Xigduo is a combination of dapagliflozin and metformin for the treatment of type 2 diabetes. NICE recommends this combination as an alternative to metformin plus a sulfonylurea for second-line therapy.

- the recommended dose is 5/850mg or 5/1000mg twice daily; a month’s treatment costs £36.59
- in a 4-year study, it achieved glycaemic control similar to that with glipizide/metformin but was associated with fewer hypoglycaemic events and weight loss
- common adverse effects include urinary tract and genital infections, mostly occurring during the first year of treatment
- the combination offers an alternative escalation therapy, especially in non-adherent patients

**Xigduo**

Xigduo is a combined formulation of dapagliflozin 5mg with metformin 850 or 1000mg. It is licensed for adults with type 2 diabetes mellitus as an adjunct to diet and exercise when glycaemic control is inadequate with the maximally tolerated dose of metformin or other glucose-lowering medicinal products, including insulin, when the patient is already being treated with dapagliflozin and metformin as separate tablets.

The recommended dose is 5mg dapagliflozin twice daily, with the metformin dose most closely corresponding to previous treatment. The prescribing precautions of the component drugs apply to Xigduo, notably a contraindication in patients with moderate or more severe renal impairment and any hepatic impairment.

**Clinical trial**

In a noninferiority study, dapagliflozin was compared with glipizide as add-on therapy in 801 patients with inadequate glycaemic control (HbA1c >6.5 to ≤10 per cent) with metformin alone. The mean HbA1c at baseline was 61mmol per mol (7.7 per cent). The mean dose of dapagliflozin was 9.2mg daily and for glipizide 16.4mg daily; the dose of metformin was 1.5–2.5g daily. The primary end-point was the change in HbA1c after 52 weeks. About 20 per cent of patients in each treatment arm did not complete the trial, due mainly to withdrawal of consent, adverse effects and no longer meeting the study criteria.

The mean change in HbA1c from baseline a reduction of about 3mmol per mol (-0.52 per cent; see Figure 1a). The proportion of patients with HbA1c ≤53mmol per mol (7 per cent) was 27 per cent with
dapagliflozin and 32 per cent with glipizide. The corresponding figures for a threshold of 48mmol per mol (6.5 per cent) were 17 and 28 per cent. The proportion of patients discontinuing treatment due to inadequate glycaemic control was 0.2 per cent with dapagliflozin and 3.6 per cent with glipizide.

Mean body mass index at baseline was 31–32kg per m². Patients treated with dapagliflozin lost approximately 3–4kg compared with a weight gain of 1–2kg in patients taking glipizide (see Figure 1b).

Of the patients who completed this trial, 302 subsequently completed a four-year extension study. By this time the change in HbA₁c from baseline was -0.10 per cent with dapagliflozin and +0.20 per cent with glipizide.

**Adverse events**

The adverse events associated with Xigduo are typical of its component drugs. The proportion of patients reporting any hypoglycaemic event was 41 per cent with glipizide and 3.5 per cent with dapagliflozin in the first year.

In the four-year extension study, this difference was maintained and three major hypoglycaemic episodes were associated with glipizide. Discontinuation due to adverse events was 13 per cent with dapagliflozin compared to 11 per cent with glipizide. Urinary tract infections were reported by 14 and 9 per cent of patients respectively and genital infections by 14 and 3 per cent, mostly in the first year of treatment.

**References**

1. NICE. **Dapagliflozin in combination therapy for treating type 2 diabetes. TA288.** June 2013

**Declaration of interests**

Steve Chaplin has none to declare. Steve Chaplin is a pharmacist who specialises in writing on therapeutics

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**Place in therapy**

*Claire McCourt and Frank Joseph*

As the population of people with type 2 diabetes becomes more complex with increasing age and a heightened awareness of hypoglycaemia risk and obesity, traditional treatment paradigms fall short of the expectations of both clinicians and patients. Initial treatment is usually metformin alone, with the addition of a second agent, such as a sulfonylurea, DPP-4 inhibitor or thiazolidinedione, when glycaemic control becomes suboptimal. These drug options are limited by their adverse effects including weight gain, hypoglycaemia and cardiovascular complications or their modest efficacy when it comes to impact on glycaemia or weight.

There is a role, therefore, for a drug that when combined with metformin provides both efficacy and beneficial effects on weight and hypoglycaemia. Dapagliflozin appears to present this profile and has potential to improve well-being and cardiovascular outcomes as a result of the weight loss. The evidence has also shown that dapagliflozin reduces mean systolic blood pressure, indicating that it
could further minimise cardiovascular risk, a subject that is the focus of ongoing clinical trials.3

The role of Xigduo in clinical practice falls into two realms. In the primary care realm it is used as a second-line oral agent as an alternative to sulfonylureas. Dapagliflozin has been the subject of a NICE technology appraisal recommending its use as a second-line agent as an alternative to sulfonylureas, in a manner similar to that stipulated in guideline CG87 covering the use of newer agents, ie ‘if there is a significant risk of hypoglycaemia (or its consequences) or a sulfonylurea is contraindicated or not tolerated.’4

Clinicians and medicines managers are in an almost impossible situation where the use of newer agents is still a focus of intense scrutiny, as the advantages of a new agent that helps weight loss and decreases hypoglycaemia are not easy to quantify or ignore, especially when it comes to the individual patient in front of you. Additional work is required to look at the acceptability of dapagliflozin compared to sulfonylureas especially in those that are obese or overweight. Should there be a certain level of body mass index at which the benefits of using dapagliflozin in the individual patient outweigh the cost-effectiveness of sulfonylurea use in a population?

The second realm of use is in the obese insulin-resistant patient who has suboptimal glycaemic control despite high doses of insulin, usually managed in a specialist unit. Early personal experience from our site, albeit anecdotal, has been very positive in this group with significant reductions in insulin dosing and weight loss. Thus the benefits of dapagliflozin appear to occur in patients at different stages of disease progression, presumably both when there is still beta-cell secretory function and when this is depleted, as such its final place in the therapeutic pathway still remains to be defined.

The main adverse effects of dapagliflozin are urinary tract and genital infections.3 Adherence, therefore, will be subject to tolerability. There is also a risk of dehydration for patients taking this drug, although the research reports that there is no increased risk of impaired renal function.5,6 The usual difficulties with combination drugs apply to Xigduo, in that the dose of concomitant metformin is restricted to 2g compared with 3g when used as a single agent.

The evidence suggests Xigduo reduces HbA1c and sustains this over time.3 It has beneficial qualities as described but it is not licensed in patients over 75 years, or those with an estimated glomerular filtration rate (eGFR) <60ml per min per m2 or recurrent urinary tract infections.3 With an aging population of patients with type 2 diabetes and co-morbidities including chronic kidney disease, the use of Xigduo is therefore limited to a subgroup of younger patients with normal renal function.

Dapagliflozin is licensed for use in combination with sulfonylureas but at this time NICE only recommends this combination in a trial setting. It could be some time before NICE approves this and in reality, this limits triple therapy escalation for a vast numbers of patients who are on sulfonylureas.

For those patients that dapagliflozin could be used, Xigduo is a combination pill that offers an alternative escalation therapy, especially in nonadherent patients. Looking to the future, there are further SGLT2 inhibitors emerging, which will hopefully provide us with a broader range of clinical scenarios in which this class of drug can be utilised, including certain stages of chronic kidney disease and possibly even type 1 diabetes.

References

Declaration of interests
Dr McCourt has none to declare. Dr Joseph has received honoraria from NovoNordisk, Eli Lilly, Sanofi Aventis, Boehringer Ingelheim, AstraZeneca and MSD, and his department has received research grants from Sanofi Aventis, NovoNordisk and Eli Lilly.

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