

# Ertugliflozin with metformin and a dipeptidyl peptidase-4 inhibitor for treating type 2 diabetes

Technology appraisal guidance

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[www.nice.org.uk/guidance/ta583](https://www.nice.org.uk/guidance/ta583)

## 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.

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# 1 Recommendations

- 1.1 Ertugliflozin with metformin and a dipeptidyl peptidase-4 (DPP-4) inhibitor is recommended as an option for treating type 2 diabetes in adults when diet and exercise alone do not provide adequate glycaemic control, only if:
- the disease is uncontrolled with metformin and a DPP-4 inhibitor, and
  - a sulfonylurea or pioglitazone is not appropriate.
- 1.2 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.
- 1.3 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

Ertugliflozin is a sodium-glucose cotransporter 2 (SGLT-2) inhibitor. Other SGLT-2 inhibitors are already used with metformin and a DPP-4 inhibitor for treating type 2 diabetes. Ertugliflozin appears to have similar health benefits to other SGLT-2 inhibitors when taken with metformin and a DPP-4 inhibitor, and it has a lower acquisition cost. But it has only been compared with other SGLT-2 inhibitors, not with other third-line treatments for type 2 diabetes (sulfonylureas or pioglitazone). Ertugliflozin is therefore recommended as an option for treating type 2 diabetes that is uncontrolled with metformin and a DPP-4 inhibitor, only if a sulfonylurea or pioglitazone is not appropriate.

## 2 Information about ertugliflozin

### Marketing authorisation indication

- 2.1 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

- 2.2 The recommended dosage for monotherapy is 5 mg once daily, increasing to 15 mg once daily if additional glycaemic control is needed. In combination therapy, dosage should be individualised using the recommended daily dose of 5 mg or 15 mg.

### Price

- 2.3 The list price for 28 tablets of ertugliflozin 5 mg or 15 mg is £29.40 per pack (company submission). Costs may vary in different settings because of negotiated procurement discounts.

## 3 Committee discussion

The [appraisal committee](#) 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.

### Clinical need and current management

#### **Ertugliflozin would offer an additional option alongside other sodium-glucose cotransporter 2 inhibitors (SGLT-2 inhibitors) available in the NHS**

- 3.1 Ertugliflozin is a SGLT-2 inhibitor, a class of drugs that is already used in the NHS for treating type 2 diabetes. [NICE has produced technology appraisal guidance on canagliflozin, dapagliflozin and empagliflozin](#), 3 other SGLT-2 inhibitors in triple therapy regimens for treating type 2 diabetes. These treatments are recommended with metformin and a sulfonylurea (dapagliflozin), and with metformin and a thiazolidinedione (canagliflozin and empagliflozin). The clinical experts explained that, in addition to lowering haemoglobin A1c (HbA1c), which is a measure of blood glucose levels over the previous 2 to 3 months, SGLT-2 inhibitors help to reduce blood pressure and body weight. Weight loss is a particularly important outcome for people with type 2 diabetes because there is a strong association with excess body weight, and some treatments such as sulfonylureas, insulin and pioglitazone can result in weight gain. The clinical experts also explained that new evidence suggests that SGLT-2 inhibitors provide cardiovascular protection and, although there are no data on cardiovascular outcomes for ertugliflozin yet, this appears to be a class effect. The new data also suggest that SGLT-2 inhibitors have a protective effect on kidney function. The committee concluded that ertugliflozin offers similar benefits to the other SGLT-2 inhibitors.

## **SGLT-2 inhibitors are already used with metformin and a DPP-4 inhibitor for treating type 2 diabetes in the NHS**

- 3.2 The company compared ertugliflozin with metformin and DPP-4 inhibitor against other SGLT-2 inhibitors. The NICE scope specified other comparators (sulfonylureas, pioglitazone, glucagon-like peptide-1 [GLP-1] mimetics and insulin) that were not included in the company's submission. The company justified its approach on the basis that the combination of an SGLT-2 inhibitor with metformin and DPP-4 inhibitor is sufficiently used in clinical practice for it to be regarded as standard therapy, and therefore the main comparison is with other SGLT-2 inhibitors. It presented data from a panel of 150 general practices (800 GPs) in the UK, showing that 11.4% of people taking triple therapy in 2017 were on this combination. The data showed that SGLT-2 inhibitors are also used with metformin and a sulfonylurea (by 15% of people on triple therapy). However, the company and the clinical experts explained that taking an SGLT-2 inhibitor with a sulfonylurea may increase the risk of hypoglycaemia and lead to weight gain, because sulfonylureas have an opposite effect on weight to SGLT-2 inhibitors. The company supplied additional prescribing data showing that prescriptions for an SGLT-2 inhibitor with metformin and a DPP-4 inhibitor increased from less than 10% in January 2017 to almost 15% in December 2018. Data from the Clinical Practice Research Datalink showed a similar pattern of increased use. The committee noted that the combination is recommended in the [European Association for the Study of Diabetes and American Diabetes Association 2018 consensus guidelines](#) when there is a compelling need to minimise hypoglycaemic events, and it is recommended in some NHS local guidelines. The company presented extracts from clinical experts about the use of the combination in clinical practice. The committee heard that advantages include different and complementary modes of action, favourable effect on weight reduction, low risk of hypoglycaemia, reduced heart failure risk and positive effects on blood pressure and cardiovascular outcomes, and that it is particularly used in patients at risk of hypoglycaemia or weight gain. The committee noted that NICE has not previously appraised the combination of metformin, a DPP-4 inhibitor and a SGLT-2 inhibitor. However, it accepted that the combination is used in the NHS, particularly in patients at risk of hypoglycaemia or weight gain when sulfonylureas and pioglitazone would be considered less suitable.

## **Other SGLT-2 inhibitors are appropriate comparators for ertugliflozin, but sulfonylureas and pioglitazone may also be relevant**

- 3.3 The committee considered that the company's exclusion of some comparators in the NICE scope (GLP-1 mimetics and insulin) is appropriate because these are injectable agents usually used later in the course of diabetes. The committee noted the company's opinion that sulfonylureas are not relevant comparators. This is because it intends to position ertugliflozin for use when sulfonylureas are not appropriate because of the risk of hypoglycaemia and weight gain. The committee accepted that there is an increased risk of hypoglycaemia with sulfonylureas, and that ertugliflozin would be an alternative treatment when sulfonylureas are not appropriate. It also noted that the company excluded pioglitazone as a comparator because of clinical expert opinion expressed in previous NICE technology appraisal guidance for SGLT-2 inhibitors. This stated that the use of pioglitazone is decreasing annually and is low in triple-therapy combinations because of concerns about adverse effects (such as risk of heart failure, oedema and weight gain). The committee noted the ERG's opinion that pioglitazone is less costly than ertugliflozin, and that prescription data suggest it is still widely used in the NHS and is a valid comparator. However, it accepted that pioglitazone use is decreasing in triple therapy and that it is unsuitable for some patients because of adverse effects. The committee concluded that other SGLT-2 inhibitors are appropriate comparators for ertugliflozin (see [section 3.2](#)). However, it also concluded that sulfonylureas and pioglitazone are also relevant options for use in a triple therapy regimen with metformin and a DPP-4 inhibitors when they are not ruled out by concerns about their adverse effects.

## **Clinical evidence**

### **Ertugliflozin with metformin and a DPP-4 inhibitor is clinically effective compared with placebo**

- 3.4 The clinical evidence came from VERTIS-SITA 2, which was a double-blind randomised placebo-controlled trial. It assessed the clinical effectiveness of ertugliflozin at the licensed doses (5 mg and 15 mg) in 462 adults with type 2



diabetes who were also taking metformin and sitagliptin (a DPP-4 inhibitor) and had inadequate glycaemic control on the dual therapy. The ERG noted that although VERTIS-SITA 2 did not include any patients from the UK, it was generally well conducted and representative of patients with type 2 diabetes in the NHS. 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. There was also a statistically significant improvement with ertugliflozin in patients with an HbA1c less than 7% (less than 53 mmol/mol) at week 26, and for changes in body weight and systolic blood pressure from baseline to week 26. The committee concluded that ertugliflozin added to treatment with metformin and a DPP-4 inhibitor in people with inadequate glycaemic control on the dual therapy is clinically effective compared with placebo.

## **Ertugliflozin has similar clinical effectiveness to other SGLT-2 inhibitors when added to metformin and a DPP-4 inhibitor**

- 3.5 The company presented a network meta-analysis comparing the clinical effectiveness of ertugliflozin against canagliflozin, dapagliflozin and empagliflozin, all taken with metformin and a DPP-4 inhibitor. The network meta-analysis included data from VERTIS-SITA 2 and 4 other trials, and all outcomes were assessed at 24 to 26 weeks. The results showed that ertugliflozin, canagliflozin, dapagliflozin and empagliflozin have similar efficacy and safety. The ERG considered that the included trials are of good quality and broadly similar but noted that a simpler comparison of clinical effectiveness could have been carried out against 1 of the SGLT-2 inhibitors already recommended as an option by NICE. The ERG compared the data for ertugliflozin from VERTIS-SITA 2 against another well-matched study (a dapagliflozin trial by Mathieu et al. 2015). It concluded that this comparison provides reasonable evidence that ertugliflozin is at least as effective as dapagliflozin. The committee also acknowledged the clinical experts' opinions that the clinical effectiveness of ertugliflozin is likely to be similar to other SGLT-2 inhibitors. The committee concluded that ertugliflozin has similar clinical effectiveness to canagliflozin, dapagliflozin and empagliflozin when added to metformin and a DPP-4 inhibitor.

## **Ertugliflozin has an acceptable adverse-event profile that is likely to be similar to that of other SGLT-2 inhibitors**

- 3.6 The company's network meta-analysis showed no statistically significant differences in adverse-event rates between ertugliflozin and the other SGLT-2 inhibitors (canagliflozin, dapagliflozin and empagliflozin). The committee noted that ertugliflozin was well-tolerated in VERTIS-SITA 2. The overall frequency of adverse events, serious adverse events and treatment-related adverse events leading to stopping treatment were similar in the ertugliflozin and placebo arms of the trial. The clinical experts explained that the main adverse effects of treatment are genital mycotic infections, which are unpleasant but are usually easy to treat. They also explained that the adverse-effects profile of ertugliflozin is likely to be similar to that of other SGLT-2 inhibitors. The committee heard that diabetic ketoacidosis is an extremely rare adverse effect of SGLT-2 inhibitors but was not reported in VERTIS-SITA 2. It was also aware that a warning about Fournier's gangrene (an infection of the perineum and genital region) has been added to the product information for all SGLT-2 inhibitors, after post-marketing reports that this was possibly related to using SGLT-2 inhibitors. The committee noted that this is a potentially life-threatening but very rare condition. It concluded that ertugliflozin has an acceptable adverse-event profile that is likely to be similar to that of other SGLT-2 inhibitors recommended by NICE.

## **Company's economic analysis**

### **The company's cost-minimisation approach is appropriate for the population who cannot take pioglitazone and sulfonylureas**

- 3.7 The company considered cost minimisation to be the most appropriate form of economic evaluation because it believed that the relevant comparators were other SGLT-2 inhibitors with metformin and DPP-4 inhibitor (see [section 3.2](#) and [section 3.3](#)). It also considered that the results of the network meta-analysis suggested that ertugliflozin and other SGLT-2 inhibitors with metformin and a DPP-4 inhibitor all have similar health benefits (see [section 3.5](#)). The committee heard that differences in cost between the SGLT-2 inhibitors relate to drug acquisition costs only because there are no differences in testing, initiation,

administration or monitoring costs. The company therefore presented a cost-comparison analysis for 1 year of treatment comparing the drug acquisition costs of ertugliflozin against canagliflozin, dapagliflozin and empagliflozin, all with metformin and DPP-4 inhibitor. The committee concluded that the company's cost-minimisation approach is appropriate for comparing ertugliflozin with other SGLT-2 inhibitors. However, having concluded that sulfonylureas and pioglitazone are relevant comparators for ertugliflozin used with metformin and a DPP-4 inhibitor (see section 3.3), it could not conclude that ertugliflozin is cost effective relative to these comparators, which are relatively inexpensive, without having seen a full cost-effectiveness analysis. Therefore, the committee concluded that it could only make a recommendation for ertugliflozin, with metformin and DPP-4 inhibitor, for people in whom sulfonylureas and pioglitazone are not appropriate.

## **Ertugliflozin with metformin and a DPP-4 inhibitor is cost effective compared with other SGLT-2 inhibitors with metformin and a DPP-4 inhibitor**

- 3.8 The committee noted that the overall health benefits of ertugliflozin are similar to other SGLT-2 inhibitors recommended as an option by NICE and the acquisition costs are lower. It therefore agreed that ertugliflozin with metformin and a DPP-4 inhibitor is cost effective compared with other SGLT-2 inhibitors. However, the committee noted that the cost effectiveness of ertugliflozin had not been compared with sulfonylureas or pioglitazone (see [section 3.3](#) and [section 3.7](#)). Therefore, the committee concluded that ertugliflozin with metformin and a DPP-4 inhibitor could be recommended as an option for type 2 diabetes in adults when it is uncontrolled with metformin and a DPP-4 inhibitor, but only when sulfonylureas and pioglitazone are not appropriate.

## 4 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.

#### **Sana Khan**

Technical lead

#### **Zoe Charles**

Technical adviser

#### **Thomas Feist**

Project manager

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