NICE National Institute for Health and Care Excellence

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Ertugliflozin in triple therapy for treating type 2 diabetes

Chair's presentation

2nd appraisal committee meeting
Committee A
Lead team:Graham Ash and Olivia Wu
ERG: University of Warwick Medical School
NICE technical team: Sana Khan, Zoe Charles
Company: MSD
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Definition of terms

Sodium–glucose co-transporter 2 inhibitors (SGLT-2 inhibitors)	
Ertugliflozin (ERTU)	**Referred to collectively hereafter as ‘flozins’**
Canagliflozin (CANA)	
Dapagliflozin (DAPA)	
Empagliflozin (EMPA)	
Dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors)	
Such as sitagliptin, saxagliptin and linagliptin	**Referred to collectively hereafter as ‘gliptins’**

Key issues for consideration

- Should ERTU in triple therapy only be considered on a background of metformin and gliptin, in line with the clinical trial evidence?
- Is the committee convinced that the metformin + gliptin + flozin combination is sufficiently used in the NHS to be considered standard of care?
- The company has provided further evidence to exclude sulfonylureas and pioglitazone as relevant comparators. What is the committee's view on this?
- Does the committee accept that the only relevant comparators for ERTU on a background of metformin and gliptin are other flozins?
- Does the committee accept the company's cost-minimisation approach based on the assumption that flozins have similar efficacy and safety and only differ in terms of drug acquisition costs?
- Is the committee minded to accept the cost comparison approach if sulfonylureas and pioglitazone are not considered suitable for the patient?

The technology: ertugliflozin

Marketing authorisation	Indicated in adults aged 18 years and older with type 2 diabetes 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 This appraisal is only looking at ERTU in triple therapy
Mechanism of action	SGLT2 inhibitor: reduces conservation of glucose by kidneys, leading to loss of glucose in urine
Administration & dose	5 mg once daily for monotherapy, 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
Acquisition cost	Ertugliflozin (Steglatro®) 5 mg or 15 mg * 28 tablets: £29.40 per pack

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Summary of clinical effectiveness evidence

- The trial population for VERTIS SITA 2 included adults with type 2 diabetes who had inadequate glycaemic control on a dual therapy regimen of metformin and sitagliptin
- There was a statistically significant improvement for ERTU versus placebo in the primary outcome of change in HbA1c at week 26
- Statistically significant improvements versus placebo also seen for percentage of patients with HbA1c less than 7% and for changes in body weight and systolic blood pressure at week 26
- ERTU was well-tolerated and the overall frequency of adverse events (AEs), serious AEs and treatment related AEs leading to discontinuation did not differ significantly between ERTU and placebo arms
- Company's network meta-analysis comparing the clinical effectiveness of ERTU with CANA, DAPA and EMPA on a background of metformin and gliptin showed that ERTU has similar efficacy and safety to other flozins

[redacted]

Decision problem

	NICE scope	Company submission	Rationale if different from scope
Population	Adults with type 2 diabetes that is inadequately controlled on combination therapy with anti-diabetic agents	As per scope	
Intervention	ERTU in triple therapy	As per scope	
Comparator	• Sulfonylureas • DPP-4is • Pioglitazone • SGLT-2is • GLP-1 mimetics • Insulin	SGLT-2is (flozins)	Evidence base for ERTU in triple therapy is with metformin + a gliptin only. The company believes the only relevant comparators are other flozins used in a triple therapy regimen with the same background therapies
Outcomes	• Mortality • Complications of diabetes • HbA1c/glycaemic control • Changes in cardiovascular (CV) risk factors • Adverse events • Health-related quality of life	As per scope	
Economic analysis	Cost-utility analysis	Cost-minimisation analysis	An indirect comparison showed similar efficacy and safety of all flozins. Company considered cost-minimisation analysis the most appropriate form of economic evaluation

Company's proposed positioning of ERTU

- Proposed positioning in triple therapy is with metformin and a gliptin compared with other flozins with the same background therapy. Other comparators in scope were excluded
- Company presented 2017 IQVIA data from a panel of 150 UK general practices showing that 11.4% of people on triple therapy are on this combination
- Flozins are otherwise only used with metformin and a sulfonylurea (by 15% of people on triple therapy) but company warned that a flozin and sulfonylurea combination increases risk of hypoglycaemia and is cautioned in the flozin SPCs
- No other data/justification to support this positioning was provided

Triple therapy	Moving annual total 2017	
	patients	%
MET + SU + PIO	23,806	7.8
MET + SU + gliptin	138,287	45.1
MET + SU + GLP-1	21,172	6.9
MET + SU + flozin	45,792	15.0
MET + gliptin + PIO	10,059	3.3
MET + gliptin + GLP-1	1,724	0.5
MET + gliptin + flozin	34,775	11.4
Other	30,656	10.0
Total	306,271	100

REMINDER:

- ERTU is recommended in a dual therapy regimen with metformin as an option for treating type 2 diabetes. It is therefore possible to achieve the triple therapy combination of metformin + flozin + gliptin using different routes
- Uncertain what proportion of the 11.4% on MET + gliptin + flozin included the addition of a flozin to metformin and gliptin

Abbreviations:
SU: sulfonylurea, MET: metformin, PIO: thiazolidinedione, GLP-1: glucagon-like peptide-1 agonist, gliptin: DPP-4 inhibitor, flozin: SGLT-2 inhibitor

Company's economic analysis

- Company conducted a cost minimisation analysis as NMA showed that flozins have similar health benefits
- Only included drug acquisition costs as no differences in administration or monitoring costs between flozins

Therapy	Price per pack	Price per tablet	Dose per tablet	Daily dose	Annual cost
Background therapy					
Metformin	£0.90 per 28 pack	£0.03	500 mg	2000 mg	£43.83
Gliptin (sitagliptin)	£33.26 per 28 pack	£1.19	100 mg	100 mg	£434.65
Intervention					
ERTU	£29.40 per 28 pack	£1.05	5 mg or 15 mg	5 mg or 15 mg	£383.51
Comparators					
CANA	£39.20 per 30 pack	£1.31	100 mg or 300 mg	100 mg or 300 mg	£478.48
DAPA	£36.59 per 28 pack	£1.31	10 mg	10 mg	£478.48
EMPA	£36.59 per 28 pack	£1.31	10 mg or 25 mg	10 mg or 25 mg	£478.48
Combination					
Met + gliptin + ERTU		£2.27			£861.99
Met + gliptin + CANA		£2.53			£956.96
Met + gliptin + DAPA		£2.53			£956.96
Met + gliptin + EMPA		£2.53			£956.96

Company's base case results

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs vs. ERTU
Metformin + gliptin + ERTU 5 mg /15 mg	£861.99	-	-	
Metformin + gliptin + CANA100 mg /300 mg	£956.96	-	-	£94.97
Metformin + gliptin + DAPA 5 mg /10 mg	£956.96	-	-	£94.97
Metformin + gliptin + EMPA 10 mg /25 mg	£956.96	-	-	£94.97

- CANA, DAPA and EMPA all have an annual cost of £478.48 (£1.31 per day * 365.25 days)
- ERTU is cost saving to the NHS with an annual cost of £383.51 (£1.05 per day * 365.25 days), producing an annual saving per patient of £94.97, driven by the lower acquisition cost of ERTU

[redacted]

Committee's conclusions – ACM1

- ERTU in a triple therapy regimen with metformin and a gliptin is clinically effective and well tolerated compared with placebo
- ERTU has similar efficacy and safety to other flozins in triple therapy regimens with metformin and a gliptin (based on indirect comparison and clinical expert views)
- Lack of justification by the company for limiting the assessment of cost effectiveness to a simple cost comparison of ERTU (with metformin and a gliptin) versus other flozins with the same background therapies
- Therefore, committee unable to make a recommendation – no ACD issued, further information requested from company:
  - additional data to support the company's claim that the combination of a flozin, metformin and a gliptin is a standard triple therapy regimen in the NHS e.g. from sources such as the Clinical Practice Research Datalink (CPRD)
  - detailed explanation for the exclusion of each comparator in the scope and why a cost-utility analysis was not considered necessary
  - justification for not reporting some of the outcomes specified in the NICE scope such as mortality and complications of diabetes
  - preliminary cardiovascular outcomes data for ERTU if available

[redacted]

Additional information provided by company (1)

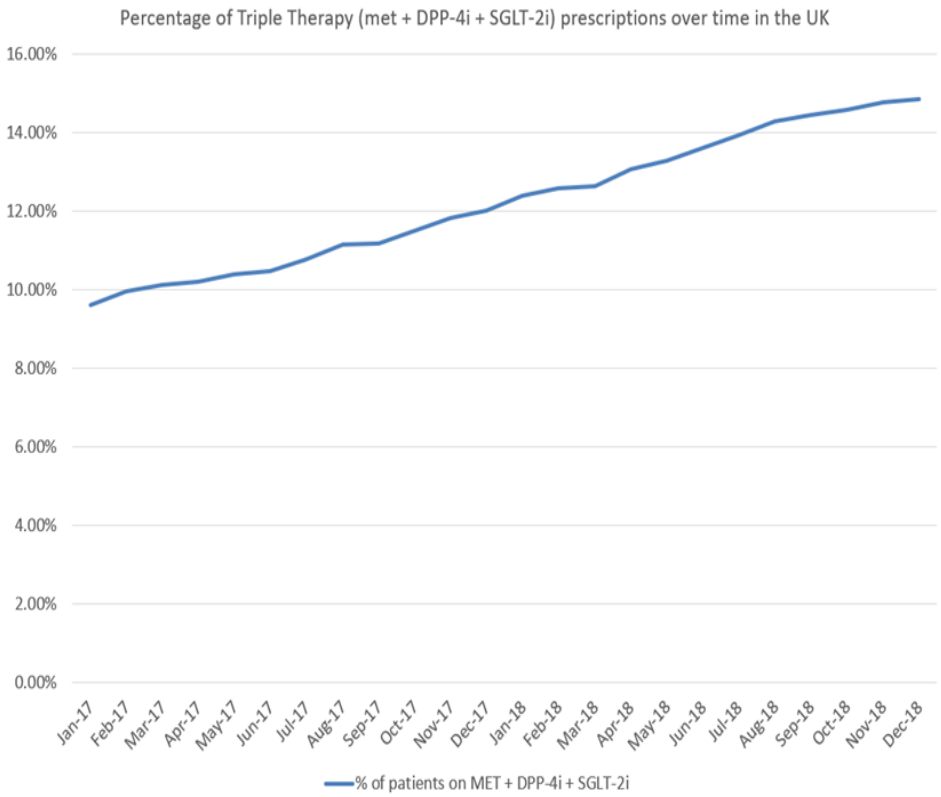
Supporting data that metformin + gliptin + flozin is an emerging standard of care

- European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) 2018 guidelines show that this combination is a recommended option when there is a compelling need to minimise hypoglycemic events
  - supports company's positioning of ERTU in treatment pathway when sulfonylureas are not appropriate
- Local trust guidelines in the NHS also recommend the use of this triple therapy combination
- Clinical expert views sought by the company on the proposed triple therapy regimen:
  - lower risk of weight gain and hypoglycaemic events with no need for self blood glucose monitoring
  - favourable cardiovascular benefit with proven cardiovascular safety data
  - different mechanism of actions of the triple therapy combination targets different glycaemic pathways
  - optimal combination for triple oral therapy for some people with type 2 diabetes. Combination is endorsed in recent EASD/ADA position statement when avoidance of hypoglycaemia or weight gain is a priority
- Additional moving annual total (MAT) data for the period January 2017 to December 2018 shows that prescriptions for the proposed triple regimen within clinical practice has increased from below 10% in January 2017 to almost 15% in Dec 201 (IQVIA database)
- Same pattern was seen in data from CPRD, showing an [redacted]

[redacted]

[redacted]

Comparison of IQVIA and CPRD prescription data



IQVIA MAT data from January 2017 up to December 2018

CPRD data on percentage of triple therapy prescriptions (Jan 2016 – June 2018)

[redacted]

Additional information provided by company (2)

Rationale for exclusion of comparators in NICE scope

Evidence base and inclusion criteria in VERTIS SITA 2

- People on background therapy of metformin and sitagliptin were included in the trial. Inclusion of triple therapy combinations with different background therapies would introduce heterogeneity as RCTs with different baseline therapies and populations would be included
- MSD is therefore seeking approval for ERTU in a triple therapy regimen only for patients uncontrolled on a dual therapy with metformin and a gliptin
- This is in line with the sequential treatment approach in NG28 whereby a gliptin can be added to first line metformin followed by a third agent such as a sulfonylurea or pioglitazone – would be unlikely for a clinician to replace the second agent (the gliptin) with pioglitazone and then add a third agent such as sulfonylurea to create a triple therapy

Decreasing use of pioglitazone/GLP-1s/insulin or use later in treatment pathway

- Committee conclusions for TA 418 and TA 288 for DAPA included clinical expert opinion that use of pioglitazone is decreasing annually and is low in triple therapy combinations due to concerns around adverse effects (risk of heart failure, oedema and weight gain)
- GLP-1s and insulin use is low as both treatments are injectable and therefore costly, and they are used towards the end of the treatment pathway

[redacted]

Additional information provided by company (3)

Comparison against sulfonylureas

- MSD is positioning the ERTU triple combination under review for use in patients for whom sulfonylureas are inappropriate due to the risk of adverse events
  - supported by committee's conclusions in previous appraisals that flozins are more likely to be used when sulfonylureas are not appropriate
  - therefore not appropriate to compare ERTU with sulfonylureas, as flozins do not replace sulfonylureas in the treatment pathway

[redacted]

Additional information provided by company (4)

Rationale for a cost-comparison approach rather than a cost-utility analysis

- Based on the info presented, the only relevant comparators are other flozins
- NMA shows that ERTU has similar efficacy and safety to other flozins and is cheaper
- Therefore, the most appropriate form of economic evaluation is a cost-comparison

Lack of data for outcomes such as mortality and diabetes complications

- Mortality and complications of diabetes outcomes (including CV, renal and eye) were not pre-specified in the clinical trial. Data was reported in company submission appendices

Cardiovascular outcomes data

- Company unable to share preliminary results for ERTU cardiovascular safety trial (VERTIS CV) as they are not available - primary completion date is September 2019
- Alternative analysis of CV events from 7 Phase 3 studies in nearly 5,000 subjects from the Broad Safety Pool shows that incidence was similar across groups (ERTU 5 mg: 4.2%; ERTU 15 mg: 2.8%; non-ERTU: 4.4%)
- Incidence of specific events in ERTU-treated subjects was low (≤0.5)
- 3 other flozin CV outcomes trials (EMPA-REG1, CANVAS2 and DECLARE3) with similar populations to VERTIS CV have produced positive CV outcome data. A positive CV class effect across flozins can therefore be expected

[redacted]

ERG critique of company additional information

- Exclusion of insulin and the GLP-1s is appropriate
- Exclusion of pioglitazone is not appropriate as:
  - prescription data suggests that it is widely used in the NHS
  - a systematic review by Liao et al 2017 states that " pioglitazone reduced major adverse cardiovascular events" and has been incorrectly quoted by company
    - Liao et al. however notes risks of weight, gain, oedema and heart failure (RR 1.32) with pioglitazone
  - reduction in pioglitazone prescribing over time probably due to the bladder cancer fear, now refuted. It remains a cheap and effective treatment for type 2 diabetes, alone or in combination
  - pioglitazone is associated with reduced risk of myocardial infarction and improved outcomes for non-alcoholic fatty liver disease (NAFLD) when attempts at weight loss are unsuccessful
- There is also an increased risk of fractures with pioglitazone, suggesting it should not be used in older people with osteoporosis
- Severe hypoglycemia is uncommon with the sulfonylureas, especially with gliclazide
- The rationale for a cost-comparison approach is appropriate for population who cannot take either pioglitazone or gliclazide
- Metformin+ gliptin+ flozin combination is much more expensive than other triple therapy combinations
  - ERG would prefer a series of cost-effectiveness analyses looking at triple therapy combinations

[redacted]

Comparators in previous appraisals of flozins in triple therapy

TA 418 (Dapa, Nov 2016), recommended with metformin and a sulfonylurea

- Company excluded pioglitazone (low use in triple therapy) and injectable treatments (used after oral treatments). Clinical experts agreed with these exclusions:
  - large number of prescriptions not representative of the number of people being newly prescribed pioglitazone which is falling year on year due to concerns about rosiglitazone and because pioglitazone is associated with increased risk of oedema and weight gain
  - patients almost always prefer a treatment that is associated with weight loss
- Committee accepted company's choice of comparators (glipins and other flozins)

TAs 315, 336 (Cana 2014 and Empa 2015), recommended with metformin and a sulfonylurea or metformin and a thiazolidinedione

- TA 315: Clinical experts: used principally in combination with metformin and a sulfonylurea
  - gliptin use increasing and pioglitazone use decreasing due to concerns about weight gain and safety
  - committee concluded that gliptins were the key comparators in triple therapy
- TA 336: Clinical experts: thiazolidinedione use falling due to safety concerns, particularly increased bladder cancer risk
  - committee persuaded that comparators in company's submission (gliptins and other flozins), which were informed by previous appraisals, were appropriate
- Dual therapy: flozins likely to be used with metformin when a sulfonylurea not appropriate. Main comparator = gliptins

[redacted]

Key issues for consideration

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