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EMPAGLIFLOZIN

▼JARDIANCE® FOR TYPE 2 DIABETES MELLITUS

dtbn
DRUG ASSESSMENT REPORT
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Sweet look, uncertain benefits

Indications

Use in adult patients with type 2 diabetes to control blood glucose level as follows:(i) in monotherapy in patients whose blood glucose levels are not satisfactorily controlled on diet and exercise alone and who cannot take metformin due to intolerance; (ii) as add-on therapy to other glucose lowering drugs, including insulin, when these medicines together with exercise and diet are not providing adequate control of the diabetes.

Mechanism of action and pharmacokinetics

Selective and reversible inhibition of the co-transporter SGLT-2, which reduces glucose re-uptake at renal level and causes glucose elimination through urine excretion, thereby reducing plasma glucose levels. The increased removal of renal glucose causes osmotic diuresis.

Empagliflozin reaches its maximum concentration (Cmax) at 1.5 h, with a protein binding of 86%. About 41-54% of the dose administered is excreted in feces and urine, respectively, with an elimination half-life of 12.4 h.

Dosage and administration

The initial dose is 10mg once a day taken with or without food. The maximum daily dose is 25 mg. Tablets need to be taken whole.

Clinical efficacy

In monotherapy, empagliflozin has been associated with a reduction of HbA1c with respect to placebo of -0.74% (10 mg) and 0.85% (25 mg).

As add-on therapy to metformin vs. placebo, empagliflozin has been related to a reduction of HbA1c of 0.57% and -0.64% for the 10 mg and 25 mg doses, respectively, at 24 weeks.

The only comparative study (104 weeks) of empagliflozin (25 mg) as add-on therapy vs. an active comparator, –glimepiride (up to 4 mg)– showed that empagliflozin produced a reduction in HbA1c of -0.66% vs. -0.55% with glimepiride. However, such a difference cannot be considered clinically meaningful. According to the FDA, the limit is a reduction of 0.3%. No intervals have been established by the EMA.

As triple therapy, empagliflozin in combination with metformin+sulphonylurea has been proven to reduce HbA1c significantly with respect to placebo (-0.64% at a dose of 10 mg and -0,59% at a dose of 25 mg). Similar results have been obtained vs. placebo when empagliflozin was combined with metformin + pioglitazone (0.48% at 10 mg and 0.61% at 25 mg). In other two placebo-controlled studies, HbA1c concentrations significantly decreased when patients received empagliflozin in combination with insulin plus other oral diabetes drugs.

The alleged reduction of CV mortality needs to be confirmed

Weight loss was also achieved by the two groups receiving empagliflozin as add-on therapy (-1.8 to 2.0 kg).

In the clinical trial carried out to assess the long-term cardiovascular safety of empagliflozin (EMPA-REG OUTCOME), 7,020 patients with type 2 diabetes and an established cardiovascular disease were followed-up for an average of 3.1 years. The main objective of the study was demonstrating the non-inferiority of empagliflozin vs. placebo on the incidence of major cardiovascular events (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke). The hazard ratio (HR) for the primary endpoint was 0.86 (95%CI, 0.74 to 0.99) as compared to placebo (added to baseline therapy). This result demonstrated the non-inferiority and statistical superiority of empagliflozin vs. placebo.

However, some concerns have been raised about the trial:

- Although superiority was achieved in statistical terms, the upper limit of the 95%CI of the HR was very near the no-effect cut-off point. Also, considering the non-inferiority limit established, and based on the results obtained, the clinical relevance of the superiority of empagliflozin is questionable.
- The statistically significant differences observed in the primary composite endpoint were caused by differences in only one of its components (cardiovascular death). In contrast, no differences were found in the other two

ABSTRACT

The EMPA-REG OUTCOME trial was designed to assess the safety of empagliflozin. Its results apparently showed that empagliflozin may reduce cardiovascular death, though this can be challenged due to methodological limitations of the trial.

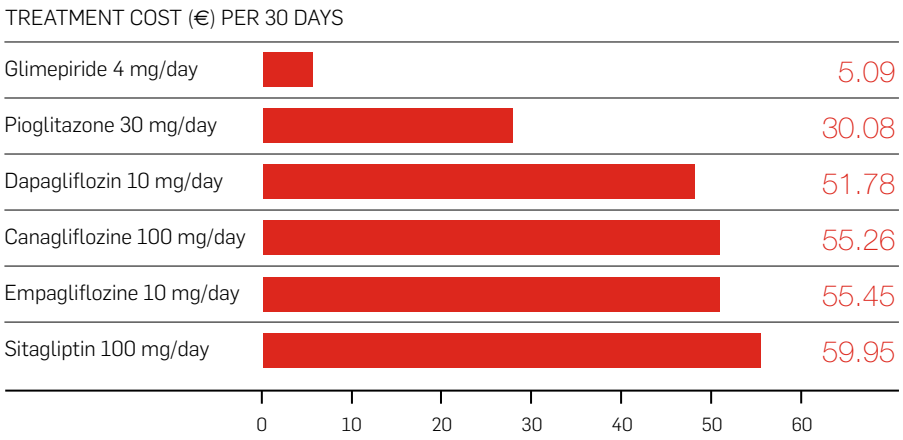
Its main adverse events include: risk of genital infections, syncope, hypotension and renal damage. Due to reported severe cases of ketoacidosis, the AEMPS has issued a safety communication reminding physicians of the need to monitor the occurrence of this adverse effect.

Empagliflozin can be used as an alternative add-on therapy in patients with a glomerular filtration rate >60 ml/min, with special caution in older patients, when first-choice antidiabetics are contraindicated or not tolerated (metformine, sulfonylurea and/or insulin).

CLASSIFICATION

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.



components (non-fatal myocardial infarction and non-fatal stroke).

- Subgroup analysis by geographical regions did not show any superiority in Europe and North America, which is suggestive of the non-applicability of the results in our environment.
- There is uncertainty about the impact of the results obtained due to the high proportion of drop-outs –23.4% in the treatment group and 29.3% in the placebo group–.
- The mechanism of action does not explain the benefits presumably observed.
- The external validity of results is limited due to the exclusion and inclusion criteria employed, especially the one regarding patients with established cardiovascular disease.

Safety

Adverse Reactions

Empagliflozin does not cause hypoglycemia per se. The use of empagliflozin as add-on therapy to other known glucose-lowering drugs (sulphonylureas or insulin) was observed to increase the incidence of hypoglycemia.

Due to its mechanism of action, the appearance of signs of volume depletion and related adverse reactions during empagliflozin therapy is foreseeable.

A clear increase in the incidence of urinary and genital infections was observed in women receiving empagliflozin as compared to those receiving placebo.

Severe cases of diabetic ketoacidosis associated with SGLT-2 inhibitors have been reported, most of which required hospitalization. In June 2015, the AEMPS issued a safety communication about this severe adverse effect.

The EMA has impelled the investigation of the possible link between SGLT2 inhibitors and limb amputations.

A slight 1.5% increase in bone fractures has been observed in all patients treated with empagliflozin. This phenomenon might be due to the increase of falls caused by volume depletion.

Warnings and precautions

Empagliflozin should not be administered for diabetic ketoacidosis to patients with type 1 mellitus diabetes.

Usage in special situations

Renal failure: Empagliflozin therapy should not be initiated in patients with a glomerular filtration rate < 60 ml/min. Dosage needs to be adjusted up to 10 mg/day when the glomerular filtration rate is < 60 ml/min. Empagliflozin must be discontinued if glomerular filtration rate < 45 ml/min. The renal function should be monitored before initiating empagliflozin therapy, when other drugs impairing the renal function are added, and at least once a year. **Severe hepatic impairment:** The use of empagliflozin is not recommended in patients with severe liver failure. **Patients aged ≥ 75 years:** increased risk for dehydration, hypovolemia or hypotension. **Patients aged ≥ 85 years:** not recommended. **Pregnancy:** avoid its use. **Breastfeeding:** do not use.

Drug-to-drug interactions

Empagliflozin can boost the effect of diuretics and increase the risk for dehydration and hypotension.

Lower doses of insulin or sulphonylureas may be required when used in combination with empagliflozin.

Place in therapeutics

Clinical guidelines recommend a stepped individualized therapy for type 2 diabetes. The first step involves initiating metformin therapy plus diet and exercise. When glucose levels are not sufficiently controlled, the following step is adding an oral diabetic agent. When glucose control is not achieved despite double therapy, insulin therapy is recommended. Triple oral therapy is an alternative for patients with insulinization problems.

According to the manufacturer, the results of the EMPA-REG OUTCOME study on the cardiovascular safety of empagliflozin reveal that the use of empagliflozin as add-on therapy to standard therapy for type 2 diabetes patients and established cardiovascular disease reduces the incidence of major cardiovascular events —more specifically, cardiovascular mortality. However, these results are controversial due to concerns about and limitations of the study. The benefits of empagliflozin should be balanced against its associated risks such as volume depletion and ketoacidosis.

Empagliflozin can be used as an alternative add-on therapy in patients with a glomerular filtration rate of >60 ml/min, with special caution in older patients, in cases where other first-choice antidiabetic drugs are contraindicated, or in cases of intolerance (metformin, sulphonylurea and/or insulin).

For a more detailed review of the EMPAREG-OUTCOME study, please visit DTB Navarre review.

Presentations

▼Jardiance® (Boehringer Ingelheim International Gmbh) 10 mg, 30 film-coated tablets (€55.45); 25 mg, 30 film-coated tablets (55.45 €)

References

Based on the report by the Spanish Ministry of Health.

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