SAXAGLIPTIN / DAPAGLIFLOZIN (QTERN®) FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS
NOT RECOMMENDED FOR PRESCRIBING (DOUBLE RED)

Name: generic (trade)	What it is	Indication	Decision last revised	Decision Status	NICE / SMC Guidance
Saxagliptin / dapagliflozin (Qtern®)	fixed dose combination of saxagliptin and dapagliflozin	Treatment of type 2 diabetes mellitus (T2DM) in adults	December 2017 HMMC WEMOPB non-formulary	Final	NICE - No Guidance SMC – accepted for restricted use

Saxagliptin / dapagliflozin (Qtern®) for the treatment of type 2 diabetes mellitus in adults is NOT RECOMMENDED for prescribing in primary or secondary care (DOUBLE RED)

Background Information

- Qtern® is a fixed dose combination (FDC) of saxagliptin and dapagliflozin. Each tablet contains 5 mg saxagliptin and 10 mg dapagliflozin. The recommended dose is one tablet once daily.
- Qtern® is licensed in adults aged 18 years and older with type 2 diabetes mellitus:
  - to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Qtern® do not provide adequate glycaemic control,
  - when already being treated with the free combination of dapagliflozin and saxagliptin.

Note concomitant add on has not been licensed for use.

Assessment against Ethical Framework

Evidence of Clinical Effectiveness

CV181168 - Randomised, double-blind, placebo-controlled, parallel-group, multicentre study to compare saxagliptin vs placebo added to dapagliflozin and metformin

- ***Patients:*** Patients with T2DM, ≥18 years with inadequate glycaemic control (HbA1c ≥8.0% and ≤11.5%) under current metformin therapy stable at ≥1500 mg for at least 8 weeks prior to screening.
- ***Intervention and comparator*:** At initial screening all patients received open-label dapagliflozin (10 mg/day) in addition to metformin for 16 weeks. Patients with inadequate glycaemic control (HbA1c 7–10.5%) (mean baseline HbA1c 7.9%) were then randomised to receive placebo (n=162) or saxaglitin 5 mg/day (n=153) in addition to background dapagliflozin and metformin for the 24 double-blind treatment period (total population n=315).
- ***Primary Outcome***: There was a significantly greater reduction in HbA1c at 24 weeks with saxagliptin add-on (–0.51% [–5.6 mmol/mol]) vs. placebo (–0.16% [–1.7 mmol/mol]) (difference, –0.35% [95% CI –0.52% to –0.18%] and –3.8 [–5.7 to –2.0 mmol/mol], respectively p<0.0001).
- ***Secondary Outcomes***:
  - A larger proportion of patients achieved HbA1c <7% (53 mmol/mol) with saxagliptin add on (35.3%) vs. placebo add-on (23.1%) (difference 12.2%)

MB102129 - Randomised,double-blind, placebo-controlled, parallel-group, multicentre study to compare dapagliflozin vs placebo added to saxagliptin and metformin

- ***Patients:*** Patients with T2DM, ≥18 years with inadequate glycaemic control receiving treatment with stable metformin (stratum A) (screening HbA1c level 8.0–11.5% [64–102 mmol/mol]) or stable metformin and a DPP-4 inhibitor (stratum B) (HbA1c 7.5–10.5% [58–91 mmol/mol]) for ≥8 weeks
- ***Intervention and comparator*:** Patients received open-label saxagliptin 5 mg/day and metformin for 16 weeks (stratum A) or 8 weeks (stratum B) (saxagliptin replaced any DPP-4 inhibitor). Patients with inadequate glycaemic control (HbA1c 7.0–10.5% [53–91 mmol/mol]) (mean baseline HbA1c 8.2%) were randomised to receive placebo (n=160) or dapagliflozin 10 mg/day (n=160) added to a background of saxagliptin and metformin (total population n=320).
- ***Primary Outcome***: There was a significantly greater reduction in HbA1c at 24 weeks with dapagliflozin add-on (–0.82% [–9.0 mmol/mol]) vs. placebo (–0.10% [–1.1 mmol/mol]) (difference, –0.72% [95% CI –0.91% to –0.53%] and –7.9 [–9.9 to –5.8 mmol/mol], respectively p<0.0001).
- ***Secondary Outcomes***:
  - Significantly more patients achieved HbA1c <7% (53 mmol/mol) with dapagliflozin add on (38%) vs. placebo add-on (12.4%) (difference 25.5%, p<0.0001)

Following open label extension in both studies effects on HbA1c were sustained at week 52

- ***Limitations and Comments***
  - **Limited long term efficacy and safety data**

- **No data on patient orientated outcomes eg cardiovascular**
- **No comparisons with alternative triple therapy options recommended by NICE**
- **Results suggest dapagliflozin add on has more effect than saxagliptin add on:** The additional efficacy of saxagliptin on top of dapagliflozin + metformin in trial CV181168 is limited (HbA1c difference = -0.35%). This figure is very close to the delta of 0.30% used in non-inferiority trials. Although this difference is statistically significant, the clinical relevance is doubtful. Even the response rate is not convincingly superior for saxagliptin add on vs placebo (35% vs 23%). The EPAR concludes that the effect of adding saxagliptin to dapagliflozin is limited, in particular in patients with a high baseline HbA1c.
- The total number of elderly patients was limited in the trials, and especially the number of subjects of 75 years and above
- Switching from other DPP4-inhibitors and SGLT2-inhibitors other than the monocomponents to saxagliptin/dapagliflozin combination has not been studied.
- Although combination with sulfonylureas has not been studied for the FDC, combination use with sulfonylurea has been licensed on the basis of investigations for the individual components.

- ***Safety***
  - The cautions, contra-indications, interactions & adverse-effects from the monocomponents apply to the FDC.

The EPAR report included pooled data from 3 studies (the 2 studies above and a concomitant add on study of similar design):

- There were no differences in hypoglycaemia, SAEs, related AEs or SAEs and no deaths occurred during the studies.
- Incidence of subjects who discontinued study treatment due to an AE was low.
- Adverse events of special interest: no differences between treatment groups, and there were no unexpected findings.
- Female subjects experienced more AEs than males, especially UTIs & vulvovaginal mycotic infections.
- Overall, the common AEs reported were generally consistent with the known safety profiles of saxagliptin or dapagliflozin. 3 most common AEs reported in the saxagliptin + dapagliflozin + metformin group were nasopharyngitis (3.7%), headache (3.5%) & UTI (3.5%); in the saxagliptin + metformin group were UTI (5.4%), influenza (4.5%) & headache (4.2%); in the dapagliflozin + metformin group were UTI (3.8%), influenza (3.2%) & nasopharyngitis & headache (2.9% each).

In conclusion: As expected, specific side effects related to the monocomponents, such as UTI for dapagliflozin & GI events for saxagliptin may occur when the two products are given together such as in a fixed dose combination, but in general the FDC was tolerated reasonably well. It is acknowledged that only a relatively small number of uncomplicated patients were tested.

Cost of treatment and Cost Effectiveness

- **Qtern® is currently the highest cost oral treatment for T2DM:** £49.56 x 28 - £646/year
- Costs are lower than if the combination of dapagliflozin & saxagliptin used separately – cost £889/year.
- Qtern® is lower cost than any combination of DPP4 inhibitor with SGLT2 inhibitor – cost £824-£911/year
- Qtern® is lower cost than GLP-1 agonists but higher cost than insulin
- **This combination with metformin is higher cost than alternative oral triple therapy regimes recommended by NICE** but lower cost than triple therapy regimes with GLP-1 mimetic or if DPP4is or SGLT2is are combined with insulin.
- **No cost-effectiveness analysis available for this combination.**
- Cost effectiveness analysis was undertaken by NICE in the development of current guidelines for T2DM. Use of high cost combinations (DPP4i with SGLT2i and GLP1 mimetic with SGLT2i) which are not included in NICE recommendations are likely to increase costs for T2DM treatment. The cost-effectiveness of these combinations is uncertain.

The needs of the population

- The needs of the population appear low as there are a range of alternative options approved by NICE.
- If this combination is indicated patients may prefer a FDC rather than taking separate monocomponents.
- There will be patients who will not be controlled on current triple therapy regimes recommended by NICE. Patients may prefer an alternative oral treatment combination rather than progressing to injectable therapy with GLP1 agonists or insulin.

The needs of the community

- **If this combination is used as part of a triple therapy regime in preference to current NICE approved oral triple therapy regimes then this would have a significant cost impact.**
- If this combination is an additional option there may not be a requirement or a delayed requirement for progression to injectable higher cost GLP-1 agonists or insulin which may avoid costs.
- The current level of SGLT2i with DPP4i prescribing is uncertain.
- If Qtern®/ a combination of DPP4i with SGLT2i is recommended as an option, to realise the lower cost of Qtern® vs monocomponents then it would appear that 1st line choices would have to be saxagliptin and dapagliflozin.
- A FDC combination of empagliflozin with linagliptin is in development. It would appear likely that A FDC of canagliflozin with a DPP4i will be available in the future.

Policy Drivers

- Current local recommendations:
  - **DPP4 inhibitor preferred choice is sitagliptin**: sitagliptin is recommended within license for new patients requiring gliptin therapy, **unless the patient has impaired renal function. In these circumstances, linagliptin is the agent of choice as no dosage adjustment is required. Advocating the use of Qtern® which does not contain the usual preferred**

choices is likely to cause confusion.

- All SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) are recommended as treatment options for restricted use in accordance with the relevant NICE TA recommendations. Feedback from some local specialists is that empagliflozin may be the preferred choice.

- Patients initiated on this fixed dose combination product who develop renal function decline would be required to change to two separate and different agents.
- **The NICE TAs for SGLT2 inhibitors did not include recommendations for the combination with DPP4 inhibitors (including as FDC) (not considered)**

Note the TA evaluated triple therapy including SGLT2i vs triple therapy including DPP4is not a triple therapy combination including SGLT2i with DPP4i. No TAs in development reviewing this combination.

- **The NICE Guidelines for T2DM did not include recommendations for the combination of SGLT2 with DPP4 inhibitors (including as FDC) (not considered)**
- SMC: following an abbreviated submission: Qtern® in combination with metformin when the use of a sulphonylurea is inappropriate is accepted for restricted use for adults aged 18 years and older with type 2 diabetes mellitus.
- No local ICBs appear to have considered Qtern® for use for T2DM.

Equity

- No impact anticipated

Implementability

- No issues identified

References

- HWE recommendations Prescribing, Policies and Pathways (hweclinicalguidance.nhs.uk)
- European Public Assessment report (EPAR) (May 2016) https://www.ema.europa.eu/en/medicines/human/EPAR/qtern
- Scottish Medicines Consortium (SMC) Advice (July 2017) https://www.scottishmedicines.org.uk/medicines-advice/saxagliptindapagliflozin-fixed-dose-combination-qtern-abbreviatedsubmission-125517/
- NICE guideline [NG28] : Type 2 diabetes in adults: management (December 2015) https://www.nice.org.uk/guidance/ng28
  - Appendix F: Full Health Economics Report https://www.nice.org.uk/guidance/ng28/evidence
- Dapagliflozin in combination therapy for treating type 2 diabetes (TA288) and Dapagliflozin in triple therapy for treating type 2 diabetes (TA418)
- RDTC cost comparison chart (Aug 2017) https://rdtc.nhs.uk/prescribing-support-document/comparison-of-dpp-4-inhibitors-gliptins/
- Qtern® for the treatment of T2DM: Medicines evidence pack to support formulary and guidelines (Oct 2017)

Version	1.1 Harmonisation of Hertfordshire Medicines Management Committee (HMMC) guidance and West Essex Medicines Optimisation Programme Board (WEMOPB) guidance updates include: • Rebadging with HWE ICB and removal of ENHCCG and HVCCG headers • Reference to ICB in place of CCG
Developed by	HWE PMOT
Approved by	HMMC
Date approved/updated	December 2017
Review date:	The recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.
Superseded version	1.0 HMMC document