Dapagliflozin

▼Forxiga® in type Diabetes Mellitus
Urinating glucose has its problems

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ABSTRACT

The hypoglycaemic action of dapagliflozin is the result of an increase in urinary glucose excretion (glycosuria).

Given its mechanism of action, the incidence of genital and urinary tract infections is increased.

Its efficacy is not better than sulphonylureas or metformin, and it has not been compared with gliptins.

There is uncertainty on its effects on the kidney function, mortality and cancer incidence.

Indications[1]

In adult patients ≥ 18 years with type 2 diabetes mellitus. **Monotherapy.** When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. **Add-on combination therapy:** In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Spain's National Health Service has restricted financing this product to combined therapy with metformin when dapagliflozin together with diet and exercise, do not produce adequate glycaemic control, and in place of sulphonylureas, when these are not tolerated or are contraindicated.

Mechanism of action and pharmacokinetics[1,2]

This drug produces a selective and reversible inhibition of the human sodium-glucose cotransporter 2 (SGLT2), reducing glucose renal absorption and thus incrementing its excretion. It is rapidly absorbed after oral ingestion and reaches its peak plasma concentrations after 2 hours. The absolute oral bioavailability is 78%. Less than 2% is eliminated unaltered, and the rest is metabolized in the liver and kidney, producing an inactive metabolite that is eliminated mainly through renal excretion.

Posology and administration[1]

In monotherapy or combination therapy use 10 mg daily. It can be taken at any time of the day, with or without food. The tablets should be swallowed entirely.

Clinical efficacy

Monotherapy

Compared to placebo: the average reduction of HbA1c (%) after 24 weeks was 0.66 (0.36 to 0.96).[2,3]

Compared to metformin. In a 52-week trial (n=427 patients) non-inferiority was shown in comparison to long-acting metformin (not marketed in Spain) with a difference between groups in HbA1c (%) reduction = -0.01 (-0.22 to 0.20).[5]

Combination therapy

Compared to sulphonylureas. Combination therapy with metformin (n=801), showed non-inferiority vs dapaliflozin associated with glipizide, producing a reduction in HbA1c (%) = 0.52 in both groups after 52 weeks. There was an average reduction of body weight of 3.2 kg with dapagliflozin in contrast to a 1.4 kg increase under glipizide. The effect of weight reduction was maintained after two years.[11]

Safety

Adverse reactions[1]

Very frequent: Hipoglycaemia (when added to sulphonylurea or insulin). **Frequent (1/100 to <1/10):** Vulvovaginitis, balanitis and genital infections, urinary tract infections, back pain, dysuria, polyuria, dyslipidaemia, increase in hematocrit. **Less frequent (1/1.000 to <1/100):** Vulvovaginal pruritus, volume depletion, thirst, constipation, hyperhidrosis, nicturia, increase in blood creatinin levels, increase in blood urea.[1,2]

The incidence of adverse effects with dapagliflozin in monotherapy was 22% compared to 15% under metformin. Severe adverse effects occured in 2.3% and 1.9% of the cases, leading to discontinuation in 4.1% and 3.8% respectively.[5]

Modest efficacy at the expense of genital and urinary tract problems

When combined with metformin, the incidence of adverse effects was similar to that with glipizide (27%), and 8.7% of the cases were severe in the case of dapagliflozin compared to glipizide (11.3%) while treatment withdrawal was similar in both groups (2.2% and 2.0% respectively).[11]

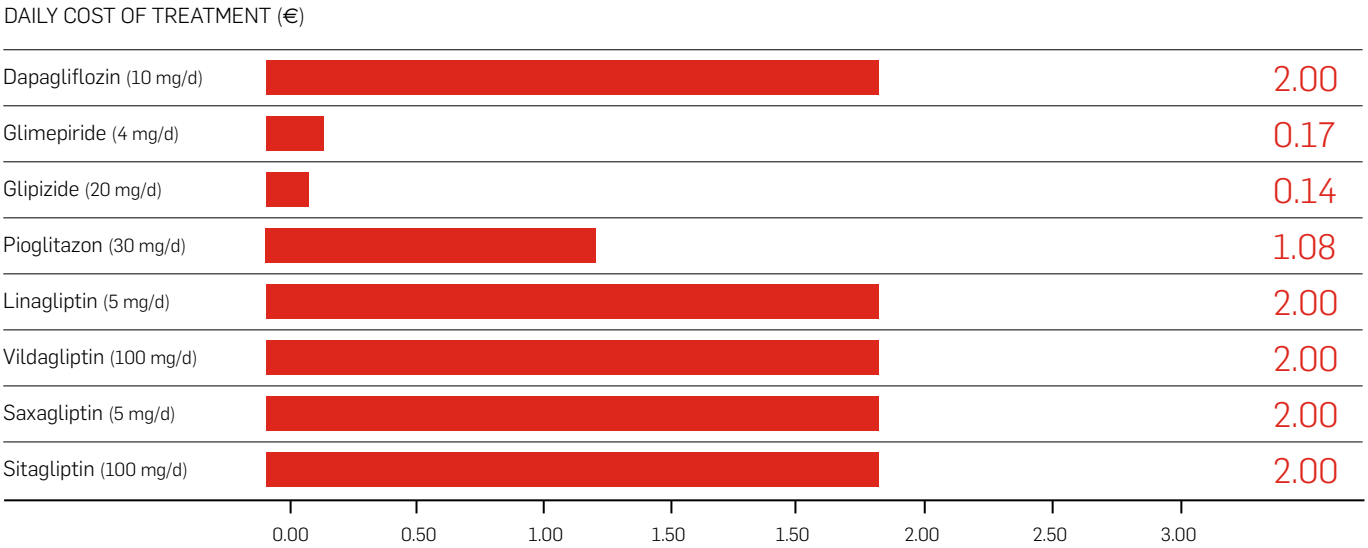
Hipoglycaemia. The incidence of hypoglycaemia under dapagliflozin in monotherapy was similar to placebo.[5] In combination with sulphonylureas, a higher rate of hypoglycaemia was observed (6.0%) compared to the placebo-sulphonylurea group (2.1%). In add-on therapy to insulin, there was also a higher incidence of hypoglycaemia (40%) compared to the placebo-insulin group (34%).[1]

Mortality. In clinical trials, mortality rate in the dapagliflozin group was numerically higher than that in the placebo group[2]: 6.7 *vs* 2.6 deaths/1000 patients-year. The EMA does not provide any explanation to these data.

Tumors. The incidence of bladder, prostate and breast cancer was numerically higher in the dapagliflozin group with respect to its comparators (0.16 vs 0.03 cases/100 patients-year). In the EMA Risk Management Plan monitoring these types of tumours is required.[2]

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	SOME ADDED VALUE IN SPECIFIC SITUATIONS
1	**NO THERAPEUTIC INNOVATION**
0	INSUFFICIENT EVIDENCE

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.



Contraindications[1]

Hypersensitivity to the main substance or any of its excipients.

Warnings and precautions[1]

• Use in patients at risk of volume loss, hypotension and/or electrolytic disturbances.
• This drug increases diuresis, and can cause a mild reduction in blood pressure that can be higher in patients with elevated glycaemia. In patients with diseases that are prone to a loss in volume (such as gastro-intestinal disease), close monitoring is advised (physical examination, blood pressure, hematocrit, serum electrolyte concentrations). Treatment should be discontinued when hypovolemia is produced until it is corrected.
• Increase in hematocrit. Caution in patients with prevailing elevated hematocrit.
• Genital and urinary tract infections. Glucose excretion may be associated with an increase in the risk of urinary tract infections. In clinical trials, urinary tract infections were notified with greater frequency in patients under dapagliflozin 5 mg and 10 mg (5.7% and 4.3% respectively) compared to placebo (3.7%), occurring more frequently in women. Pyelonephritis incidence was similar to that in the control group. Dapagliflozin withdrawal should be considered during the treatment of pyelonephritis or urinary tract related sepsis.
• Genital infections (vulvovaginits, balanitis, etc.) were more frequent in patients under dapagliflozin (4.8%) compared to placebo (0.9%).
• Bladder cancer. As a precautionary step, combination therapy with pioglitazone is not recommended.
• Heart failure. Experience in NYHA class I and II patients is limited, and there are no clinical studies in class III and IV patients.
• Urine test findings. Glycosuria will be present.

Use in special situations[1]

Pregnancy and lactation: do not use. **Renal impairment:** in cases of mild renal impairment, no dose adjustment is necessary. It is not recommended in cases of moderate and severe renal failure. Renal function should be monitored before initiating treatment and at least once a year during treatment. If moderate impairment, renal function monitoring should be done 2 to 4 times a year. Renal function should be monitored before initiating treatment with drugs that can affect its function and thereafter regularly. If ClCr<60 mL/min or GFR<60 mL/min/1.73 m^2 then treatment should be stopped.[1,2] **Liver failure:** in cases of severe liver failure, the initial recommended dose is 5 mg daily, and if well tolerated it can be increased up to 10 mg. No dose adjustments are required for mild and moderate live impairment.[1,2] **Children:** there are no data in children under 18 year. **Elderly:** do not initiate treatment in patients ≥ 75 years.

Interactions[1]

The effect of thiazides and loop diuretics can be increased producing a greater risk of dehydration and hypotension. In combination therapy, lower insulin doses are required given the risk of hypoglycaemia.

EMA Risk Management Plan[2]

Important risks identified: genital infections, urinary tract infections. **Potential risks:** hypoglycaemia, volume depletion, renal failure, bone fractures, liver toxicity, bladder, prostate, and breast cancer.

Place in therapeutics

Dapagliflozin is an antidiabetic agent with a different mechanism of action. No data on morbimortality and quality of life are available. Data from comparative studies with metformin in monotherapy and in association with glipizide showed no differences in glycated haemoglobin reduction.

It presents a low incidence of hypoglycaemia that increases when combined with sulphonylureas or insulin. The main limitation is renal function, and therefore it is not recommended in patients with renal impairment, or in patients over 75 years. It produces glycosuria that leads to a higher incidence of genital and urinary tract infections.

Its long-term efficacy and safety profile have not been established as yet, especially in terms of the potential increase in the risk of cancer, mortality and effects on renal function.

Presentations

Forxiga ® (Bristol-Myers Squibb / AstraZeneca EEIG) 10 mg 28 film coated tablets (55.95€).

References

A complete report on dapagliflozin can be found at: http://www.bit.navarra.es

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