Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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levonorgestrel 13.5mg intrauterine delivery system (Jaydess®)

SMC No. (1036/15)

Bayer

6 March 2015

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

levonorgestrel (Jaydess®) is accepted for use within NHS Scotland.

Indication under review: Contraception for up to 3 years.

A phase III, open-label, randomised study confirmed the contraceptive efficacy of levonorgestrel 13.5mg intrauterine delivery system according to the Pearl Index.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortiu

Indication

Contraception for up to 3 years.

Dosing Information

The levonorgestrel 13.5mg intrauterine delivery system (IUS) (Jaydess®) is to be inserted into the uterine cavity within seven days of the onset of menstruation to provide contraception for up to 3 years. Jaydess® can be replaced by a new system at any time in the cycle, and can also be inserted immediately after first trimester abortion. An average of 6 micrograms levonorgestrel per 24 hours is released over the 3 years.

The system should only be inserted by physicians or healthcare providers who are experienced in the placement of intrauterine delivery systems, and removal should occur by no later than the end of the third year. If a woman wishes to continue with treatment beyond 3 years, a new system can be inserted immediately following removal of the original system.

Product availability date

April 2014

Summary of evidence on comparative efficacy

The levonorgestrel 13.5mg IUS is a progestogen-only long-acting reversible contraceptive (LARC). The system exerts local progestogenic effects in the uterine cavity to prevent egg implantation within the endometrium, thicken the cervical mucus to prevent the passage of sperm, and prevent fertilisation by inhibiting sperm mobility and function within the uterus and fallopian tubes.[1]

The clinical evidence derives from a phase III, multicentre, open-label, randomised, parallel-group study to evaluate the safety and efficacy of two low-dose levonorgestrel intrauterine contraceptive delivery systems.[2,3] The study recruited nulliparous and parous women aged 18 to 35 years with regular 21 to 35 day menstrual cycles; women were randomised equally to treatment with levonorgestrel 13.5mg IUS (n=1,432) or levonorgestrel 19.5mg IUS (n=1,453) for a duration of three years. Analysis of efficacy and safety was conducted in the full analysis set for all randomised women in whom placement of an intrauterine system was attempted (1,432 women in the levonorgestrel 13.5mg group, of which 39% [n=556/1,432] were nulliparous, and 1,452 women in the levonorgestrel 19.5mg group, of which 40% [n=574/1,452] were nulliparous). Exposure time was calculated from time of placement until expulsion/removal of the intrauterine system, or until the end of the three-year study. The total number of months exposure excluded those during which women used concomitant contraception or sex steroid hormones. Any pregnancies occurring during these months were however included in the efficacy calculations. The efficacy analysis also included women with a failed placement attempt (as they were assumed to have had an exposure time of 1 day), and any pregnancies that occurred before detection of expulsion. Study completion with the levonorgestrel 13.5mg IUS was 57% (n=819/1,432), and with the 19.5mg IUS was 60% (n=870/1,452).

The primary outcome was the pregnancy rate, calculated as the Pearl Index (the number of pregnancies per 100 woman-years). A total of ten pregnancies occurred in the levonorgestrel 13.5mg IUS group over the 3-year study (Pearl Index of 0.33 pregnancies per 100-woman years; 95% confidence interval [CI]: 0.16 to 0.60), four of which were as a result of expulsion of the system. Ten pregnancies occurred in the 19.5mg IUS group (Pearl Index 0.31 per 100 woman-years; 95% CI: 0.15 to 0.57), one of which was as a result of expulsion of the system. The Kaplan-Meier method was used to calculate the 3-year cumulative failure rate as 0.9% for the 13.5mg levonorgestrel IUS and 1.0% for the 19.5mg IUS. For each individual year of the study, and for the cumulative three-year data, the Pearl Indices showed no major difference in pregnancy rates.[2,3]

Placement of the system was successful in 99.5% (n=2,871/2,884) of women overall, with 96% (n=2,770/2,884) having successful placement at the first attempt. In the combined 13.5mg and 19.5mg levonorgestrel IUS groups, investigators rated placement as 'easy' in 90% (n=2,585/2,884) of women. Pain on placement was rated by the study participants with 20% (n=563/2,884), 46% (n=1,312/2,884), 27% (n=790/2,884) and 8% (n=218/2,884) respectively rating pain as 'none', 'mild', 'moderate' or 'severe'. Use of cervical dilation was required in 6% of women (n=159/2,884). Prophylactic local anaesthesia was used in 9% (n=248/2,884) of women, and 32% (n=929/2,884) received prophylactic analgesia.[3]

At the end of the study (or final study visit for those who discontinued early), participants completed a user satisfaction questionnaire. Of those surveyed on the 13.5mg IUS (74%; n=1,053/1,432), 95% were "very satisfied" or "somewhat satisfied" with treatment, and 77% indicated they would have continued with treatment after the study. Similarly, of those surveyed on the 19.5mg IUS (73%; n=1,063/1,452), 96% of women in the 19.5mg treatment group were "very satisfied" or "somewhat satisfied" with treatment and 82% indicated they would have continued with treatment after the study.[3]

Prior to the phase III study, a randomised, open-label, phase II study was conducted to establish a suitable dose for the levonorgestrel low-dose IUS.[4,5] Parous and nulliparous women aged 21 to 40 years were randomised equally to three years treatment with a levonorgestrel IUS with an initial release rate of 12 micrograms/day (LNG-IUS12), 16 micrograms/day (LNG-IUS16), or to the 52mg total dose IUS (Mirena®) releasing approximately 20 micrograms per day. All women who were randomised and received successful placement of a system were included in efficacy and safety analyses (n=738/742). Outcome measures included contraceptive efficacy (assessed by the unadjusted Pearl Index), bleeding patterns, ease/pain of placement, and adverse events. In the LNG-IUS12, LNG-IUS16, and Mirena® treatment groups, the respective number of pregnancies (Pearl Index) over the 3-year study were one (0.17 pregnancies per 100 woman-years; 95% CI: 0.00 to 0.93), five (0.82 per 100 woman-years; 95% CI: 0.27 to 1.92), and zero (0 pregnancies per 100 woman-years; 95% CI: 0.00 to 0.59).The study was not sufficiently powered to detect a statistically significant difference between the treatment groups. LNG-IUS12 and LNG-IUS16 were subsequently taken forward to the phase III safety and efficacy study.

Summary of evidence on comparative safety

In the phase III study, adverse events were reported in the levonorgestrel 13.5mg and 19.5mg treatment groups, respectively, by 84% (n=1,194/1,432) and 86% (n=1,246/1,452) of women, with 0.6% (n=8/1,432) and 1.0% (n=15/1,452) reporting a treatment-related serious adverse event. The most common adverse events considered to be possibly treatment-related were, for the 13.5mg and 19.5mg treatment groups respectively, acne (10% versus 9.9%), ovarian cysts (7.7% versus 14%), dysmenorrhoea (6.8% versus 5.2%), pelvic pain (4.7% versus 6.0%), and vaginal haemorrhage (4.5% versus 4.8%). Discontinuation of treatment due to any adverse event over the three years occurred in 22% (n=313/1,432) of women in the levonorgestrel 13.5mg group, and in 19% (n=278/1,452) of women in the 19.5mg group. The most common adverse events resulting in discontinuation were bleeding disturbances including amenorrhea (4.7% and 4.9% in the respective groups). Treatment was discontinued as a result of serious adverse events by 1.0% and 1.2% of women in the 13.5mg and 19.5mg groups, respectively.[2,3]

Uterine perforations, ectopic pregnancy and pelvic inflammatory disease were classed as serious adverse events. One partial perforation occurred with the levonorgestrel 19.5mg IUS; no complete perforations were reported in the study. Three ectopic pregnancies were reported with levonorgestrel 13.5mg IUS versus seven in the 19.5mg IUS group. Pelvic inflammatory disease was reported in two and four women in the respective groups.[2,3]

The adverse event profile of the levonorgestrel 13.5mg IUS is described in the summary of product characteristics. With continued use of the device, there is generally an increased frequency of amenorrhoea and infrequent bleeding, and a reduction in the occurrence of prolonged bleeding.[1]

Summary of clinical effectiveness issues

A number of factors influence the choice of method of contraception, with continued and effective contraceptive use being directly related to user-acceptability.[6] Available contraceptive methods include the combined hormonal contraceptives (oral, transdermal and vaginal preparations), the progestogen-only contraceptives (oral, injection, implant and intrauterine system preparations), and other intrauterine devices (e.g. copper devices).[7] The only alternative levonorgestrel-releasing IUS currently licensed in the UK is Mirena®, containing levonorgestrel 52mg. The levonorgestrel 13.5mg IUS would offer women an alternative choice of LARC to those methods already available. Healthcare professionals experienced in the insertion of other intrauterine systems can fit the levonorgestrel 13.5mg IUS and do not necessarily require further training.[1]

The Pearl Index (number of pregnancies per 100 woman-years), is used as a measure of hormonal contraceptive efficacy in line with guidance issued by the European Medicines Agency.[8] In the phase III randomised study, the Pearl Index for the levonorgestrel 13.5mg IUS was 0.33 pregnancies per 100-woman years (95% CI: 0.16 to 0.60), with a three-year cumulative failure rate of 0.9%.[2,3] Approximately half of all pregnancies that occur during use of the levonorgestrel 13.5mg IUS are likely to be ectopic, with an overall incidence of ectopic pregnancy of approximately 0.11 per 100 woman-years.[1]

There was a high drop-out rate from the study overall and drop-out rates were similar in both treatment groups. Study completion was 57% (n=819/1432) in the levonorgestrel 13.5mg group and 60% (n=870/1452) in the 19.5mg group. As a result of the visible differences in length of the hormone reservoirs in the intrauterine systems, investigators were not blind to the treatment allocations. Ease of placement was a subjective assessment rated by the investigators, who could also permit use of a local anaesthetic, oral analgesics, or cervical dilation as deemed necessary; pain on insertion was similarly a subjective assessment, rated by the study participants. The user satisfaction questionnaire was not completed by 27% of women, and those who discontinued the study prior to the introduction of the survey were not captured in the results, therefore limiting how the results can be generalised.

Despite the smaller IUS T-frame and drug reservoir, and the narrower insertion tube (compared to Mirena®), it is unclear if the levonorgestrel 13.5mg IUS would be more suitable in women with a narrower cervical canal and/or a smaller uterine cavity. The levonorgestrel 13.5mg IUS is not recommended as a first-line contraceptive in nulliparous women due to a lack of clinical experience in this patient group.[1] In the phase II study, the Mirena® IUS had an insertion tube of greater diameter than the tube currently used in practice which may limit the generalisability of the results.[4,9]

There are limited comparative data of the levonorgestrel 13.5mg IUS with other licensed contraceptives. The phase III study compared the levonorgestrel 13.5mg IUS with an alternative strength levonorgestrel IUS (19.5mg) that is not available in the UK. The phase II, open-label, dose-finding study included Mirena® as a comparator but it was not sufficiently powered to establish if the levonorgestrel low-dose systems were non-inferior to Mirena®. As there was no relevant active comparator group in the study, the failure rate can only be compared naively to the failure rates reported in other studies or in clinical practice.

Summary of comparative health economic evidence

The submitting company presented a cost-effectiveness analysis comparing levonorgestrel 13.5mg IUS to a 'mixed market' comparator comprising all possible reversible contraceptive options (and including 'no contraception' in 8.5% of women). A Markov model with a one year cycle length was used in which women started on their initial contraception and then could either discontinue or experience contraceptive failure (unintended pregnancy). Women would then move into the unintended pregnancy state or move on to a subsequent contraceptive method. For women in both arms of the model, the subsequent contraceptive method was the mixed market comparator i.e. for women who started on the mixed market comparator, their second contraceptive method would be the same mixed market option. A three year time horizon was used in the base case. The submitting company also presented the results in terms of Net Monetary Benefit (NMB) based on an estimate of the willingness to pay to avoid an unintended pregnancy (assumed to be equivalent to the NHS cost of a termination).

Clinical data on the effectiveness of treatments were taken from the 3 year Pearl Index (PI) from the phase III study for levonorgestrel 13.5mg IUS and for the weighted average comparators, taken from a published paper which reported 'typical use' year 1 failure rates from women in the USA. As such, the comparative data driving the model were essentially taken from a naive indirect comparison. Discontinuation rates were taken from the same sources. Where unintended pregnancies occurred, the outcomes of those pregnancies (full term birth, terminations, miscarriage, ectopic pregnancy) were estimated from NHS Scotland statistics.

Costs in the model related to the cost of the contraception method, any associated costs of insertion/ removal, annual follow up costs and the costs associated with unintended pregnancy (based on a weighted average of the pregnancy outcomes as noted above).

The results showed that in the base case, levonorgestrel 13.5mg IUS was dominant i.e. more effective at avoiding unintended pregnancies and less expensive. The company estimated that for a population of 1000 women, levonorgestrel 13.5mg IUS would result in £1,050,789 in savings and result in 276 fewer unintended pregnancies from the initial contraception method. In terms of the NMB results, this was reported as £1,469; a positive NMB is an indicator of a cost-effective treatment, as the monetary value of the incremental effectiveness (in terms of pregnancies averted) exceeds the incremental cost of achieving the outcome.

One-way, scenario and probabilistic sensitivity analysis were provided and all showed that levonorgestrel 13.5mg IUS remained a cost-effective treatment option (dominant, or positive NMB). The results were most sensitive to the failure rate assumed for oral contraceptives and barrier methods (the 2 predominant options in the mixed market comparator), the weighted average cost of a birth and the uptake rate of 'no method' within the mixed market comparator.

There were a number of weaknesses with the analysis:

- The weighted average comparator includes 'no contraception.' This may not be appropriate and will have biased the base case results. Additionally, the use of a weighted average is likely to mask widely differing cost effectiveness ratios if levonorgestrel 13.5mg IUS was compared to individual methods e.g. other LARCs like IUS, IUD and implants. The submitting company provided additional analysis that removed 'no contraception' from the weighted average; this resulted in the treatment remaining dominant (savings reduced to £737,936 per 1000 women and 193 fewer pregnancies) and the NMB reduced to £1,041. This may represent a more appropriate base case weighted average result. The company also provided analysis against a weighted average of only long acting methods. This resulted in reduced savings of £282,090 and 38 fewer pregnancies and a reduced NMB of £354. Further supplementary analysis comparing only to the alternative IUS (Mirena®) resulted in a saving of only £2,725 per 1000 women and one fewer unintended pregnancy and a NMB of £3. The company argued that comparing only to an alternative IUS is too restrictive given the possible advantages of levonorgestrel 13.5mg IUS, but it is helpful to see the analysis against different comparator options.
- The method used to estimate the overall cost of an unintended pregnancy may over-represent the costs (and thus bias in favour of levonorgestrel 13.5mg IUS) given that the rate of induced abortion may be higher than the rate reflected in the general population birth statistics. The submitting company provided additional analysis using a cost of unintended pregnancies based on a NICE clinical guideline and, while the results remained dominant, this reduced the cost savings to £736,585.
- Combining the two sets of sensitivity analyses above, the company was asked to provide analysis using the adjusted cost of unintended pregnancies and removing 'no method' from the comparator. This resulted in dominance being maintained but the cost savings fell to £510, 206 for 193 fewer pregnancies (NMB fell to £813) when 'no method' was excluded or savings of £228,331, 38 fewer events and an NMB of £300 if the comparison was only against other LARCs.
- As there is a lack of direct data against the range of other contraception products, the analysis is based on a naive indirect comparison using 'imperfect use' data from a review paper presenting USA data from 1995 to 2002. As such, there are uncertainties associated

with the estimates of incremental effectiveness for levonorgestrel 13.5mg IUS.

- There is a limitation in terms of the time horizon. A 3 year time horizon will have truncated some of the contraceptive benefits associated with some of the LARCs which are effective for up to 5 years, compared to the 3 years for the levonorgestrel 13.5mg IUS. The company was asked to provide an analysis that would give a common time horizon based on effectiveness duration, but was not able to do so. As such, the base case analysis contains a limitation in that it will reflect the full cost of some alternative LARCs but will not have captured the all benefits of these treatments, meaning that the analysis is biased in favour of the levonorgestrel 13.5mg IUS.
- The model assumes that women who experience failure on, or discontinue, the mixed market comparator will move to the 'subsequent contraception' state and that this will be the 'mixed market' comparator. This will mean that the women in this arm of the model will continue for the duration of the model to be subject to the comparatively higher risks of failure/ discontinuation and this may bias the results in favour of levonorgestrel 13.5mg IUS by keeping women on less effective methods of contraception given the averaging of the mixed market comparator. While more complex, a model which compared against different individual therapies rather than a weighted average may have been an advantage in being able vary the effectiveness of subsequent contraceptive choices
- The company has used the 3 year PI figure for levonorgestrel 13.5mg IUS but, for the comparators, the one year PI figure has been used. PI figures for each year for levonorgestrel 13.5mg IUS are available and as the 3 year figure is lower than the year 1 figure there may be bias from using the 3 year figure for their product but the year 1 figure for the comparators. The company provided some additional analysis using the year 1 figures for both arms of the model where dominance maintained, but with lower savings of £1,043,876 and 274 fewer events compared to the original base case result.
- The 3 year analysis does not include the cost of removal of levonorgestrel 13.5mg IUS at the end of the 3 year period. Combining the impact of removing 'no method' and revising the cost of an unintended pregnancy as above, and including the cost of removal of levonorgestrel 13.5mg IUS changed the results to a saving of £451,468, 193 avoided pregnancies and a NMB of £754.
- In terms of the NMB approach used, the cost of an induced abortion has been used as a proxy for the willingness to pay to avoid an unintended pregnancy. There is limited information to support this financial cost being an appropriate measure for WTP among women.

While there remains uncertainty associated with the comparative effectiveness data, given the additional analyses provided by the company to address some of the weaknesses, the economic case has been demonstrated.

Summary of patient and public involvement

A patient group submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) Clinical Guideline on long-acting reversible contraception (September 2014 update) advises that women who require contraception should be provided with information about, and offered a choice of, all available methods including long-acting reversible contraception (LARC). Women should receive the method of contraception that is most suitable for them, ensuring there are no contraindications. Women considering a LARC should receive detailed verbal and written information to enable them to select a method and use it effectively. This information should take into consideration their individual needs and should include: contraceptive efficacy, duration of use, risks and possible side-effects, non-contraceptive benefits, the procedure for initiation and removal/discontinuation and when to seek help when using the method. [10]

UK Medical Eligibility Criteria for Contraceptive Use (2009), published by the Faculty of Sexual and Reproductive Healthcare (FSRH), notes that the method of contraception selected for use is dependent on a number of factors, and that a person should be free to select the most acceptable method available to them, so long as they are medically eligible. Contraception must be used correctly and consistently in order to be effective, and continuation rates must be high for the long-acting contraceptives (e.g. intrauterine devices) to be cost-effective. Continued and effective use of a particular contraceptive method is directly related to its user-acceptability.[8]

FSRH guidance on intrauterine contraception (2007)[11] is in the process of being updated. This provides evidence-based recommendations on the use of intrauterine methods, including copper-bearing intrauterine devices and the levonorgestrel-releasing intrauterine system. Recommendations from the NICE clinical guideline on LARC (2005) are included; these have now been updated (see above).

Additional information: comparators

Progestogen-only LARCS: levonorgestrel 52mg IUS (Mirena®), medroxyprogesterone acetate contraceptive injection (Depo-Provera® and Sayana Press®), etonogestrel contraceptive implant (Nexplanon®).[7]

Other contraceptives: combined hormonal contraceptives, progestogen-only contraceptives, intrauterine devices (e.g. copper devices).

Cost of relevant comparators

Drug	Dose Regimen	Cost per unit (£)
Levonorgestrel 13.5mg IUS (Jaydess®)	**Inserted into the uterine cavity within seven days of the onset of menstruation to provide contraception for up to 3 years.**	**69**
Levonorgestrel 52mg IUS (Mirena®)	Inserted into the uterine cavity within seven days of onset of menstruation. Effective for 5 years.	88
Etonogestrel implant* (Nexplanon®)	By subdermal implantation, 1 implant inserted during first 5 days of cycle; remove implant within 3 years of insertion	83
Medroxyprogesterone acetate 104mg injection (Sayana Press®)	By subcutaneous injection, 104mg within first 5 days of cycle, repeated every 13 weeks	28
Medroxyprogesterone acetate 150mg injection (Depo-Provera®)	By deep intramuscular injection, 150mg within first 5 days of cycle, repeated every 12 weeks	26
Copper intrauterine device¥	Insert the copper intrauterine device at any time in the menstrual cycle if it is reasonably certain that the woman is not pregnant	8 to 27

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 18/12/14 for all medicines except copper intrauterine device from eMIMS on 18/12/14. Excludes the cost of insertion/injection. *Cost for up to 3 years. ¥A range of devices are available for use for up to 5 or 10 years. This list is not exhaustive.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 597,815 patients and a treatment uptake rate of 0.3% in year 1 rising to 3.9% in year 5.

The impact on the medicines budget was estimated at £101k in year 1 and £354k in year 5. The net medicines budget impact was estimated at £75k and £169k in years 1 and 5 respectively. These figures were arrived at after making assumptions to capture the year 1 and 4 costs of Levonorgestrel 13.5mg across each year and assuming the displacement of a weighted average cost of other alternative contraceptives.

References

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

1. Bayer plc. Jaydess 13.5mg intrauterine delivery system. Summary of Product Characteristics. Last updated 3 April 2014.

2. NCT00528112. Levonorgestrel contraceptive intrauterine systems (LCS) pearl index study. www.clinicaltrials.gov, accessed 22/12/14.

3. Nelson A, Apter D, Hauck B, Schmelter T, Rybowski S, Rosen K, et al. Two low-dose levonorgestrel intrauterine contraceptive systems: a randomized controlled trial. Obstet Gynecol 2013;122(6):1205-14.

4. Gemzell-Danielsson K, Schellschmidt I, Apter D. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena. Fertil Steril 2012;97(3):616-22.

5. NCT00185380. Dose-finding study for the ultralow-dose levonorgestrel intrauterine contraceptive system (LCS). www.clinicaltrials.gov, accessed 23/12/14.

6. Faculty of Sexual and Reproductive Healthcare. UK medical eligibility criteria for contraceptive use. 2009. www.fsrh.org accessed 23/12/14

7. Joint Formulary Committee. British National Formulary (Online) London: BMJ Group and Pharmaceutical Press www.medicinescomplete.com, accessed 22/12/2014

8. European Medicines Agency. Guideline on clinical investigation of steroid contraceptives in women. January 2006. www.ema.europa.eu accessed 22/12/2014

9. Bayer plc. Mirena. Summary of Product Characteristics. Last updated 3rd June 2013

10. National Institute for Health and Care Excellence (NICE) Clinical guideline 30: Long-acting reversible contraception (update). September 2014. www.nice.org.uk accessed 23/12/14

11. Faculty of Sexual and Reproductive Healthcare. Clinical guidance on intrauterine contraception. 2007. www.fsrh.org accessed 23/12/14

This assessment is based on data submitted by the applicant company up to and including 12 February 2105.

**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.