NICE National Institute for Health and Care Excellence

NICE guidance

Ertugliflozin as monotherapy or with metformin for treating type 2 diabetes

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Ertugliflozin as monotherapy is recommended as an option 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 sulfonylurea or pioglitazone is not appropriate.

1.2 Ertugliflozin in a dual-therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- a sulfonylurea is contraindicated or not tolerated or
- the person is at significant risk of hypoglycaemia or its consequences.

1.3 If patients and their clinicians consider ertugliflozin to be 1 of a range of suitable treatments including canagliflozin, dapagliflozin and empagliflozin, the least expensive should be chosen.

1.4 These recommendations are not intended to affect treatment with ertugliflozin that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Canagliflozin, dapagliflozin and empagliflozin are options for treating type 2 diabetes in adults. They are taken with metformin or on their own (that is, as monotherapy) if metformin is not appropriate. They are sodium-glucose cotransporter 2 (SGLT-2) inhibitors, as is ertugliflozin.

Indirect comparisons show that ertugliflozin has similar overall health benefits to canagliflozin, dapagliflozin and empagliflozin. The acquisition cost of ertugliflozin is lower

than the acquisition costs of these other drugs. Ertugliflozin is therefore recommended as an option for treating type 2 diabetes as monotherapy or with metformin in line with the previous recommendations for SGLT-2 inhibitors.

2 Information about ertugliflozin

Information about ertugliflozin

Marketing authorisation	Ertugliflozin (Steglatro, Merck Sharp & Dohme) is indicated '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'.
Dosage in the marketing authorisation	'The recommended starting dose of ertugliflozin is 5 mg once daily. In patients tolerating ertugliflozin 5 mg once daily, the dose can be increased to 15 mg once daily if additional glycaemic control is needed.'
Price	5 mg (28 tablets) or 15 mg (28 tablets): £29.40 per pack (excluding VAT; company submission). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Merck Sharp & Dohme and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Comparators

Canagliflozin, dapagliflozin or empagliflozin are appropriate comparators

3.1 Ertugliflozin is a sodium-glucose cotransporter 2 (SGLT-2) inhibitor. NICE has already produced technology appraisal guidance on 3 other SGLT-2 inhibitors for treating type 2 diabetes (canagliflozin, dapagliflozin and empagliflozin). These treatments are recommended:

- as monotherapy when metformin is contraindicated or not tolerated, diet and exercise alone do not provide adequate glycaemic control, a dipeptidyl peptidase 4 (DPP-4) inhibitor would otherwise be prescribed, and a sulfonylurea or pioglitazone is not appropriate
- with metformin (dual therapy) when a sulfonylurea is contraindicated or not tolerated, or the person is at significant risk of hypoglycaemia or its consequences.

The company presented a cost-comparison case in which it proposed that:

- the overall health benefits associated with ertugliflozin are similar to or greater than those associated with canagliflozin, dapagliflozin and empagliflozin for monotherapy and dual therapy

- the acquisition cost of ertugliflozin is similar to or lower than the costs associated with canagliflozin, dapagliflozin and empagliflozin.

  The committee understood that canagliflozin, dapagliflozin and empagliflozin are standard treatments for type 2 diabetes in the NHS. It concluded that canagliflozin, dapagliflozin and empagliflozin are appropriate comparators for this appraisal.

Clinical effectiveness

Ertugliflozin monotherapy is clinically effective compared with placebo

3.2 The company presented the results of the VERTIS-MONO trial. This compared ertugliflozin monotherapy at the licensed dosages (5 mg and 15 mg) against placebo in 461 people aged 18 years or older with inadequate glycaemic control (defined as HbA1c 7.0% to 10.5% [53 to 91 mmol/mol]) despite diet and exercise. The primary outcome was change in HbA1c (measured as change in least-squared means from baseline to week 26). Both doses of ertugliflozin showed a statistically significant improvement compared with placebo in the full analysis set, which included all randomised patients who took at least 1 dose of study medication and had at least 1 measurement of the outcome variable (at baseline or after baseline). The results for secondary outcomes (percentage of patients with HbA1c less than 7% [less than 53 mmol/mol] at week 26, and changes in body weight and systolic and diastolic blood pressure from baseline to week 26) were favourable for both doses, although not all findings were statistically significant. The committee concluded that ertugliflozin monotherapy is a clinically effective treatment compared with placebo.

Ertugliflozin in a dual-therapy regimen with metformin is clinically effective compared with placebo

3.3 The company presented the results of 2 clinical trials that provided evidence on the efficacy of ertugliflozin as dual therapy with metformin:

- VERTIS-MET, which compared ertugliflozin 5 mg and 15 mg with placebo in 621 people aged 18 years or older with inadequate glycaemic control (defined as HbA1c 7.0% to 10.5% [53 to 91 mmol/mol]) despite diet and exercise.
- VERTIS-FACTORIAL, which was a 5-arm study of 1,232 people aged 18 years or older with inadequate glycaemic control (defined as HbA1c 7.5% to 11.0% [58 to 97 mmol/mol]). The study had 2 arms with ertugliflozin in dual therapy, and 3 arms that looked at its use in combination with 2 other glucose-lowering medicinal products (triple therapy). Only the evidence from the dual-therapy arms was considered relevant by the company and presented in the submission.

  In both studies, the primary outcome was change in HbA1c (measured as change in least-squared means from baseline to week 26). Both doses of ertugliflozin showed a statistically significant improvement compared with placebo for all outcomes in VERTIS-MET. The results for VERTIS-FACTORIAL showed that patients having ertugliflozin had lower mean HbA1c, body weight and blood pressure at week 26 compared with baseline. The committee concluded that ertugliflozin with metformin is a clinically effective treatment compared with placebo.

Ertugliflozin has similar clinical effectiveness to canagliflozin, dapagliflozin and empagliflozin in both monotherapy and dual therapy

3.4 The company presented 2 network meta-analyses (NMAs) comparing the clinical effectiveness of ertugliflozin as monotherapy and dual therapy against canagliflozin, dapagliflozin and empagliflozin (all outcomes were assessed at 24 to 26 weeks). The NMAs included the pivotal trials for ertugliflozin (VERTIS-MONO, VERTIS-MET and VERTIS-FACTORIAL). The results showed that ertugliflozin, canagliflozin, dapagliflozin and empagliflozin had similar efficacy and safety. The trials included in the NMAs were generally the same as the trials that were assessed for the previous NICE technology appraisals of canagliflozin, dapagliflozin and empagliflozin. The ERG commented that differences between the studies included in the company's NMAs and the NMAs in the previous appraisals were either well-justified by the company or had little impact on the overall results of the analyses. However, the ERG also

took the view that it was unnecessary, under the fast track appraisal cost-comparison process, for the company to have conducted the NMAs at all because they only needed to show that ertugliflozin has similar health benefits compared with 1 previously recommended product. In its own analysis, the ERG compared the results from each of the placebo-controlled trials for ertugliflozin against the results of another well-matched study; VERTIS-MONO was compared with the CANTATA-M trial of canagliflozin by Stenlof et al. 2013 and VERTIS-MET was compared with a dapagliflozin trial by Bailey et al. 2010. The ERG did not do any statistical analysis but presented the results of the selected trials alongside the results of the VERTIS studies for the committee to compare visually. The ERG's interpretation of its additional analysis aligned with the company's conclusion that ertugliflozin and its comparators have similar efficacy and safety. The committee concluded that the clinical effectiveness of ertugliflozin, both as monotherapy and in dual therapy, is likely to be similar to that of the comparator treatments.

Adverse events with ertugliflozin are likely to be similar to those with canagliflozin, dapagliflozin and empagliflozin in monotherapy and dual therapy

3.5 The company's NMAs showed no statistically significant differences in adverse-event rates between ertugliflozin and its comparators (canagliflozin, dapagliflozin and empagliflozin). The committee noted that women taking ertugliflozin monotherapy (5 mg and 15 mg) in VERTIS-MONO had a statistically significantly higher rate of genital mycotic infections than women in the placebo group. Similarly, women taking the 15-mg dose in VERTIS-MET had a statistically significantly higher rate of genital mycotic infections than women in the placebo group. However, the committee noted the ERG's comment that the event rate observed in VERTIS-MONO seemed high compared with the rates observed in other ertugliflozin trials, and it considered this to be reassuring. The committee concluded that the adverse events associated with ertugliflozin are likely to be similar to those for canagliflozin, dapagliflozin or empagliflozin.

Resource use

It is appropriate to assume that all resource use and costs, other than drug acquisition costs, are identical for ertugliflozin and its comparators

3.6 The company assumed that, apart from direct drug acquisition costs, resource use and costs would be identical for ertugliflozin and its comparators. These costs included starting and administering treatment, treatment monitoring, managing adverse events and long-term disease management. The committee agreed with this assumption.

Cost-comparison results

Ertugliflozin meets the criteria for recommendation on the basis of similar health benefits and similar or lower cost

3.7 The company presented the results of a cost-comparison analysis for 1 year of treatment. It showed that, at list price, the acquisition cost of ertugliflozin is lower than that of canagliflozin, dapagliflozin and empagliflozin. The committee concluded that ertugliflozin, both as monotherapy and in dual therapy, meets the criteria for recommendation on the basis of a cost comparison, because:

- the overall health benefits are similar to those of its comparators
- the acquisition costs are similar to or lower than those of its comparators.

Ertugliflozin is therefore recommended as monotherapy or dual therapy with metformin, as an option for treating type 2 diabetes in adults.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. Because ertugliflozin has been recommended through the fast track appraisal process, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has type 2 diabetes and the doctor responsible for their care thinks that ertugliflozin is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Accreditation