Qtern: DPP-4 and SGLT2 inhibitor combination for type 2 diabetes

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**Qtern is a new fixed-dose combination of the DPP-4 inhibitor saxagliptin with the SGLT2 inhibitor dapagliflozin for the control of type 2 diabetes. This article discusses its indications, place in therapy and clinical trial efficacy.**

NICE guidance on first and second intensification of treatment to lower blood glucose in people with type 2 diabetes recommends dual therapy with metformin (plus a dipeptidyl peptidase-4 (DPP-4) inhibitor, pioglitazone, a sulfonylurea or a sodium-glucose co-transporter 2 (SGLT2) inhibitor) then triple therapy (with metformin and two other drugs) or insulin-based treatment. Among the several options available, it does not specifically recommend combining a DPP-4 inhibitor with an SGLT2 inhibitor but it does add "Treatment with combinations of drugs including SGLT2 inhibitors may be appropriate for some people at first and second intensification" and "An SGLT2 inhibitor in combination with insulin with or without other antidiabetic drugs is an option."

Qtern, the first fixed-dose combination of a DPP-4 inhibitor and an SGLT2 inhibitor to be introduced in the UK, contains saxagliptin 5mg and dapagliflozin 10mg. Saxagliptin and dapagliflozin lower blood glucose by complementary mechanisms of action: SGLT2 inhibitors block renal reabsorption of glucose whereas DPP-4 inhibitors enhance glucose-mediated insulin secretion by increasing levels of incretins.

**Indications**

Qtern is licensed to improve glycaemic control in adults with type 2 diabetes when double or triple therapy (with metformin and/or a sulfonylurea and one of the component drugs of Qtern) does not provide adequate glycaemic control, or for patients already taking dapagliflozin and saxagliptin as a free combination.

In clinical trials, the combination of saxagliptin/dapagliflozin improved glycaemic control when added to metformin in patients already taking one of the component drugs plus metformin.

Adding dapagliflozin to metformin/saxagliptin is associated with a higher frequency of adverse effects, notably genital infections.

The cost of 28 days’ treatment with Qtern is £49.56 compared with £68.19 for the separate components.
licensed indication) with the component drugs added on alone in patients taking metformin with a mean baseline HbA1c of 8.9% (74mmol/mol).\textsuperscript{2} This 24-week study showed greater improvements in glycaemic control with saxagliptin/dapagliflozin/metformin (triple therapy) than with dual therapy (mean change in HbA1c -1.61mmol/mol (-1.5%) with triple therapy vs -0.66mmol/mol (-0.9%) with saxagliptin/metformin and -1.31mmol/mol (-1.2%) with dapagliflozin/metformin). In addition, a greater proportion of patients achieved good (<53mmol/mol; <7%) glycaemic control (41% with triple therapy vs 18% with saxagliptin/metformin and 22% with dapagliflozin/metformin).

The other two trials compared add-on therapy with one of the component drugs in patients taking metformin (immediate or modified-release at a dosage of ≥1500mg daily) plus the other component drug;\textsuperscript{3,4} extension studies have been reported for each.\textsuperscript{5,6} Both trials were of 24 weeks’ duration and included patients aged in their mid-50s, about half of whom were women and about 90% were white. At baseline, diabetes duration was seven to eight years and mean BMI was 31–32kg/m\textsuperscript{2}. Mean HbA1c was 63–66mmol/mol (7.9–8.2%) but glycaemic control was worse in the dapagliflozin add-on trial, in which fewer patients had HbA1c <64mmol/mol (<8%) (approximately 45% vs 58%). The primary endpoint was the mean change in HbA1c between baseline and week 24.

In both trials, add-on therapy with saxagliptin or dapagliflozin reduced HbA1c significantly more than placebo.

### Table 1. Endpoints of phase 3 trials of add-on therapy with saxagliptin and dapagliflozin\textsuperscript{3,4}

<table>
<thead>
<tr>
<th></th>
<th>Saxagliptin or placebo added to metformin/dapagliflozin\textsuperscript{3}</th>
<th>Dapagliflozin or placebo added to metformin/saxagliptin\textsuperscript{4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HbA1c at 24 weeks, mmol/mol (%)</td>
<td>-5.6 (-0.51%)*</td>
<td>-9.0 (-0.82%)*</td>
</tr>
<tr>
<td>% patients with HbA1c &lt;53mmol/mol (&lt;7%)</td>
<td>35</td>
<td>38*</td>
</tr>
<tr>
<td>Change in fasting plasma glucose (mmol/L)</td>
<td>-0.5</td>
<td>-1.8*</td>
</tr>
<tr>
<td>Change in 2h postprandial glucose (mmol/L)</td>
<td>-2.1</td>
<td>-4.1*</td>
</tr>
</tbody>
</table>

*p<0.0001

### Figure 1. Mean change in HbA1c after 52 weeks’ treatment. a. Saxagliptin added to metformin/dapagliflozin versus placebo added to metformin/dapagliflozin;\textsuperscript{3} b. Dapagliflozin added to metformin/saxagliptin versus placebo added to metformin/saxagliptin\textsuperscript{4}
(see Table 1). The proportion of patients with good glycaemic control (<53mmol/mol; <7%) was significantly greater, and fasting and postprandial glucose were significantly reduced, with the addition of dapagliflozin (in the trial in which glycaemic control was worse overall) but not when saxagliptin was added.

After a further 28 weeks’ treatment, the differences in glycaemic control were maintained (see Figure 1). The proportion of patients requiring additional treatment if HbA1c exceeded 64mmol/mol (8%) or who discontinued treatment was lower with saxagliptin or dapagliflozin add-on therapy than with placebo (19 vs 28% and 21 vs 48%)

Change in body weight was similar with add-on saxagliptin (-1.13 vs -1.50kg with placebo) but greater with add-on dapagliflozin than placebo (-2.1 vs -0.4kg).

Adverse effects
The overall frequency of adverse events in the 52-week extension studies was similar for placebo and active treatment arms. Hypoglycaemia of any severity was rare. Dapagliflozin, added to saxagliptin plus metformin therapy, was associated with a higher frequency of genital infections than saxagliptin add-on therapy (6.3% with add-on dapagliflozin vs 1.3% with placebo; and 3.3% with add-on saxagliptin vs 6.2% with placebo) but the frequency of urinary tract infections was similar to that with placebo in both studies (7–10%). Discontinuation due to adverse effects was also more frequent with add-on dapagliflozin than with add-on saxagliptin (5.6% with add-on dapagliflozin vs 1.9% with placebo; and 2.0% with add-on saxagliptin vs 3.1% with placebo).

References

Declaration of interests
None to declare.

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POEMs

Renin-angiotensin system inhibitors not useful for CAD without heart failure

Clinical question:
Do renin-angiotensin system inhibitors add additional benefit to the treatment of patients with stable coronary artery disease (CAD) but without heart failure?

Bottom line:
The use of an ACE inhibitor, an angiotensin II-receptor blocker (ARB) or a direct renin inhibitor did not decrease the likelihood of early mortality nor decrease the likelihood of experiencing a cardiovascular event as compared with other treatments of CAD. Renin-angiotensin system inhibitors did not reduce serious outcomes as compared with placebo, especially in high-risk patients. Results were similar in subgroups with either diabetes or hypertension. Treatment was associated with fewer patients developing diabetes. (LOE = 1a)

Reference:

Study design: Meta-analysis (randomised controlled trials). Funding source: Self-funded or unfunded. Setting: Various (meta-analysis).

Synopsis:
These researchers searched three databases, including Cochrane CENTRAL, as well as bibliographies of studies to identify all studies that compared a renin-angiotensin system inhibitor with placebo or active treatment in patients with CAD but without heart failure. Three authors independently assessed trial eligibility and quality and extracted the data. They identified 24 trials with 198,275 patient-years of follow-up. Compared with placebo, treatment reduced all-cause mortality (rate ratio 0.84; 95% CI 0.72–0.98), cardiovascular mortality (0.74; 0.59–0.94), myocardial infarction (0.82; 0.76–0.88), and stroke (0.79; 0.70–0.89). However, there was no difference in outcome when compared with active treatment. There was also no difference in patients with hypertension or diabetes. One potential benefit: fewer patients developed diabetes with treatment aimed at the renin system.