**Dapagliflozin: The Role of the First SGLT2 Inhibitor in Type 2 Diabetes Management**

On the 29th of March 2014, during the launch of dapagliflozin (Forxiga®) in Kuala Lumpur, three experts on the role of SGLT2 inhibitors in the management of type 2 diabetes.

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**Diabetes Mellitus in Malaysia: A Growing Epidemic**

In 2011, compared with other global regions, the onset of diabetes in South East Asia and the Western Pacific occurs in younger patients. Asians are also more likely to develop diabetes at a lesser degree of obesity. Despite increasing awareness, macrovascular and microvascular complications remain high as a large proportion of patients are still not adequately controlled. To complicate matters, the fear of hypoglycemia due to treatment is a major stumbling block as hypoglycemia symptoms are associated with reduced quality of life and increased patient worry. In short, achieving good glycaemic control remains a challenge and anti-diabetes agents that address these problems may prove to be useful in the armamentarium against diabetes.


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**Dapagliflozin: Review of Efficacy and Safety of the First SGLT2 Inhibitor**

Beta cell function deteriorates as diabetes progresses, making the selection of anti-diabetes treatment increasingly difficult. Research has now expanded into new agents that reduce hyperglycaemia via insulin-independent mechanisms that result in glucose excretion. One such agent is dapagliflozin, which is a highly selective inhibitor of sodium-glucose cotransporter 2 (SGLT2).

Dapagliflozin binds to SGLT2, which is located in the proximal tubule of the kidney nephrons, resulting in the inhibition of renal glucose reabsorption. This promotes urinary glucose excretion, resulting in the inhibition of renal glucose reabsorption. This promotes urinary glucose excretion,1 which amounts to approximately 70 g glucose excrated daily.2

The efficacy and safety of dapagliflozin have been studied in various clinical trials. When used in patients inadequately controlled with metformin alone, the addition of dapagliflozin 10 mg to metformin further reduced HbA1c by 0.84% (p<0.001).3 The reduction in HbA1c was sustained for at least 102 weeks (Figure 1).4

Dapagliflozin also resulted in significant weight loss (p<0.0001), due to fat mass reduction, compared to metformin alone, and this weight loss was also sustained for 102 weeks.4,5 The weight loss is due to associated caloric loss, and the majority of the total body weight reduction is from fat mass loss. When compared with glipizide, add-on dapagliflozin was shown to have similar 52-week glycaemic efficacy, but significant weight reduction (p<0.001) and less hypoglycaemia (p<0.001) in patients inadequately controlled with metformin.5 In addition, 4-year data showed more persistent metabolic benefits vs. glipizide (treatment difference of ~0.30%).6

**Figure 1: Dapagliflozin confines sustained reduction in HbA1c over time**

The benefits of dapagliflozin have been proven when used as monotherapy as well as add-on therapies with metformin,7,8 sulfonylureas,9 insulin10 or DPP4 inhibitors.11 Moreover there is an additional benefit of blood pressure lowering with dapagliflozin.12,13

In terms of safety and tolerability, dapagliflozin has low intrinsic risk of hypoglycaemia. However, when used with agents having known side effects of hypoglycaemia such as insulin and SUs, an increased risk of hypoglycaemic events was observed.11

There is an increased risk for genital and urinary tract infection with dapagliflozin, but these cases are mild to moderate, and rarely led to discontinuation of the drug.15

Dapagliflozin is associated with reversible volume depletion in a small number of patients,2 as well as small mean changes in fasting lipid parameters compared with placebo.16

In terms of renal function, dapagliflozin treatment is not associated with increased risk of acute renal toxicity or deterioration of renal function,1 but its effect on blood glucose lowering is reduced as renal function declines below a eGFR of 60.17 Dapagliflozin has an acutely cardiocerebrovascular (CV) risk profile, with no evidence for increased CV risk.18

In conclusion, dapagliflozin may be considered as an option for the treatment of Type 2 diabetes as it has shown to be effective in HbA1c reduction, as well as durability in sustaining the glycaemic control. It also has favorable effects on important CV risk factors such as weight and blood pressure lowering.


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**Dapagliflozin: Where Does It Fit in the Overall Scheme of Type 2 Diabetes Management?**

Dapagliflozin is available as once-daily tablets of 10 mg and can be taken at any time of the day, regardless of meals, hence making it a convenient drug to use. There is no known drug–drug interaction with other commonly prescribed Type 2 diabetes treatments; and since it works through an insulin-independent pathway, it can be added on to other current oral anti-diabetes drugs or insulin.

Using various algorithms3,4 as basis for treatment recommendations, Professor Mudalilar suggested that SGLT2 inhibitors may be introduced to patients inadequately controlled with metformin. It may be used in dual or triple drug combination (add on therapy to insulin plus metformin/SU or DPP-4 plus metformin). According to Professor Mudalilar, this is useful when the secondary goal of treatment is to avoid hypoglycaemia, hence may be added to DPP4-inhibitors +/- metformin as these are agents with low risk for hypoglycaemia. The SGLT2 inhibitors may also be added to dapagliflozin when the secondary goal is to have the additional benefit of weight loss.10

Dapagliflozin is not recommended for those with moderate to severe renal impairment, patients ≥75 years or <18 years, those being treated concomitantly with pioglitazone and those receiving loop diuretics. Those with volume depletion should not be started on dapagliflozin, while caution should be exercised in patients for whom a drug-induced drop in blood pressure could pose a risk. When using dapagliflozin with insulin or sulfonylureas, a lower dose of insulin or sulfonylureas may be started on dapagliflozin while caution should be exercised in patients for whom a drug-induced drop in blood pressure could pose a risk.

Professor Mudalilar ended the session with a brief summary of the benefits of dapagliflozin and its role in the current management scheme.

**Benefits of dapagliflozin**

1. **Dapagliflozin**, a first-in-class, highly selective SGLT2 inhibitor, removes excess glucose via an insulin-independent mechanism of action and provides: 1.1 Significant and sustained HbA1c reductions. 1.2 Additional benefits of weight loss and a reduction in blood pressure. 1.3 Low incidence of hypoglycaemia. 1.4 Convenience in once-daily 10 mg tablet, which can be taken regardless of meals.

2. Since dapagliflozin works in an insulin-independent pathway, it is a suitable add-on to other current oral anti-diabetes drugs or insulin.

Abbreviate Prescribing Information

Dapagliflozin: Preparations: Monohydrate equivalent to 5 mg or 10 mg of dapagliflozin. Indications: Forxiga is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycemic control as monotherapy, add-on combination with metformin, sulfonlurea (SU), insulin (alone or with one or both of metformin or a sulfonlurea (SU), DPP4 inhibitor (with or without metformin) when existing therapy, along with diet and exercise, does not provide adequate glycemic control and as initial combination therapy with metformin when diet and exercise have failed to provide adequate glycemic control and there are poor prospects for response to metformin monotherapy. Recommended dosing: 10 mg once daily for monotherapy and add-on combination therapy. When used in combination with insulin or an insulin secretagogue, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia. Without concomitant insulin therapy, 10 mg Forxiga plus additional insulin may be started on dapagliflozin with or without metformin. In the event of a starting dose of 5 mg is recommended. If multi-therapy, it may be increased to 10 mg. Contraindications: Hypersensitivity reaction. Precautions: Type 2 diabetes mellitus, diabetic ketoacidosis, severe hepatic impairment, patients at risk for urinary tract infection, volume depletion, hypotension and/or electrolyte imbalance, elderly cardiac failure, patients treated with pioglitazone. Forxiga is not recommended for use in patients with moderate to severe renal impairment (patients with CrCl ≥ 40 ml/min or eGFR ≥ 40 ml/min/1.73 m2). Adverse reactions: Hypoglycaemia (when used with SU or insulin), genital infections, Urinary tract infections, back pain, dysuria, pyelonephritis. Forxiga may add to the diurectic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Further information available on request

Please consult local full prescribing information before prescribing.

For healthcare professionals only.