not result in an increase in reported fractures in the previous five years.[13] The third study found an association between the number of nocturnal voids and hip fracture rate but did not analyse whether the fractures occurred during the day or night.[14] Clinical experts consulted by SMC were asked to comment on this potential relationship. Some considered the association to be plausible but acknowledged that the relationship has not been shown to be causative, and noted that other factors such as reduced balance, impaired muscle function and hyponatraemia may also be important. Treatment with desmopressin may cause hyponatraemia and dizziness.[1, 2]

For entry into the pivotal studies, patients were required to have serum sodium ≥135mmol/L. Hyponatraemia occurred in a higher proportion of desmopressin than placebo treated patients in both studies.[3, 4] The summary of product characteristics (SPC) for desmopressin oral lyophilisate (Noqdirna®) advises that, in patients aged at least 65 years, serum sodium should be within normal range before initiating treatment and monitored in the first week and at one month of treatment. Desmopressin should be discontinued if the serum sodium level falls below the lower limit of normal range. Use of desmopressin 50 microgram in females is not recommended due to increased risk of hyponatraemia at this dose compared to males.[1, 2] The SPC notes that continued therapy must be carefully reconsidered in elderly patients who show no evidence of therapeutic benefit beyond three months, and this has been confirmed by SMC clinical experts.[1, 2]

Some clinical experts consulted by SMC noted potential issues in terms of diagnosis of idiopathic nocturnal polyuria. They considered that the introduction of desmopressin may have service implications in terms of its safe and effective use as well as the monitoring requirements for serum sodium.

Desmopressin oral lyophilisate (Noqdirna®) should be stored in the original package in order to protect from moisture and light and used immediately upon opening individual tablet blister. It cannot be used in monitored dose systems. [1, 2]

## Summary of comparative health economic evidence

A cost-utility analysis was presented comparing desmopressin, at variable gender- specific doses, to no treatment (reflecting best supportive care) in a population of patients aged 65 years and over with nocturia due to idiopathic nocturnal polyuria. A Markov model with a 19 year time horizon was used. The model used 4 health states based on the number of times the patient voided urine during the night: <2 voids (remission), 2-3 voids (moderate nocturia), ≥4 voids (severe nocturia) and death. In each health state the model included a risk of fractures due to falls associated with nocturnal polyuria.

In the model all patients started in the moderate or severe nocturia health states with the distribution between these states based on the sub-group of patients aged ≥65 years from the CS40 (females only) and CS41 (males only) pivotal studies. In the base case, the transition probabilities between health states were derived separately for males and females. The first three month model cycle used change from baseline in mean number of nocturnal voids from the placebo arm of studies CS40 and CS41 for the no treatment comparator. The same studies were used for the first cycle transition probabilities in the desmopressin cohort but with the addition of data from the CS29 phase III study (four-week study of various desmopressin doses vs placebo) and the CS31 long run open label extension study of CS29, which contained only patients receiving desmopressin. For the second and subsequent model cycles transition probabilities for desmopressin were derived from the two year CS31 open label study, whereas for the no treatment cohort the post 1st cycle transition probabilities were based on the incidence of remission (<2 voids) from a published natural history study in Dutch males with nocturnal polyuria aged 65-69, and ≥70 years.[15]

In order to account for natural fluctuations in the condition whereby there may be resolution of symptoms not associated with treatment for some patients, a two year stop and review rule was included, whereby patients who are receiving desmopressin and are in remission temporarily stop treatment and cease permanently if symptoms do not return after a week. Remission incidence data from the natural history study[15] was used to estimate the three month probability of a natural resolution of the condition in desmopressin patients, with these patients assumed to cease treatment and follow the natural history probabilities for the duration of the model horizon. In both the desmopressin and no treatment groups a probability of recurrence of nocturia (i.e. movement from <2 voids to 2-3 or ≥4 void states) was estimated based on the two year desmopressin clinical study data, and the natural history study for the no treatment comparator, with the probability of recurrence estimated to be higher in the no treatment group.

The relative risk of fracture in each of the health states was calculated based on estimates from three survey/observational studies identified by the submitting company from literature searches (as summarised in the clinical effectiveness issues section above).

The CS29 study provided SF-12 data that were converted to utilities via a mapping algorithm to the SF-6D utility weights. Data were age and gender stratified to produce utility weights in three age groups for each gender ranging from 0.766-0.814 for <2 voids, 0.728-0.783 for 2-3 voids, and 0.688-0.764 for ≥4 voids. As an alternative source EQ-5D-5L derived utility estimates for patients with overactive bladder, benign prostatic hypertrophy or nocturia from a European observational study were used in scenario analysis.[16] Utility decrements were applied for each fracture type,

sourced from previously published studies in osteoporosis. A small adverse event disutility was applied for the incidence of hyponatraemia.

Medicines acquisition and monitoring costs, and costs of managing hyponatraemia adverse events only were included. Costs associated with fractures were estimated from various published sources.

The base case results and selected sensitivity analysis are presented in Table 3 below.

**Table 3: Base case and scenario analysis results**

| **Analysis** | **Incremental costs** | **Incremental QALYs*** | **ICER**** |
|---|---|---|---|
| Base case | £1,300 | 0.136 | £9,538 |
| 20% lower bound for desmopressin transition probabilities after the first 3 month cycle | £1,418 | £0.109 | £12,992 |
| Using natural history data for the first three month no treatment cycle | £1,314 | 0.158 | £8,335 |
| EQ-5D derived utilities | £1,300 | 0.178 | £7,308 |
| 5 year time horizon | £714 | 0.052 | £13,681 |
| No reduction in fractures due to desmopressin treatment | £1,552 | 0.128 | £12,101 |
| No stop and review rule | £1,741 | 0.181 | £9,613 |
| Patients who stop treatment due to stop and review rule could re-start if symptoms return | £1,534 | 0.163 | £9,416 |

* Quality Adjusted Life Year
** Incremental cost-effectiveness ratio

There were a number of uncertainties associated with the economic analysis comparing desmopressin with no treatment:

- The data to estimate transition probabilities between void frequency states after 3 months was from different sources for the desmopressin and no treatment comparator, resulting in some uncertainty in relative effectiveness estimates. There were also limitations in the data used for extrapolation of long term outcomes and a range of assumptions had to be made in order to estimate a full set of male and female transition probabilities and recurrence rates between health states.
- The impact of the stop and review rule at 2 years is associated with uncertainty, and concerns over its feasibility to implement in clinical practice. The company were asked to provide a scenario analysis based on assuming patients who cease treatment due to the rule could restart in the future if symptoms return (based on natural history probabilities), and a scenario without the stop and review rule. In both scenarios there were higher incremental costs and QALYs for desmopressin than in the base case but minimal impact on the ICER (see Table 3).
- An assumption in the model is that the relative risk of fracture associated with nocturnal polyuria in the observational studies used for estimating risk is a causal effect. There is no direct evidence on fracture risk reduction from the desmopressin clinical studies, and there are limitations with the published studies for assuming a causal relationship (as summarised in the clinical effectiveness section), hence this remains an uncertain outcome.

Despite the above uncertainties the ICER remains within acceptable limits across a range of scenario and sensitivity analyses, and so the economic case can be considered to have been demonstrated.

## Summary of patient and public involvement

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

- We received patient group submissions from Bladder Health UK and Parkinson's UK, both are registered charities.

- Bladder Health UK has received 30% pharmaceutical company funding in the past two years, with none from the submitting company. Parkinson's UK has received less than 0.01% pharmaceutical company funding in the past two years, with none for the submitting company.

- Untreated nocturia can lead to people feeling shame, and a lack of dignity with a negative impact on wider mental health. Nocturia is a very significant and distressing issue for people with Parkinson's, affecting a very high proportion of people with the condition. Getting up to go to the toilet frequently at night increases the risk of falls in the elderly which can cause bone breakages. Reduced mobility, poor balance and difficulties with fine movements make this a particular problem for Parkinson's patients.

- Current approaches to treating nocturia such as life-style modifications and medicines such as anti-muscarinics are often not particularly effective, can have unpleasant side-effects and are not suitable for everyone.

- Desmopressin oral lyophilisate (Noqdirna®) may be more effective for some patients with nocturia, helping them to restore personal dignity and control and improving their enjoyment of life due to them being able to get a better night's rest. It may also enable them to feel more confident about living independently by decreasing trips to the toilet at night and hence decreasing the risk of a fall. If it were clinically appropriate it could have a positive impact on the quality of life of Parkinson's patients with nocturia and their families.

## Additional information: guidelines and protocols

There are no relevant up-to-date guidelines relating to the use of desmopressin oral lyophilisate (Noqdirna®).

The European Association of Urology (EAU) published Guidelines on the treatment of non-neurogenic male lower urinary tract symptoms (LUTS), in 2016. This recommends that: "*Desmopressin may be prescribed to decrease nocturia due to nocturnal polyuria in men under the age of 65. Screening for hyponatremia must be undertaken at baseline, during dose titration and during treatment*."[11]

The EAU published an update on urinary incontinence guidelines in 2017.[17] This recommends considering offering desmopressin to patients requiring occasional short-term relief from daytime

urinary incontinence and informing them that this drug is not licensed for this indication. It also notes that plasma sodium levels should be monitored in patients on desmopressin.

The National Institute for Health and Care Excellence (NICE) published clinical guideline (CG) 171, Urinary incontinence in women: management, in November 2015. This states: "*The use of desmopressin may be considered specifically to reduce nocturia in women with UI or OAB who find it a troublesome symptom. Use particular caution in women with cystic fibrosis and avoid in those over 65 years with cardiovascular disease or hypertension*".[18]

NICE CG97 Lower urinary tract symptoms in men: management was published in June 2015. This states: "*Consider offering oral desmopressin to men with nocturnal polyuria if other medical causes have been excluded and they have not benefited from other treatments. Measure serum sodium 3 days after the first dose. If serum sodium is reduced to below the normal range, stop desmopressin treatment".*[19]

## Additional information: comparators

There are no licensed comparator treatments for this indication. Clinical experts consulted by SMC noted there may be some off-label use of higher strength desmopressin formulations, however these are specifically contra-indicated in the elderly.

## Cost of relevant comparators

| Drug | Dose Regimen | Cost per year (£) |
|---|---|---|
| **Desmopressin oral lyophilisate** | **25 microgram (females) or 50 microgram (males) sublingually daily, one hour before bedtime** | **184** |

Cost from MIMS on 3 May 2017.

## Additional information: budget impact

The submitting company estimated there would be 31,396 patients eligible for treatment with desmopressin oral lyophilisate in year 1 rising to 31,791 patients in year 5. The estimated uptake rate was 0.60% in year 1 (184 patients) rising to 11.84% in year 5 (3,744 patients) with a discontinuation rate of 2.4% applied in year 1 and 0.5% in year 5.

The gross impact on the medicines budget was estimated to be £34k in year 1 rising to £691k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be a saving of £16k in year 1 rising to a cost of £639k in year 5.

References

The undernoted references were supplied with the submission.


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This assessment is based on data submitted by the applicant company up to and including 16 June 2017.

*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_statements/Policy_Statements

Drug 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.

***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.*