

enzalutamide 40mg soft capsules (Xtandi[®])

SMC No. (911/13)

Astellas Pharma Ltd

04 October 2013

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 full submission

enzalutamide (Xtandi[®]) is accepted for use within NHS Scotland.

Indication under review: Treatment of adult men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel therapy.

In one randomised, double-blind, phase III clinical study, enzalutamide significantly increased overall survival compared with placebo.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of enzalutamide. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of adult men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel therapy.

Dosing Information

The recommended dose is 160mg enzalutamide (four 40mg capsules) as a single oral daily dose.¹

The capsules should be swallowed whole with water and can be taken with or without food. If a patient experiences a $\geq$ grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to $\leq$ grade 2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted.¹

Product availability date

27 June 2013

Summary of evidence on comparative efficacy

Enzalutamide is a novel androgen receptor antagonist that decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. It has no androgen receptor agonist activity.^{1,3}

The clinical evidence derives from one phase III, randomised, double-blind, placebo-controlled study (AFFIRM) to evaluate the efficacy and safety of enzalutamide compared with placebo in patients with mCRPC who had received at least one docetaxel-containing chemotherapy regimen.⁴ Patients were eligible if they had histologically or cytologically confirmed adenocarcinoma of the prostate and were receiving ongoing androgen deprivation therapy (ADT) with a gonadotrophin-releasing hormone (GnRH) analogue or orchiectomy. Patients were required to have a testosterone level of <1.7 nmol/L and progressive disease by prostate specific antigen (PSA) or imaging and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Eligible patients were randomised in a ratio of 2:1 to receive enzalutamide (160mg daily, n=800) or placebo (n=399). Randomisation was stratified by ECOG performance status and Brief Pain Inventory-Short Form (BPI-SF) question 3 score on average pain over previous 7 days. Study treatment was continued until unacceptable toxicity, documented and confirmed disease progression, subsequent new antineoplastic therapy, death or withdrawal. Patients in both treatment groups also received best supportive care, and prednisone or other glucocorticoid use was allowed but not required.^{3,4}

The primary outcome was overall survival (OS), which was analysed in the intention to treat population. After a planned interim analysis at a median follow-up of 14.4 months, when 80% of the required events had occurred, median OS was 18.4 months (95% confidence interval [CI]: 17.3 to not reached) for enzalutamide and 13.6 months (95% CI: 11.3 to 15.8) for placebo; hazard ratio for death 0.63 (95% CI: 0.53 to 0.75). The median duration of treatment was 8.3 months for enzalutamide and 3.0 months for placebo. The survival benefit was consistent across all subgroups tested. On the advice of an independent data and safety monitoring committee, the study was stopped, unblinded and eligible patients in the placebo group were offered treatment with enzalutamide.

Secondary outcomes were analysed only if the OS analysis showed superiority of enzalutamide over placebo; these were analysed in rank-prioritised order with the significance of the previous outcome gating further testing. Enzalutamide was superior to placebo for all secondary outcomes analysed, including median time to PSA progression, median time to radiographic progression-free survival (PFS) and time to first skeletal-related event (SRE). The results for these secondary outcomes (the first three ranked) and the proportion of PSA responders are shown below.⁴

	Median time to PSA progression (months)	Median time to radiographic PFS (months)	Median time to first SRE (months)	PSA response	
				≥50% decline from baseline (%; n)	≥90% decline from baseline (%;n)
Enzalutamide	8.3 (95% CI: 5.8 to 8.3)	8.3 (95% CI: 8.2 to 9.4)	16.7 (95% CI: 14.6 to 19.1)	54 (395/731)	25 (181/731)
Placebo	3.0 (95% CI: 2.9 to 3.7)	2.9 (95% CI: 2.8 to 3.4)	13.3 (95% CI: 9.9 to not reached)	2 (5/330)	1 (3/330)
Hazard ratio (HR)	0.25 (95% CI: 0.20 to 0.30), p<0.001	0.40 (95% CI: 0.35 to 0.47), p<0.001	0.69 (95% CI: 0.57 to 0.84), p<0.001	- p<0.001	- P<0.001

PSA=prostate specific antigen; PFS=progression-free survival; SRE=skeletal-related events; CI=confidence interval

Quality of life was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. Quality of life response was defined as a 10-point improvement in the global score in the FACT-P questionnaire compared with baseline on two consecutive measurements obtained at least 3 weeks apart. This was achieved in 43% (281/651) of enzalutamide patients and 18% (47/257) of placebo patients (p<0.001).⁴

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the summary of product characteristics for details of adverse effects.

In the AFFIRM study, the most common adverse events were hot flush and headache (frequency ≥10%). Other adverse events that occurred commonly (i.e. ≥1%) were neutropenia, visual hallucinations, anxiety, cognitive disorder, memory impairment, hypertension, dry skin, pruritus, fractures and falls.¹

Adverse events that occurred at a frequency of ≥5% and at a greater frequency in the enzalutamide group than placebo included diarrhoea (21% [171/800] versus 18% [70/399]), fatigue (34% [269/800] versus 29% [116/399]), peripheral oedema (15% [122/800] versus 13% [53/399]), musculoskeletal pain (14% [116/800] versus 12% [46/399]), muscular weakness (9.3% [74/800] versus 6.8% [27/399]), headache (12% [93/800] versus 5.5% [22/399]), paraesthesia (6.5% [52/800] versus 4.5% [18/399]), insomnia (8.8% [70/800] versus 6.0% [24/399]), anxiety (6.4% [51/800] versus 4.0% [16/399]), haematuria (6.5% [52/800] versus 4.5% [18/399]), hot flush (20% [162/800] versus 10% [41/399]), hypertension (6.1% [49/800] versus 2.8% [11/399]).³

Overall, adverse event rates were broadly similar although patients had been treated with enzalutamide for more than twice as long as with placebo (median of 8.3 months versus 3.0 months). However the incidence of serious adverse events, ≥grade 3 severity adverse events, discontinuation

due to adverse events and death due to adverse events were all numerically lower in the enzalutamide than placebo group.³

Enzalutamide is associated with an increased risk of seizure, and caution is advised in administering the drug to patients with a history of seizure or other predisposing factors.¹ Seizure occurred in 6 patients (0.8%) taking enzalutamide in the AFFIRM study.³

Summary of clinical effectiveness issues

Enzalutamide is an androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. It has a different mechanism of action from abiraterone, the other anti-cancer therapy licensed in this indication, which is an androgen biosynthesis inhibitor.

Clinical evidence from one phase III, randomised, double-blind, placebo-controlled study (AFFIRM) in patients with mCRPC previously treated with docetaxel showed that enzalutamide significantly increased OS by 4.8 months compared with placebo. This survival benefit was considered clinically meaningful in this patient population. Enzalutamide was superior to placebo in all secondary outcomes analysed, including median time to PSA progression, median time to radiographic progression and time to first skeletal-related event.

The study was stopped early after a planned interim analysis at a median follow-up of 14.4 months, and this may have biased the estimate of the OS benefit. The study excluded patients with clinically significant cardiovascular disease, which may limit its generalisability to Scottish patients. There were limited data in patients with an ECOG performance status ≥ 2 and in non-white patients.

Enzalutamide may offer an alternative to abiraterone in patients with mCRPC whose disease has progressed on or after docetaxel therapy but it is currently unclear how these options fit into clinical practice. There are no direct comparative data for enzalutamide and abiraterone. Very few patients in the AFFIRM study had received previous abiraterone therefore, the efficacy of enzalutamide in patients who have previously received abiraterone is unknown.

SMC advice restricts the use of abiraterone to patients who have received only one previous chemotherapy regimen. In the AFFIRM study of enzalutamide, most of the patients had received only one prior chemotherapy regimen (73%, 875/1199). A sub-group analysis in patients who had received two or more previous chemotherapy regimens (27%, 324/1199) showed a non-significant increase in OS for enzalutamide compared with placebo (median OS of 15.9 for enzalutamide versus 12.3 months for placebo; HR 0.74 [95% CI: 0.54 to 1.03]).⁴

Enzalutamide may have an advantage over abiraterone in that it can be taken without concomitant corticosteroids and is not affected by food. There is no requirement for monitoring liver function with enzalutamide, in contrast to abiraterone which requires monthly monitoring of liver function.⁵

Enzalutamide is an enzyme inducer and increases the synthesis of many enzymes and transporters. Therefore interactions with medicines that are eliminated through metabolism or active transport are expected.¹ The summary of product characteristics (SPC) for enzalutamide lists a large number of therapeutic classes of drugs that are potentially affected, including anticoagulants, antiepileptics, beta-blockers, calcium channel blockers, cardiac glycosides, statins and levothyroxine.¹

Enzalutamide is associated with an increased risk of seizure and the SPC warns that it should be used with caution in patients with a history of seizure or other predisposing factors.¹

Since no direct comparative data are available for enzalutamide in the treatment of mCRPC, the submitting company performed a Bucher indirect comparison of enzalutamide with abiraterone in the treatment of mCRPC to support the economic case. There was no significant difference in median OS between enzalutamide and abiraterone. Enzalutamide was superior to abiraterone for PFS, PSA response and time to treatment discontinuation. The indirect comparison was limited by a lack of transparency in the numbers of studies initially selected and excluded, and in differences in the baseline characteristics of the two studies.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis comparing enzalutamide to abiraterone plus prednisolone for the treatment of mCRPC in adult men with mCRPC whose disease has progressed on or after a docetaxel-based chemotherapy regimen. The comparator is appropriate given abiraterone is now the predominant treatment for these patients in Scotland. The economic model used had three health states consisting of stable disease (PFS), progressive disease and death, and included a probability of treatment-related AEs within the stable disease state and skeletal related events within the progressive disease state.

A 10-year time horizon was used in the base case analysis. The data for estimating the relative PFS and OS outcomes for enzalutamide and abiraterone came from an adjusted indirect comparison of the two pivotal randomised controlled trials for these drugs. Patient level data for the placebo arm of the enzalutamide study were used as the reference arm, and PFS and OS outcomes extrapolated by fitting a Weibull parametric function. PFS and OS for enzalutamide and abiraterone were estimated by applying the hazard ratios generated from the indirect comparison versus placebo and extrapolated using a proportional hazard functions, with the exception of the abiraterone OS extrapolation where a time dependent hazard function was used on the grounds that this provided a better visual fit and that using a constant HR for abiraterone could overestimate the survival benefits associated with this drug.

Treatment duration estimates were based on time to treatment discontinuation data from the clinical trial for each drug. Time to treatment discontinuation was also used as the measure of PFS in the base case. Costs associated with concomitant medication, patient monitoring, terminal care, AE and SRE management were included. Concomitant medication use for enzalutamide was derived from the AFFIRM trial and was assumed to be the same for abiraterone, with the exception of concomitant steroid use which was estimated to be 47% with enzalutamide, but 100% with abiraterone as it requires to be administered with prednisone or prednisolone. Patient monitoring involved outpatient visits and tests and was assumed to be the same for enzalutamide and abiraterone, based on the monitoring specified in abiraterone submission to NICE. However, abiraterone was assumed to require an outpatient visit every 4 weeks compared to every 6 weeks with enzalutamide because of the increased risk of hepatotoxicity and the need for regular monitoring of blood pressure with abiraterone which is not required with enzalutamide. Resource use estimates for the management of AEs were derived from previous National Institute for Health and Care Excellence (NICE) appraisals for mCRPC drugs, and SRE management resource use was based on a published study with updated unit costs applied. Terminal care costs were based on the abiraterone submission to NICE.

The baseline utility of the stable disease health state in the base case was derived from EQ-5D data collected within the AFFIRM trial. A mapping exercise was performed using the FACT-P and EQ-5D data in the trial which produced a similar utility estimate. However, to take account of the impact of enzalutamide on patient pain, an additional treatment specific utility gain for enzalutamide was estimated using the mapping function, and the same utility gain was assumed for abiraterone in the base case. A disutility of -0.085 was applied to the progressive disease state based on published EQ-5D values for patients with end-of-life prostate cancer. Disutilities for SRE's were based on the FACT-

P–EQ-5D mapping function applied to the AFFIRM clinical trial data and published estimates for grade 3 and 4 adverse events. Duration of AEs (1-2 weeks) and SREs (1 month) were from expert opinion or literature estimates.

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 NHS Scotland. Under the PAS, a confidential discount was offered on the list price of enzalutamide. The economic evaluation also took account of an estimate of the PAS that is in place for abiraterone in Scotland. With the enzalutamide PAS, the incremental cost-effectiveness ratio (ICER) estimated by the company was £15,696 per QALY gained, based on an incremental cost that is commercial in confidence. The driver of the incremental cost associated with enzalutamide was additional treatment costs associated with a longer time in PFS as measured by time to treatment discontinuation. The ICERs in the sub-group with one prior chemotherapy were similar to the whole patient population (£15,711 with PAS) as although the gain in time in stable disease and total life years were higher for enzalutamide versus abiraterone relative to the whole population analysis, incremental treatment costs also increased due to a longer time to treatment discontinuation for enzalutamide in the sub-group.

Sensitivity and scenario analysis using the company estimated PAS discount for abiraterone demonstrated that without PAS the lowest ICER estimated was £66k/QALY. The ICER was most sensitive to varying the time dependent HR for abiraterone with a range of £13,355 to £48,542 estimated with PAS. The ICER did not exceed £23k/QALY with PAS under all other scenarios tested, including varying the other HRs for PFS and OS and using an alternative extrapolation function for BSC. Using a definition of PFS including radiographic criteria rather than time to treatment discontinuation did not have a significant impact on the ICER. Variations around resource use, costs and utilities also had a low impact on the ICER.

The main issues with the economic analysis were as follows:

- The ICER was based on an estimate of superior survival outcomes for enzalutamide versus abiraterone although the hazard ratio for median OS from the indirect comparison was non-significant. The company presented a scenario in which no differences in survival and other outcomes were assumed. This therefore became a cost-minimisation analysis in which the same QALYs and drug costs were estimated but with lower costs for enzalutamide due to less monitoring and steroid requirements than for abiraterone. Additional sensitivity analysis was requested in which non-significant differences in outcomes between enzalutamide and abiraterone from the indirect comparison were excluded so that only the significant differences in PFS were retained. This had the impact of increasing the ICER to £55,394 per QALY gained with PAS.
- Sub-group analysis was not initially performed for patients treated with >1 prior chemotherapy. An appropriate comparator for this sub-group may include BSC. However, the company provided an additional analysis for this sub-group which produced estimated ICERs of £12,408 per QALY gained versus abiraterone, and £45,831 per QALY gained versus BSC. This analysis had some limitations in particular due to a relatively small proportion of patients receiving >1 prior chemotherapy in the studies but did provide an indicator of cost-effectiveness across different patient groups.
- There were some concerns with the robustness and transparency of the indirect comparison, and with the mixed use of proportional and time dependent hazards to estimate the survival outcomes of each drug.
- There were a number of other uncertainties including the choice of extrapolation methods, methods for estimating OS and PFS hazard ratios for the comparator, and the appropriate definition of PFS, but the sensitivity/scenario analyses performed demonstrated that varying the approaches used did not have a major impact on the ICERs generated. In addition, the

utility estimated for progressive disease may be too high. Additional sensitivity analysis was performed applying a 0.5 utility for progressive disease but this did not have a significant impact on the ICER.

Despite the concerns over the indirect comparison, the economic case for enzalutamide with PAS is considered to be demonstrated in patients with mCRPC.

It is SMC policy to include the incremental costs and the estimated QALY gain in the detailed advice document for all submissions. The PAS for enzalutamide includes a discount to the NHS that is commercial in confidence and the submitting company has advised that publication of the incremental costs and QALY gain, when considered with other cost-effectiveness data in the public domain, could reveal the level of discount. For this reason SMC is unable to publish the incremental costs and estimated QALY gain for enzalutamide in the treatment of adult men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel therapy.

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

A Patient Interest Group Submission was received from Prostate Cancer UK.

Additional information: guidelines and protocols

The European Association of Urology (EAU) Guidelines on Prostate Cancer^{6,7} were updated in March 2013 and discuss various chemotherapeutic options for patients with advanced, relapsing and castration-resistant prostate cancer. In patients who are candidates for chemotherapy, docetaxel 75mg/m² every three weeks is the first-choice cytotoxic regimen as it confers a significant survival benefit. Docetaxel or, mitoxantrone with prednisolone or hydrocortisone, are recommended for patients with symptomatic osseous metastases due to hormone-resistant prostate cancer. Docetaxel offers significant advantages in pain relief compared with mitoxantrone so is the preferred option. Patients who relapse following first-line docetaxel should be considered for cabazitaxel, abiraterone or enzalutamide as second-line treatment based on the results of prospective, randomised phase III studies. Docetaxel as a second-line option can be considered in patients who previously responded to docetaxel.

The European Society for Medical Oncology published “Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up” in 2013.⁸ In relation to castration-refractory metastatic disease, docetaxel given every three weeks is recommended for consideration for symptomatic patients. In patients progressing following docetaxel, treatment with abiraterone or enzalutamide should be considered. Cabazitaxel in combination with prednisone may also be considered in patients who progress on or after docetaxel and this has been shown to be more effective than mitoxantrone. In patients with painful bone metastases external beam radiotherapy, or radio-isotope therapy are recommended.

The National Institute for Health and Clinical Excellence (NICE) published clinical guideline 58, “Prostate cancer: diagnosis and treatment” in February 2008.⁹ The goals of treatment in hormone-refractory prostate cancer are to improve survival and quality of life and to control symptoms. Advice following a previous technology appraisal of docetaxel was adopted; that docetaxel is recommended as a treatment option in men with metastatic hormone-refractory prostate cancer if their Karnofsky performance status score $\geq 60\%$. The regimen was recommended up to 10 cycles, but should be

stopped on the advent of severe adverse events or disease progression. Repeat cycles of treatment with docetaxel are not recommended.

Additional information: comparators

Abiraterone, cabazitaxel (not recommended by SMC). Some current guidelines recommend repeated courses of docetaxel or mitoxantrone plus prednisolone (unlicensed).

Cost of relevant comparators

Drug		Dose Regimen	Cost per cycle	Cost per course*
Enzalutamide		160mg orally once daily	2,053	n/a
Abiraterone* prednisolone)	(plus	1g orally once daily Prednisolone 10mg orally daily	2,053	n/a
Cabazitaxel prednisolone)	(plus	25mg/m ² intravenously every 3 weeks Prednisolone 10mg orally daily	3,698	36,980
Docetaxel prednisolone)	(plus	75mg/m ² intravenously every 3 weeks Prednisolone 5mg orally daily	1,024	10,240
Mitoxantrone** prednisolone)	(plus	12mg/m ² intravenously every 3 weeks Prednisolone 10mg orally daily	154	1,539

Doses are for general comparison and do not imply therapeutic equivalence. Cost for enzalutamide from eVadis on 31/07/13; costs for other drugs from MIMS on-line accessed 05/08/13. Costs are based on an adult with a body surface area of 1.8m² rounded to the nearest vial size, given 10 cycles and does not include the cost of infusion fluids and pre-medication.

*Abiraterone and enzalutamide are given continuously but have been calculated as a 21-day cycle to allow comparison with other agents. Cost for 28 days is £2,735 and for 1 year is £35,551 for both drugs (excluding the cost of prednisolone).

**Mitoxantrone is not licensed for prostate cancer, and the dosage is based on a comparative study with cabazitaxel.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 273 in year 1 and 278 in year 5. Based on an estimated uptake of 10% in year 1 (27 patients) rising to 50% in year 5 (139 patients), the impact on the medicines budget was estimated at £668k in year 1 and £3.4m in year 5 without the PAS. The net medicines budget impact was estimated at £395k in year 1 and £2m in year 5 without the PAS.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Astellas Pharma Ltd, enzalutamide (Xtandi®) 40mg soft capsules, Summary of product characteristics, last updated 26/06/2013. <http://www.medicines.org.uk/emc/>
2. Rathkopf D, Scher HI. Androgen Receptor Antagonists in Castration-Resistant Prostate Cancer. *The Cancer Journal* 2013; 19 (No. 1): 43 -49
3. European Medicines Agency, CHMP assessment report EMA/CHMP/383457/2013, Xtandi, enzalutamide, 25 April 2013. www.ema.europa.eu [accessed 22/07/13]
4. Scher H I, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *New England Journal of Medicine* 2012;367:1187-97.
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6. Mottet N, Bellmunt J, Bolla M et al. EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and castration-Resistant Prostate Cancer. *European Urology* 2011; 59: 572-83.
7. Heidenreich A, Bastian PJ, Bellmunt J et al. Guidelines on prostate cancer. Update March 2013. European Association of Urology website Accessed 24/07/2013 [European Association of Urology \(EAU\) - Guidelines](http://www.european-urology.com/guidelines/)
8. Horwich A, Parker C, de Reijke T et al, Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology Advance Access* published June 27, 2013.
9. National Institute for Health and Clinical Excellence (NICE). Clinical guideline 58: Prostate cancer: diagnosis and treatment, February 2008.

This assessment is based on data submitted by the applicant company up to and including 10 September 2013.

**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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug 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 NHS Scotland 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 NHS Scotland 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.