NICE National Institute for Health and Care Excellence

FOR PUBLIC

Ertugliflozin as monotherapy and in dual therapy for treating type 2 diabetes
Technical briefing

This slide set is the technical briefing for this appraisal. It has been prepared by the technical team and it is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the appraisal committee meeting and is expected reading for committee members. The submissions made by the company, consultees and nominated experts as well as the ERG report are available for committee members, and are optional reading.

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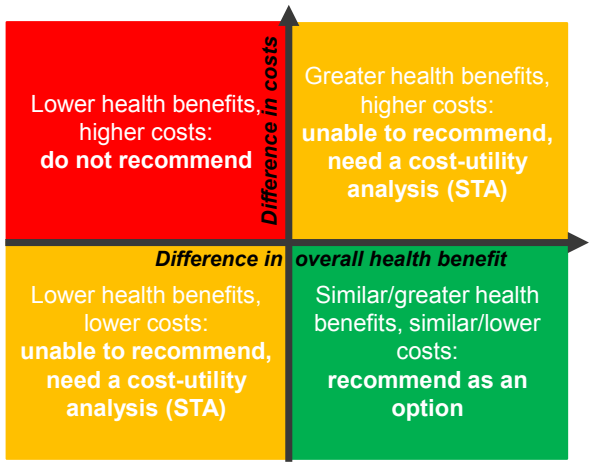
Potential recommendations: cost comparison



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Key issues

- The company has made a case for this appraisal to follow the FTA process (cost comparison) based on ertugliflozin having similar health benefits to dapagliflozin, canagliflozin and empagliflozin, appraised in:
  - TA 390 for monotherapy
  - TA 288 (dapagliflozin), TA 315 (canagliflozin) and TA 336 (empagliflozin) for dual therapy.
- Is the committee satisfied with the evidence for the efficacy and safety of ertugliflozin compared with placebo?
- Does the committee accept the design and reliability of the company's network meta-analyses (NMAs) and/or the ERG's indirect comparisons?
- Does ertugliflozin have similar resource requirements compared with the other recommended treatments?
- Are the lifetime costs and benefits of ertugliflozin likely to be similar to other recommended treatments?
- In light of the above is it reasonable to recommend ertugliflozin in the same way as TAs 390 (mono) and 288, 315 and 336 (dual)?

[redacted]

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The technologies

	Intervention: Ertugliflozin (ERTU)	Comparators: Canagliflozin (CANA); dapagliflozin (DAPA); empagliflozin (EMPA)
Mechanism of action	Sodium–glucose co-transporter 2 inhibitor (SGLT2i)	
Marketing authorisation	Adults aged 18+ 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	
Dose (administered orally, once daily)	Monotherapy: starting dose 5 mg increasing to 15 mg if needed; combination therapy: individualised using recommended 5 mg or 15 mg dosages	CANA – Monotherapy: starting dose 100 mg increasing to 300 mg if needed; combination therapy: individualised using recommended 100 mg or 300 mg dosages DAPA – Monotherapy and dual therapy: 10 mg EMPA - Monotherapy: starting dose 10 mg increasing to 25 mg if needed; combination therapy: individualised using recommended 10 mg or 25 mg dosages

[redacted]

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Monotherapy: company's clinical effectiveness evidence

VERTIS MONO (Terra 2017) was only ERTU RCT:

- 52-week, multicentre, randomized study (first 26 weeks double blind, placebo controlled)
- 81 centres in USA, Canada, Israel, Italy, Mexico, S. Africa, UK (total n=30 UK patients)
- **Population**: N=461 adults, aged ≥18 years with inadequate glycaemic control (HbA1c 7.0% to 10.5% [53-91 mmol/mol]) despite diet and exercise
- **Outcomes**: include change in HbA1c from baseline to week 26 (primary), HbA1c/glycaemic control, body mass index (BMI), hypoglycaemia (frequency/severity), changes in cardiovascular risk factors, adverse events (AEs)

Baseline characteristics were similar across treatment groups

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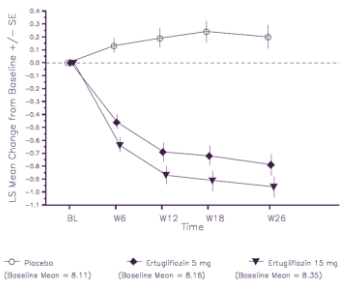
Monotherapy: clinical effectiveness results (1)

Primary efficacy outcome: HbA1c change from baseline to week 26 - Least Squares mean change (constrained longitudinal data analysis [cLDA] using full analysis set [FAS] population)



Treatment	Differences in LS means vs. PBO at W26 (95% CI; p-Value)
ERTU 5 mg	-0.99 (-1.22, -0.76); <0.001)
ERTU 15 mg	-1.16 (-1.39, -0.93); <0.001)

Analysis of patients with HbA1c <7% (<53 mmol/mol) at week 26 – Logistic regression using multiple imputations (FAS)

Treatment	N	Number (%) with HbA1c <7.0% at W26
PBO	153	20 (13.1)
ERTU 5 mg	156	44 (28.2)
ERTU 15 mg	151	54 (35.8)

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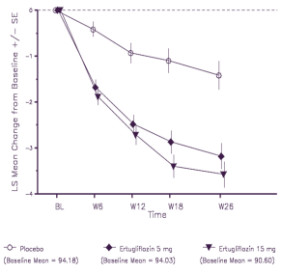
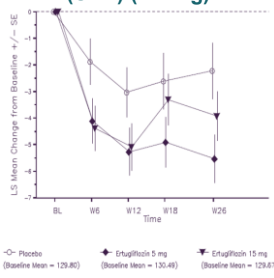
Monotherapy: clinical effectiveness results (2)

Other continuous efficacy outcomes – change from baseline at week 26 - Least Squares mean change (cLDA, FAS)

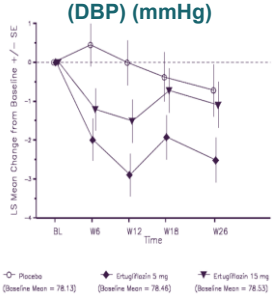
Body Weight (kg)



Systolic blood pressure (SBP) (mmHg)



Diastolic blood pressure (DBP) (mmHg)



Outcome	Differences in LS means vs. PBO at wk 26 (95% CI; p-Value)	
	ERTU 5 mg	ERTU 15 mg
Body Weight (kg)	-1.76 (-2.57, -0.95; <0.001)	-2.16 (-2.98, -1.34; <0.001)
SBP (mmHg)	-3.31 (-5.98, -0.65; 0.015)	-1.71 (-4.40, 0.98; 0.213)
DBP (mmHg)	-1.80 (-3.51, -0.09; 0.039)	-0.37 (-2.09, 1.35; 0.669)

[redacted]

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Monotherapy: adverse events

VERTIS MONO	PBO N = 153	ERTU5 N = 156	ERTU15 N = 152
AEs related to study drug (ER)	19 (12.4)	32 (20.5)	28 (18.4)
Genital mycotic infection (women)	4 (5.6)	**11 (16.4)**	**14 (22.6)**
Genital mycotic infection (men)	1 (1.2)	3 (3.4)	5 (5.6)

ER, analysis excluding events occurring after rescue medication
Bold text = Incidence significantly higher than PBO group

[redacted]

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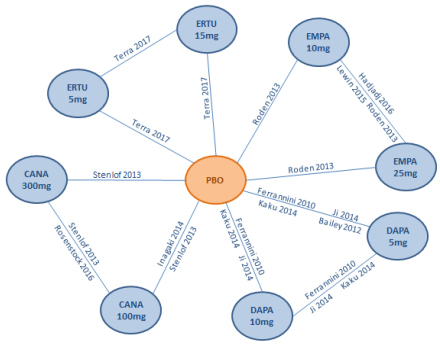
Monotherapy: company's network meta-analysis (NMA)

NMA outcomes:
- Continuous: change in HbA1c, weight and SBP
- Binary: HbA1c in target, UTIs and genital mycotic infections
- All measured at week 24 to 26



Differences between company NMA and TA390:
- SLR underpinning NMA included publications up to May 2018
- Includes Bailey 2012 – DAPA 5 mg vs. PBO
  - Study was excluded from the AG's NMA in TA 390 because DAPA 5 mg is not licensed
  - Company rational for inclusion: "to allow the comparison of the ERTU lower dose (5 mg) against the DAPA lower dose (5 mg)"
- Excludes Kaku 2014 (DAPA 5 mg and 10 mg vs. PBO) from the base case because:
  - SLR inclusion criteria not met (HbA1c threshold of ≥6.5% not ≥7%)
  - Average baseline HbA1c of patients was lower than other included studies (7.5%)

Company sensitivity analyses showed minimal impact on results

[redacted]

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Monotherapy: company's NMA results

Continuous outcomes

- Change in HbA1c: ERTU 15 mg statistically superior to both doses of DAPA/EMPA
- Weight change: [redacted]
- Change in SBP: CANA 300 mg statistically superior to ERTU 15 mg

Binary outcomes

- HbA1c at target (<7.0%): no significant differences between flozins
- All AEs: no significant differences between flozins
- UTIs: [redacted]

Company's conclusion

- ERTU has similar efficacy and safety in monotherapy to other flozins
- Sensitivity analyses confirmed that the base case results were robust

[redacted]

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Monotherapy: ERG review, clinical effectiveness evidence (1)

Key issues with VERTIS MONO trial

- Patients were randomised to 5 mg/day or 15 mg/day from the start, whereas in practice, patients start on 5 mg and increase to 15 mg. Those who do not respond well to 5 mg might do less well on 15 mg than patients who went straight to 15 mg (same problem noted in CANA and EMPA trials)
- Reservations about the statistical analysis which may have over-estimated the reduction in HbA1c compared with placebo. However independent FDA analysis reports both doses of ERTU are clinically effective, with improvements in HbA1c that are similar to those seen with other flozins

[redacted]

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Monotherapy: ERG review, clinical effectiveness evidence (2)

Key issues with company NMA

- Unnecessary, could have compared ERTU against one previously approved flozin (as per ERG's own analysis)
- Consistency with TA 390
  - Company's inclusion of DAPA 5 mg is not appropriate - not relevant dose
  - Company's exclusion of Kaku 2014 is ok - appropriate justification given
  - Overall ERG agree inclusion/exclusion makes minimal impact on results
- Other issues (also applying to TA 390)
  - Some included trials were carried out in East Asian (Japanese and Chinese) populations that have lower baseline BMIs - would have been better to include only trials with similar characteristics to VERTIS MONO
    - Results of NMAs vary according to the trials included (also noted in TA 390)
  - The higher doses of several drugs are included - results may not reflect effectiveness as used in routine care, when the dose is increased only in those who do not respond adequately to the lower dose

[redacted]

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Monotherapy: additional work undertaken by ERG

- As per their comments on company analysis, ERG only compared ERTU against one of the previously approved flozins
- ERG reviewed monotherapy trials and found that CANTATA-M trial (Stenlöf 2013) was the most similar to VERTIS MONO in terms of design and population

Baseline characteristics	VERTIS MONO (ERTU 5 mg)	CANTATA-M (CANA 100 mg)
Mean age (years)	57	55
Mean BMI (kg/m^2)	33	31
Ethnicities	86% white	64% white
Proportion that had previous treatment with glucose lowering drugs	65%	48%
Mean duration of diabetes (years)	5.1	4.5
Mean SBP (mmHg)	130.5	126.7
Mean DBP (mmHg)	78.5	77.7
Mean HbA1c	8.16%	8.1%

[redacted]

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Monotherapy: results of additional work undertaken by ERG

Comparing the results of the studies, ERG concluded that ERTU 5mg had similar health benefits to CANA 100 mg

Results (at 26 weeks)	VERTIS MONO (ERTU 5 mg)	CANTATA-M (CANA 100 mg)
Mean HbA1c changes (LS means)	ERTU 5 mg: - 0.79% PBO: + 0.20%	CANA 100 mg: -0.77% PBO: + 0.14%
Mean HbA1c change vs PBO (LS means)	0.99%	0.91%
Mean change in weight vs PBO	1.76kg	1.9kg
Mean change SBP vs PBO (mmHg)	-3.3	-3.7
Mean change DBP vs PBO (mmHg)	-1.8	-1.6
Proportions with urinary tract infections, both sexes	ERTU 5 mg: 7.1% PBO: 8.5%	CANA 100 mg: 7.2% PBO: 4.2%
Proportions with genital tract infection, women	ERTU 5mg: 16.4% PBO: 5.6%	CANA 100 mg: 8.8% PBO: 3.8%

[redacted]

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Dual therapy: company's clinical effectiveness evidence

VERTIS MET (Rosenstock 2018)	VERTIS Factorial (Pratley 2018)
Design: 104-week, multicentre, randomized study (first 26 weeks double blind, placebo controlled)	**Design:** 52-week, multicentre, randomized study (first 26 weeks double blind)
Population: N=621 patients aged ≥18 years with inadequate glycaemic control (HbA1c 7.0% to 10.5% [53-91 mmol/mol]) on metformin therapy at a dose ≥1500 mg/day	**Population**: N=1232 patients aged ≥18 years with inadequate glycaemic control (HbA1c 7.0% ≤11% [≥58 mmol/mol and ≤97 mmol/mol]) on a stable dose of metformin monotherapy
Interventions/Comparators: ERTU 5 mg, ERTU 15 mg and PBO with background metformin	**Interventions/Comparators:** ERTU 5 mg, ERTU 15 mg with background metformin (also included a sitagliptin and ERTU with sitagliptin arms not relevant to this FTA)
Outcomes: change in HbA1c from baseline to week 26 (primary), body weight, blood pressure, proportion of patients with HbA1c <7.0%, AEs	**Outcomes**: change in HbA1c from baseline to week 26 (primary), body weight, blood pressure, proportion of patients with HbA1c <7.0%, AEs
Location: 103 centres worldwide incl. Australia, US and UK (total n=2 UK patients)	**Location:** 242 centres worldwide incl. Canada and US. None in UK

Baseline characteristics were similar between treatment arms

[redacted]

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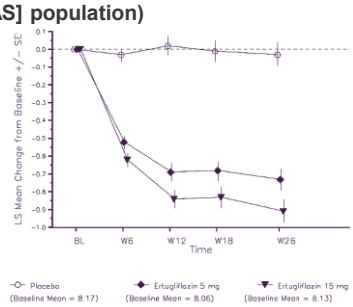
Dual therapy: clinical effectiveness results, VERTIS MET (1)

Primary efficacy outcome: HbA1c change from baseline to week 26 - Least Squares mean change (constrained longitudinal data analysis [cLDA] using full analysis set [FAS] population)



Treatment	Differences in LS means vs. PBO at W26 (95% CI; p-Value)
ERTU 5 mg	-0.7 (-0.9, -0.5; <0.001)
ERTU 15 mg	-0.9 (-1.1,- 0.7; <0.001)

Analysis of patients with HbA1c <7% (<53 mmol/mol) at week 26 – Logistic regression using multiple imputations (FAS)

Treatment	N	Number (%) with HbA1c <7.0% at W26
PBO	209	33 (15.8)
ERTU 5 mg	207	73 (35.3)
ERTU 15 mg	205	82 (40.0)

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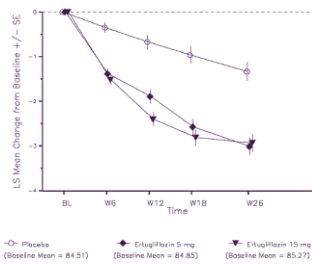
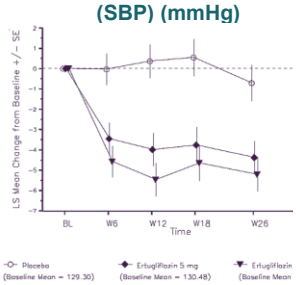
Dual therapy: clinical effectiveness results, VERTIS MET (2)

Other continuous efficacy outcomes – change from baseline at week 26 - Least Squares mean change (cLDA, FAS)

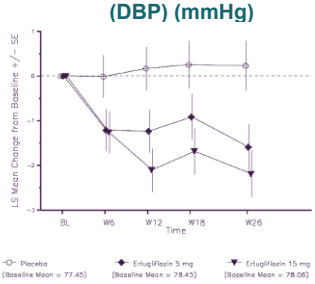
Body Weight (kg)



Systolic blood pressure (SBP) (mmHg)



Diastolic blood pressure (DBP) (mmHg)



Outcome	Differences in LS means vs. PBO at wk 26 (95% CI; p-Value)	
	ERTU 5 mg	ERTU 15 mg
Body Weight (kg)	-1.67 (-2.24, -1.11; <0.001)	-1.60 (-2.16, -1.03; <0.001)
SBP (mmHg)	-3.68 (-5.96, -1.39; 0.002)	-4.50 (-6.81, -2.19; <0.001)
DBP (mmHg)	-1.82 (-3.24, -0.39; 0.013)	-2.42 (-3.86, -0.98; 0.001)

[redacted]

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Dual therapy: clinical effectiveness results, VERTIS Factorial

Continuous efficacy outcomes – change from baseline at week 26 - Least Squares mean change (cLDA, FAS)

Outcome	Differences in LS means vs baseline (95% CI)	
	ERTU 5mg	ERTU 15mg
HbA1c (%)	-1.02 (-1.14, -0.90)	-1.08 (-1.20, -0.96)
Body Weight (kg)	-2.69 (-3.13, -2.25)	-3.74 (-4.18, -3.29)
SBP (mmHg)	-3.89 (-5.28, -2.50)	-3.69 (-5.08, -2.30)
DBP (mmHg)	-1.11 (-1.96, -0.26)	-0.97 (-1.81, -0.12)

Number (%) of patients with HbA1c <7.0% (raw proportion)	
ERTU 5 mg	ERTU 15mg
66 (26.4)	79 (31.9)

[redacted]

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Dual therapy: adverse events

	VERTIS MET			VERTIS Factorial	
Trial arm	PBO N = 209	ERTU5 N = 207	ERTU15 N = 205	ERTU5 N = 250	ERTU15 N = 248
AEs related to study drug (ER)	13 (6.2)	24 (11.6)	25 (12.2)	42 (16.8)	30 (12.1)
Genital mycotic infection (women)	1 (0.9)	6 (5.5)	**7 (6.3)**	6 (4.9)	8 (7.0)
Genital mycotic infection (men)	0 (0)	3 (3.1)	3 (3.2)	6 (4.7)	5 (3.7)

ER, analysis excluding events occurring after rescue medication
Bold text = Incidence significantly higher than PBO group

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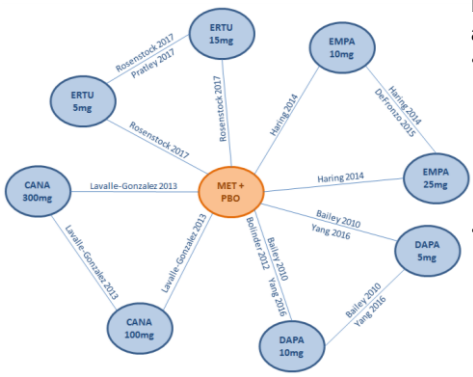
Dual therapy: company's NMA



NMA outcomes – as per monotherapy

Difference between company NMA and NMAs in TA288, TA315 and TA336

- Excluded Bolinder 2012 (metformin + DAPA 10 mg vs. metformin + PBO) :
  - SLR inclusion criteria not met (HbA1c threshold <7%)
  - primary outcome was change in weight, not change in HbA1c
- Included Yang 2016 (DAPA 10 mg, DAPA 5 mg and PBO all with metformin): published after TA288

Company sensitivity analysis showed minimal impact of excluding Bolinder 2012 but did not test the impact of including DAPA 5 mg

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Dual therapy: company's NMA results

Continuous outcomes

- Change in HbA1c: ERTU 15 mg statistically superior to other flozins apart from CANA 300 mg
- Weight change: no statistically significant differences between flozins
- Change in SBP: no statistically significant differences between flozins

Binary outcomes

- HbA1c at target (<7.0%): no significant differences between **********
- All AEs / UTIs : no significant differences **********

Company's conclusion

- ERTU has similar efficacy and safety in dual therapy to other flozins
- Sensitivity analyses confirmed that the base case results were robust

[redacted]

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Dual therapy: ERG review, clinical effectiveness evidence

Key issues with VERTIS Met and Factorial trials

- Similar to VERTIS MONO, in particular
  - Patients were randomised to 5 or 15 mg/day from the start – not in line with practice
  - For VERTIS Met, FDA analysis for change in HBA1c gave slightly less favourable results for ERTU compared with placebo

Key issues with company NMA

- As per monotherapy
  - Unnecessary
  - DAPA 5 mg - not relevant dose
  - trials with East Asian/low BMI populations should have been excluded
  - higher doses should have been excluded
- Bolinder 2012 trial was correctly excluded from base case NMA

[redacted]

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Dual therapy: additional work undertaken by ERG

- ERG preferred to compare ERTU against one previously approved flozin
- ERG found that Bailey 2012 (DAPA + metformin) was the most similar to VERTIS Met (ERTU + metformin) in terms of design and population

Baseline characteristics	VERTIS MET		Bailey 2012	
	ERTU 5 mg	PBO	DAPA 10 mg	PBO
Mean age (years)	56.6	56.5	52.7	53.7
Mean BMI (kg/m²)	30.8	30.7	31.2	31.8
Ethnicities	64.7% white	68.9% white	Mainly white (no % given)	
Duration of diabetes (years)	7.9	8.0	6.1	5.8
Mean SBP (mmHg)	130.5	129.3	126.0	127.7
Mean HbA1c	8.1%	8.2%	7.92 %	8.11%

[redacted]

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Dual therapy: Results of additional work undertaken by ERG

Comparing the results of the studies, ERG concluded that ERTU 5mg had similar health benefits to DAPA 10 mg

Results (at 26 weeks)	VERTIS MET		Bailey 2012	
	ERTU 5 mg	PBO	DAPA 10 mg	PBO
HbA1c week 26	7.3%	7.8%	7.13 %	7.79%
HbA1c change from baseline	-0.73%	-0.03%	-0.84%	-0.30%
Proportion of patients achieving HbA1c target of ≤7.0	35.3%	15.8%	40.6%	25.9%
Mean weight change from baseline (kg)	-3.01	-1.33	-2.9	-0.9
Mean SBP change from baseline (mmHg)	-4.38	-0.70	-5.1	-0.2
Mean DBP change from baseline (mmHg)	-1.59	0.23	-1.8	-0.1
Proportions with urinary tract infections	2.9	1.9	7	5
Proportions with genital tract infections	M: 3.1%* F: 5.5%*	M: 0%* F: 0.9%*	M+F: 9%	M+F: 5%

[redacted] *Genital mycotic infection

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Company resource use assumptions – monotherapy and dual therapy

- Main NHS resource use associated with flozins = drug acquisition costs
- No difference in other resource use between flozins as per assumptions applied in previous NICE appraisals
- Drug acquisition costs are presented based on publically available list prices (there are no PASs for ERTU or its comparators)
- ERTU **********

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Company resource use assumptions – monotherapy and dual therapy

ERG review

- No major concerns
- Note that incidence of GTI events was higher in the VERTIS MONO trial for ERTU 5mg and 15mg compared with frequency reported in the CANTATA-M trial of CANA 100mg and 300mg – not accounted for in cost comparison analysis
  - If this frequency of mycotic infections in women is accepted, annual cost of treating AEs with ERTU increases – impact of this is that **********
    **********)
  - However also note that very high rate of GTI seen in VERTIS MONO was not seen in other trials of ERTU

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Company submission

Cost comparison - monotherapy

Technologies	Acquisition costs per pack (£)	Resource costs (£)	AE costs (£)	Other costs (£)	Annual cost (£)	TOTAL COSTS (£)	Incremental cost to ERTU
ERTU5 or ERTU15	*****	N/A	N/A	N/A	******	*******	-
CANA100 or CANA300 (BNF 2017)	39.20	N/A	N/A	N/A	478.48	478.48	*****
DAPA5 or DAPA10 (BNF 2017)	36.59	N/A	N/A	N/A	478.48	478.48	*****
EMPA10 or EMPA25 (BNF 2017)	36.59	N/A	N/A	N/A	478.48	478.48	*****
Time horizon: 1 year (365.25 days)							

[redacted]

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Company submission

Cost comparison - dual therapy

Technologies	Acquisition costs per pack (£)	Resource costs (£)	AE costs (£)	Other costs (£)	Annual cost (£)	TOTAL COSTS (£)	Incremental cost to ERTU
Met 500* + ERTU 5/15	***** (0.90 + ******)	N/A	N/A	N/A	*******	*******	-
Met 500* + CANA 100/300	40.10 (0.90 + 39.20)	N/A	N/A	N/A	525.96	525.96	*****
Met 500* + DAPA 5/10	37.49 (0.90 + 36.59)	N/A	N/A	N/A	525.96	525.96	*****
Met 500* + EMPA 10/25	37.49 (0.90 + 36.59)	N/A	N/A	N/A	525.96	525.96	*****
Time horizon: 1 year (365.25 days)							

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Technical team recommendation and rationale – monotherapy and dual therapy

Criteria for cost comparison case are met

- The key clinical outcome measures in the ERTU trials and NMAs are consistent with those used in the pivotal trials and cost effectiveness models of the NICE recommended comparators
- Evidence from company NMAs shows that both ERTU 5 and 15 mg have similar clinical effectiveness and safety profile to previously approved flozins in mono and dual therapy – conclusion supported by ERG analysis
- No difference in resource use beyond drug acquisition costs – view supported by ERG. Drug acquisition costs for ERTU *********.

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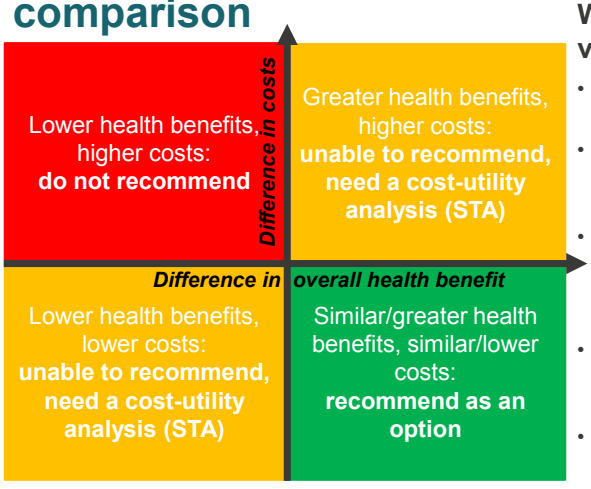
Potential recommendations: cost comparison



What is the committee view on:

- The clinical efficacy and safety of ERTU vs. placebo?
- The design and reliability of the indirect comparisons for the purposes of decision making?
- The similarity of the resource requirements of ERTU compared with other recommended treatments?
- Whether the lifetime costs and benefits are likely to be similar to other recommended treatments?
- Whether in light of the above it is reasonable to recommend ERTU in the same way as TAs 390 (mono) and 288, 315 and 336 (dual)?

[redacted]

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Frequently used abbreviations/terms

BMI	Body mass index
CANA	Canagliflozin
DAPA	Dapagliflozin
DBP	Diastolic blood pressure
DPP-4i	Dipeptidyl peptidase 4 inhibitor
EMPA	Empagliflozin
ERTU	Ertugliflozin
Flozins	Ertugliflozin, canagliflozin, dapagliflozin and empagliflozin
HBA_{1c}	Haemoglobin A1c
NMA	Network meta-analysis
mg	Milligram
PBO	Placebo
SBP	Systolic blood pressure
SGLT-2i	Sodium –glucose co-transporter 2 inhibitor

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