Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2102

ertugliflozin 5mg, 15mg film-coated tablet (Steglatro®)

Merck Sharp & Dohme

7 December 2018

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 full submission

ertugliflozin (Steglatro®) is accepted for restricted use within NHSScotland.

Indication under review: in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- As monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
- In addition to other medicinal products for the treatment of diabetes.

SMC restriction: ertugliflozin is accepted for use as monotherapy and as add-on therapy. When used as monotherapy it is restricted to patients who would otherwise receive a dipeptidyl peptidase-4 inhibitor and in whom a sulphonylurea or pioglitazone is not appropriate.

Ertugliflozin was superior to placebo in lowering HbA1c in adults with type 2 diabetes mellitus in phase III studies in monotherapy, dual therapy and triple therapy settings.

Chairman
Scottish Medicines Consortium

Indication

In adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- As monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
- In addition to other medicinal products for the treatment of diabetes.[1]

Dosing Information

The recommended starting dose is 5mg orally once daily which can, if tolerated, be increased to 15mg once daily if additional glycaemic control is needed. When ertugliflozin is used in combination with insulin or an insulin secretagogue, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia. Ertugliflozin should be taken in the morning, with or without food. In case of swallowing difficulties, the tablet could be broken or crushed as it is an immediate-release dosage form.[1]

Product availability date

2 January 2019

Summary of evidence on comparative efficacy

Ertugliflozin is a potent, selective and reversible inhibitor of sodium glucose co-transporter 2 (SGLT-2) which is the principal transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. SGLT-2 inhibitors decrease the renal threshold for glucose and increase urinary glucose excretion.[1] Three SGLT-2 inhibitors, canagliflozin, dapagliflozin and empagliflozin are currently available in NHSScotland for the indication under review.

The evidence supporting the submission is from four phase III, randomised studies evaluating two doses of ertugliflozin, 5mg and 15mg. Three of the studies were similarly designed, placebo-controlled studies; VERTIS MONO (monotherapy); VERTIS MET (dual therapy, added to metformin) and VERTIS SITA2 (triple therapy, added to metformin plus sitagliptin). VERTIS FACTORIAL was of factorial design and compared the combination of ertugliflozin (both doses) plus sitagliptin with each of the individual medicines, in patients receiving background metformin. All studies had the same primary outcome; change from baseline in glycosylated haemoglobin (HbA1c) measured at week 26. All studies continued for a further 26 weeks (78 weeks for VERTIS MET) but only the initial phase of each study is discussed in this document. In three studies the primary outcome was analysed in the full analysis set which consisted of all randomised patients who received at least one dose of study medication and had at least one measurement of the primary outcome.[2-4] In VERTIS MET, the analysis set included all randomised patients who had received any study treatment.[5] The placebo-controlled studies had a two-week, single-blind placebo run-in during which patients had to achieve ≥80% adherence to study treatment in order to continue in the study. Data obtained after glycaemic rescue were censored to prevent confounding.[2-5]

In all four studies the key inclusion criteria were generally similar except for factors concerning line of treatment. The studies recruited patients ≥18 years with inadequately controlled type 2

diabetes mellitus, defined as HbA1c 7.0% to 10.5% (53 to 91mmol/mol) (≥7.5% to 11% [58 to 97mmol/mol] in VERTIS FACTORIAL) despite the following management plus diet and exercise for at least eight weeks prior to screening: VERTIS MONO, no treatment with an anti-hyperglycaemic agent; VERTIS MET and VERTIS FACTORIAL, metformin monotherapy ≥1500mg daily; VERTIS SITA2, metformin ≥1500mg daily plus sitagliptin 100mg daily. For VERTIS MET and VERTIS SITA2, body mass index had to be between 18 and 40kg/m^2.[2-5] In the placebo-controlled studies, following the run-in period, patients were randomised to receive once daily treatment with ertugliflozin 5mg, ertugliflozin 15mg or placebo.[2, 3, 5] See results in Tables 1 to 3 below.

Table 1: Monotherapy setting VERTIS MONO efficacy results at week 26 (excludes data post glycaemic rescue) [2, 6, 7]

Outcome	Ertugliflozin 5mg N=156	Ertugliflozin 15mg N=151	Placebo N=153
Primary outcome			
Change from baseline			
HbA1c, %	-0.79[A]	-0.96[A]	0.2
Secondary outcomes			
Change from baseline			
Body weight, kg	-3.18[A]	-3.58[A]	-1.42
SBP, mmHg	-5.5	-3.9	-2.2
Rate at 26 weeks			
HbA1c <7.0%, proportion of patients	28% [A]	36% [A]	13%
Glycaemic rescue, proportion of patients	2%	3%	26%

Data are given as least squares means for all outcomes except for proportions of participants with HbA1c <7.0% and glycaemic rescue. N=number of patients, HbA1c=glycosylated haemoglobin, FPG=fasting plasma glucose, SBP=systolic blood pressure, DBP=diastolic blood pressure.
p values versus placebo: [A] p<0.001

Table 2: Dual therapy setting VERTIS MET efficacy results at week 26[5] (excludes data post glycaemic rescue)

Outcome	Ertugliflozin 5mg N=207	Ertugliflozin 15mg N=205	Placebo N=209
Primary outcome			
Change from baseline			
HbA1c	-0.7[A]	-0.9[A]	0
Secondary outcomes			
Change from baseline			
Body weight, kg	-3.0[A]	-2.9[A]	-1.3
FPG, mmol/L	-1.5[A]	-2.2[A]	-0.1
SBP, mmHg	-4.4[B]	-5.2[A]	-0.7
DBP, mmHg	-1.6[C]	-2.2[D]	0.2

Rate at 26 weeks			
HbA1c <7.0%, proportion of patients	35%[A]	40%[A]	16%
Glycaemic rescue, proportion of patients[E]	<3%	<3%	18%

Data are given as least squares means for all endpoints except for proportions of participants with HbA1c <7.0% and glycaemic rescue. N=number of patients, HbA1c=glycosylated haemoglobin, FPG=fasting plasma glucose, SBP=systolic blood pressure, DBP=diastolic blood pressure. p values versus placebo: [A]p<0.001,[B]p=0.002, [C]p=0.013, [D]p=0.001, [E]no statistical test performed.

Table 3: Triple therapy setting VERTIS SITA2 efficacy results at 26 weeks (excludes data post glycaemic rescue)[3, 6]

Outcome	**Ertugliflozin 5mg N=156**	**Ertugliflozin 15mg N=153**	**Placebo N=153**
Change from baseline			
Primary outcome			
HbA1c %	-0.78[A]	-0.86[A]	-0.09
Secondary outcomes			
Body weight, kg	-3.4[A]	-3.0[A]	-1.3
FPG, mmol/L	-1.5[A]	-1.8[A]	-0.1
SBP, mmHg	-3.8[B]	-4.8[C]	-0.9
Rate at 26 weeks			
HbA1c <7.0% proportion of patients	32%[A]	40%[A]	17%
Glycaemic rescue, proportion of patients[D]	1.3%	2.0%	16%

Data are given as least squares means for all endpoints except for proportions of participants with HbA1c <7.0% and glycaemic rescue. N=number of patients, FPG=fasting plasma glucose, SBP=systolic blood pressure, HbA1c=glycosylated haemoglobin. p values versus placebo: [A] p<0.001, [B] p=0.019, [C] p=0.002, [D]no statistical test performed.

In VERTIS FACTORIAL, patients were randomised equally to receive one of five daily blinded treatments: ertugliflozin 5mg, ertugliflozin 15mg, sitagliptin 100mg, ertugliflozin 5mg plus sitagliptin 100mg or ertugliflozin 15mg plus sitagliptin 100mg.[4]

Table 4: Mixed dual, triple therapy setting VERTIS FACTORIAL efficacy results at week 26 (excludes data post glycaemic rescue)[4]

Outcome	Ertugliflozin 5mg N=250	Ertugliflozin 15mg N=248	Sitagliptin 100mg N=247	Ertugliflozin 5mg plus Sitagliptin 100mg N=243	Ertugliflozin 15mg plus Sitagliptin 100mg N=244
Change from baseline					
Primary outcome					
HbA1c %	-1.0	-1.1	-1.1	-1.5[A]	-1.5[A]
Secondary outcomes					
Body weight, kg	-2.7	-3.7	-0.7	-2.5[A]	-2.9[A]
FPG, mg/dL	-36	-37	-26	-44[A]	-49[A]
SBP, mmHg	-3.9	-3.7	-0.7	-3.4[B]	-3.7[C]
Rate at 26 weeks					
HbA1c <7.0% proportion of patients	26%	32%	33%	52%[A]	49%[A]
Glycaemic rescue, proportion of patients[D]	6.4%	2.8%	6.5%	2.5%	0

Data are given as least squares means except for proportions of participants with HbA1c <7.0% and glycaemic rescue. N=number of patients, FPG=fasting plasma glucose, SBP=systolic blood pressure, HbA1c=glycosylated haemoglobin. p values versus sitagliptin: [A] p<0.001, [B] p=0.005, [C] p=0.002, [D] no statistical test performed.

Quality of life was assessed in VERTIS SITA2 using the EuroQol five dimensions three level tool (EQ-5D-3L) at baseline, week 26 and week 52. The mean change from baseline at these time points was reported to be negligible in all treatment groups.[3]

Maintenance of ertugliflozin efficacy was reported up to 52 weeks of treatment in VERTIS MONO, VERTIS SITA2 and VERTIS FACTORIAL.[2-4]

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

Summary of evidence on comparative safety

Pooled results from the primary safety assessment include the initial 26 week phases of the three placebo-controlled studies described above.[1] Similar proportions of patients in each treatment group reported adverse events (AE): 46% (236/519), 50% (257/510) and 51% (263/515) in the ertugliflozin 5mg, ertugliflozin 15mg and placebo groups respectively, and there were serious AE in 3.3%, 2.4% and 2.9% of patients.[6]

The most frequently reported AE with higher frequency for ertugliflozin than placebo were headache (3.2% versus 2.3%) and vulvovaginal mycotic infection (2.7% versus 0.6%), respectively.[6]

Treatment-related AE (TRAE) were reported in 14% (74/519), 15% (75/510) and 9.3% (48/515) of patients in the ertugliflozin 5mg, ertugliflozin 15mg and placebo groups. Only one event, in a patient receiving ertugliflozin 15mg, was considered to be a serious TRAE, however the patient continued study treatment.[6, 8] Study treatment was discontinued due to a TRAE in five patients receiving ertugliflozin 5mg, three patients receiving ertugliflozin 15mg and in five patients receiving placebo.[6]

The European Public Assessment Report noted that there is a higher incidence of renal and urinary AE and of reproductive system disorders for ertugliflozin than placebo.[6] In August 2018 the U.S. Food and Drug Administration issued a warning that cases of a rare but serious infection, necrotising fasciitis of the perineum (Fournier's gangrene) have been reported with SGLT-2 inhibitors.[9] Rare cases of diabetic ketoacidosis (SGLT-2 inhibitor class effect) have been reported.[1] An increased frequency of lower limb amputations has been seen in studies of canagliflozin and the European Medicines Agency (EMA) recommended that the summary of product characteristics (SPC) for each licensed SGLT-2 inhibitor should include information on this risk.[1, 10]

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

Summary of clinical effectiveness issues

The mode of action of SGLT-2 inhibitors is independent of insulin and pancreatic β-cell function. As plasma glucose levels decrease, the rate of urinary glucose excretion also decreases, therefore hypoglycaemia is unlikely.[6] Efficacy is dependent on renal function, and is reduced in patients with moderate renal impairment and likely to be absent in severe renal impairment. Ertugliflozin is formulated as an immediate-release tablet that is taken once daily.[1] Current UK guidance recommends that SGLT-2 inhibitors used as monotherapy be considered as options for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulphonylurea or pioglitazone is not appropriate. The guidance also advises that SGLT-2 inhibitors be considered as add-on therapy to metformin.[10]

In phase III studies ertugliflozin 5mg and 15mg daily doses demonstrated superiority to placebo in lowering HbA1c, increasing the proportion of patients with HbA1c <7.0%, reducing body weight and reducing fasting plasma glucose in monotherapy, dual therapy and triple therapy settings.[2, 3, 5] The VERTIS FACTORIAL study showed that the combination of ertugliflozin plus sitagliptin was superior to the individual medicines in reducing HbA1c.[4]

A limitation of the monotherapy study (VERTIS MONO) is that patients were not required to have intolerance or contraindications to metformin, which differs from the licensed indication for ertugliflozin monotherapy. The placebo-controlled studies included only patients who were at least 80% compliant with medication during the placebo run-in.[2, 3, 5] In Scottish clinical practice, there may be a lower level of compliance. Some study patients would only have received 8 weeks of treatment with metformin or background antihyperglycaemic agent prior to commencing study medication. This may not have been sufficiently long to fully reflect the benefit of their pre-study

treatment. There is no robust evidence of benefit with ertugliflozin in patients receiving insulin or a sulphonylurea as background therapy, but the EMA considered that there were sufficient data to support this use from a study, P001/1016, that included patients with renal impairment who were receiving stable antihyperglycaemic treatment of any type except metformin, rosiglitazone and other SGLT2-inhibitors.[6] There is no reported evidence of benefit on long term diabetes related complications, including cardiovascular outcomes, or on patient reported outcomes.

There is no direct evidence comparing ertugliflozin with other SGLT-2 inhibitors: dapagliflozin, empagliflozin, canagliflozin.

To support a cost minimisation analysis, the submitting company presented three Bayesian network meta-analyses (NMA) that compared ertugliflozin (5mg and 15mg) with canagliflozin (100mg and 300mg), dapagliflozin (5mg and 10mg) and empagliflozin (10mg and 25mg) in mono-, dual and triple therapy settings, using placebo as the common comparator. Dapagliflozin 5mg is not used in Scottish practice and is not considered a relevant comparator.
The target populations were:
Adult patients with uncontrolled type 2 diabetes mellitus having previously received one of the following interventions:

- population 1 (monotherapy): diet and exercise, no background pharmacological therapy (eleven studies, including VERTIS MONO)
- population 2 (dual therapy): metformin alone (eight studies, including VERTIS MET and VERTIS FACTORIAL)
- population 3 (triple therapy): metformin plus a DPP-4 inhibitor (five studies, including VERTIS SITA2)

The outcomes evaluated were change from baseline in HbA1c, body weight, systolic blood pressure, proportion of patients with HbA1c at target (<7.0%), AEs and urinary tract infections.

Limitations of the NMAs included the small number of studies within networks, potential heterogeneity between studies which was not adequately assessed, the use of a fixed effects model over a random effects model, and a lack of sensitivity analysis. However despite these limitations, the NMAs appear to indicate that ertugliflozin has similar efficacy, in terms of reducing HbA1C, body weight and systolic blood pressure, and safety to other SGLT-2 inhibitors.

Clinical experts consulted by SMC considered that the place in therapy of ertugliflozin is as an alternative option to the three currently available SGLT-2 inhibitors. They noted that there is evidence of benefit in cardiovascular outcomes with other SGLT-2 inhibitors.[11, 14, 15]

The SPC includes advice on the use of ertugliflozin in renal impairment.[1] Similar advice exists for the other SGLT-2 inhibitors.[11-13]

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

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis (CMA) comparing ertugliflozin to other licensed SGLT-2 inhibitors - canagliflozin, dapagliflozin and empagliflozin in adults aged 18 years and older with type 2 diabetes mellitus.

The analysis covers the use of ertugliflozin prescribed either: as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications; dual therapy for patients receiving metformin; triple therapy for patients receiving metformin with a DPP-4 inhibitor.

The company presented indirect evidence to support similarity of outcomes between treatments. The findings of the NMAs showed that ertuglifozin was similar in terms of efficacy and safety to all three of its comparators. Some differences in outcomes were observed in the fixed effects model of the NMA. However, the random effects model, which the SMC statistician considered to be more appropriate, did not show differences in any outcomes.

Medicine acquisition costs were the only costs included in the CMA as there was no additional resource use or administration costs associated with ertugliflozin. The cost of each individual SGLT-2 inhibitor was the same regardless of the dosage. The annual cost of treatment with ertugliflozin and each of the three comparators was calculated separately for monotherapy, dual therapy and triple therapy. The total treatment cost for dual therapy included the costs of SGLT-2 inhibitor plus metformin. The total treatment cost for triple therapy included the costs of SGLT-2 inhibitor plus metformin and sitagliptin. Ertugliflozin was found to be cost saving versus all comparators in mono, dual, and triple therapy. An annual saving of £94.97 per patient was estimated with the use of ertugliflozin. The results are presented in the table below:

Table 1: base case results

	Treatment	Annual cost		Incremental cost
		SGLT-2 inhibitors	Total *	
Monotherapy	Ertugliflozin (5mg + 15 mg)	£383.51	£383.51	-
	Canagliflozin (100mg + 300mg)	£478.48	£478.48	£94.97
	Dapagliflozin (5mg + 10mg)	£478.48	£478.48	£94.97
	Empagliflozin (10mg + 25mg)	£478.48	£478.48	£94.97
Dual therapy	Ertugliflozin (5mg + 15 mg)	£383.51	£427.34	-
	Canagliflozin (100mg + 300mg)	£478.48	£522.31	£94.97
	Dapagliflozin (5mg + 10mg)	£478.48	£522.31	£94.97
	Empagliflozin (10mg + 25mg)	£478.48	£522.31	£94.97

Triple therapy	Ertugliflozin (5mg + 15 mg)	£383.51	£861.99	-
	Canagliflozin (100mg + 300mg)	£478.48	£956.96	£94.97
	Dapagliflozin (5mg + 10mg)	£478.48	£956.96	£94.97
	Empagliflozin (10mg + 25mg)	£478.48	£956.96	£94.97

** Includes cost of metformin (£43.83) in dual therapy and cost of metformin and sitagliptin (£434.65) in triple therapy*

The key weakness with the analysis is the lack of direct clinical effectiveness or safety evidence between ertugliflozin and any of the comparator SGLT-2 inhibitors. Although the NMA found ertugliflozin to have similar effectiveness and safety versus comparators, the meta-analysis itself had some limitations. These include the small number of studies included within networks, potential heterogeneity between studies which was not adequately assessed, the use of a fixed effects model over a random effects model, and a lack of sensitivity analysis.

Despite the weaknesses outlined above, the economic case has been demonstrated. In line with current advice for other SGLT-2 inhibitors when used as monotherapy, use is restricted to patients who would otherwise receive a dipeptidyl peptidate-4 inhibitor and in whom a sulphonylurea or pioglitazone is not appropriate.

Summary of patient and carer involvement

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

- We received a patient group submission from Diabetes Scotland which is a Scottish Charitable Incorporated Organisation (SCIO).

- Diabetes Scotland has not received any funding from pharmaceutical companies in the past two years.

- Diabetes can affect every part of someone's life. It impacts on family life, mealtimes, work, exercise and social life. Living with diabetes is difficult, people face managing both the short and long term complications on a daily basis, which is frequently described as relentless, life limiting, stressful, unpredictable and exhausting. The emotional and mental health aspects of living with a long-term condition such as diabetes are not widely recognised, with many people experiencing depression, anxiety and stress because of the need to manage the condition.

- For some a single medication along with diet and physical activity appears to be sufficient to manage their condition. Others will require more complex regimens of anti-diabetic medications to achieve glycaemic control.

- Improved glycaemic control has a positive impact on physical and emotional wellbeing, and has the potential to improve patient quality of life. This may also have a positive impact on family members and carers.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published national guideline 154: Pharmacological management of glycaemic control in people with type 2 diabetes in November 2017.[10] It recommends that:

- Metformin should be considered as the first-line oral treatment option for people with type 2 diabetes.
- Sulphonylureas should be considered as first-line oral agents in people who are intolerant of, or have contraindications to metformin.
- Linagliptin, sitagliptin and vildagliptin are accepted for use as monotherapy by SMC. They should be considered for use in those for whom both metformin and sulphonylureas are inappropriate due to contraindications or intolerance.
- Pioglitazone is accepted for restricted use by SMC as monotherapy for individuals who have already experienced severe hypoglycaemia or in whom metformin and sulphonylureas are contraindicated or not tolerated. It is not accepted as monotherapy for any other group.
- Based on a NICE technology appraisal, canagliflozin, dapagliflozin and empagliflozin monotherapies are accepted as options for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:
    - a DPP-4 inhibitor would otherwise be prescribed, and
    - a sulphonylurea or pioglitazone is not appropriate.
- SGLT-2 inhibitors should be considered as an add-on therapy to metformin in people with type 2 diabetes.[10]

SIGN guideline 154 also includes a treatment algorithm which outlines the second, third, and fourth line treatment options for patients with type 2 diabetes. In addition to lifestyle interventions it is recommended that either a sulphonylurea, SGLT-2 inhibitor, DPP-4 inhibitor, or pioglitazone is added to first line treatment (usually metformin) if a patient has failed to reach their HbA1c target within three to six months. The algorithm recommends the addition of a further agent, from a different class, is added if after a further three to six months a patient receiving dual therapy has failed to achieve their glycaemic target. The guidance also recommends that the addition of an injectable agent, either a glucagon-like peptide-1 (GLP-1) agonist or basal insulin, be considered as a third line treatment option. If after receiving triple therapy for three to six months a patient has failed to meet their HbA1c target guided by the patient profile an additional third line agent can be added following specialist assessment.[10]

Additional information: comparators

Comparators are other SGLT-2 inhibitors: dapagliflozin, empagliflozin, canagliflozin.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Ertugliflozin	**5mg to 15mg orally once daily**	**382**
Canagliflozin	100mg to 300mg orally once daily	476
Dapagliflozin	10mg orally once daily	476
Empagliflozin	10mg to 25mg orally once daily	476

Doses are for general comparison and do not imply therapeutic equivalence. Cost of ertugliflozin from company submission and costs of other medicines from eVadis on 21 September 2018. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 15,524 patients eligible for treatment in year 1 rising to 16,639 patients in year 5. The estimated uptake rate was 2.8% in year 1 (367 patients), rising to 26% in year 5 (3,642 patients) with a 16.1% discontinuation rate applied.

The gross impact on the medicines budget was estimated to be £141K in year 1 rising to £1.4m in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be savings of £35K in year 1 rising to savings of £346K in year 5.

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This assessment is based on data submitted by the applicant company up to and including 12 November 2018.

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

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

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.