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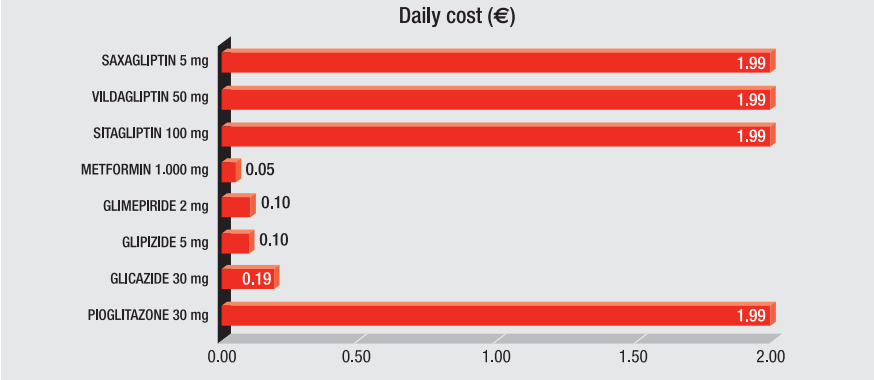
08/2011

Saxagliptin▲ (Onglyza®) in type 2 diabetes

The third DPP-4 inhibitor... and the last one in line

No improvement in efficacy with respect to the rest of oral antidiabetic agents



Therapeutic indications[1]

Saxagliptin is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin, a sulphonylurea or a thiazolidinedione, when the antidiabetic drug, with diet and exercise, does not provide adequate glycaemic control.

Mechanism of action and pharmacokinetics[1,2]

Saxagliptin is a dipeptidil-peptidase-4 inhibitor, otherwise known as a gliptin. It increases incretin hormone levels, among them GLP-1 (Glucagon Like Peptide-1) and GIP (Glucose dependent Insulinotropic Peptide) which stimulates insulin secretion and reduces glucagon.

Its bioavailability is high (75%) and its metabolism is mediated mainly through P450 cytochrome (CYP3A4/5). Its elimination is renal (75%) and hepatic. Its half life is 2-5 hours and that of its main metabolite is 3.1 hours.

Posology and administration[1]

The recommended dose is 5 mg daily in combined therapy with metformin, sulfonylureas or thiazolidinediones. If a dose is missed then it should be taken as soon as the patient remembers. Two doses should not be taken on a single day. It can be taken with or without food at any time of the day.

Clinical efficacy

In published trials, only secondary endpoints were evaluated, and so, long term effects of treatment on the complications of type 2 diabetes or on mortality remain unknown. The authorization report for saxagliptin cites three studies involving combined therapy with metformin[3], glibenclamide[4] and thiazolidinediones[5] (pioglitazone and rosiglitazone). Although only one study has been published, there are two trials that evaluated saxagliptin in monotherapy[6]. There is also one trial evaluating the efficacy of initiating diabetes management by combining saxagliptin and metformin[7].

Recently, one non-inferiority trial was published[8], which was not included in the authorization report, in which the effect of ad-

- Saxagliptin is a hypoglycaemic agent indicated as combined therapy with metformin, sulphonylureas or thiazolidinediones.
- It is not authorized as monotherapy, or in triple therapy, or as combined therapy at the onset of diabetes treatment, or in combination with insulin.
- Its effect on mortality and morbidity has not been evaluated.
- Its safety profile has not been suficiently established.
- Monitoring of possible skin disorders is recommended
- It does not present any advantage over other gliptins.

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.

ding 5 mg daily saxagliptin was compared to the addition of glipizide. In this study there were 858 type 2 diabetes patients under stable treatment with metformin (≥1.500 mg daily) and who presented inadequate control. A comparison was made between the additon of saxagliptin (5 mg daily) and glipizide (average dose 14.7 mg). The primary endpoint of the study was the change in HbA1c with respect to initial values. After 52 weeks of treatment the variation in HbA1c was -0.74% in the saxagliptin+metformin group compared to -0.80% in glipizide+metformin group thus reaching previously established non-inferiority criteria (average modification ≤ 0.35%).

Combined therapy: in three trials a comparison was made of the addition of saxagliptin to metformin[3] (saxagliptin + metformina vs placebo + metformin), glibenclamide[4] (saxagliptin + glibenclamide *vs* placebo + glibenclamide), and thiazolidinedione[5] (30-45 mg pioglitazone or 4-8 mg rosiglitazone). In all these trials, statistically significant differences were observed in all combinations when compared to placebo. All three trials also showed statistically significant differences in the reduction of fasting glucose levels and in the proportion of patients who responded to treatment when compared to placebo.

Only surrogate endpoints have been evaluated, and so long term effects on the complications of diabetes are still unknown.

Adverse reactions[1]

The clinical safety profile of saxagliptin is based on trials lasting between 24 and 52 weeks, which limits the extrapolation to treatments which are normally expected to last a long time.

The most frequent adverse effects (1-10%) in monotherapy were: respiratory tract infection, urinary tract infection, gastroenteritis, sinusitis, headache and vomiting[1]. Skin adverse effects were the most frequent (13.7%) when compared to placebo (9.5%). Treatment withdrawal due to adverse effects caused by saxagliptin in monotherapy ranged between 2.8% and 5.2% compared to 0% in the placebo group.

The incidence of hypoglycemia in the groups under saxagliptin was low. Only in combined treatement with sulphonylureas was there a greater incidence (13.3% with 2-5 mg saxagliptin, 14.6% with 5 mg saxagliptin and 10.1% with placebo).

The saxagliptin risk management plan includes the study of severe infections, lymphopenia, liver, renal and cardiovascular safety (including a randomised clinical trial to study the effect of saxagliptin on the incidence of severe cardiovascular events) and the possibility of producing skin lesions[2].

Contraindications and precautions[1]

This drug should not be employed in type 1 diabetes patients nor in the management of diabetic ketoacidosis. Combined therapy with insulin has not been studied.
· **Use with sulfonylureas:** this combination may require a lower dose of sulfonylureas to reduce the risk of hypoglycaemia.
· **Heart failure:** there is no experience.
· **Skin disorders:** skin eruptions related to the use of DPP-4 inhibitors have been reported to the pharmacovigilance system. Therefore, in line with the usual management approach to diabetes patients, monitoring is recommended for any skin alterations, such as blisters, ulcers or skin eruptions.
· **Immune compromised patients:** there are no established safety and efficacy profiles in this group of patients.
· **Hypersensitivity reactions:** do not use in patients who have suffered from any severe hypersensitivity reaction to any DPP-4 inhibitor.

Special situations[1]

Renal impairment: mild, no dose adjustments are necessary; moderate to severe, not recommended. **Liver impairment:** mild, no dose adjustments required; moderate, use with precaution; severe, not recommended. **Elderly:** no dose adjustments are necessary. The experience in patients >75 years is limited and therefore use of this agent should be done with precaution. **Children:** its use is not recommended. **Pregnancy/lactation:** saxagliptin should not be used in either situation.

Interactions[1]

The use of potent inducers of CYP3A4 such as carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin reduces the glycaemia lowering effect of saxagliptin. Careful glucose monitoring should be considered when saxagliptin is employed in combination with any potent CYP3A4/5 inhibitor (diltiazem, ketoconazole).

Place in therapeutics

Saxagliptin is the third DPP-4 inhibitor or gliptin released on the market. The last recommendations for the management of type 2 diabetes mellitus[9,10] indicate that, in case of no adequate response to non-pharmacological measures or when monotherapy with metformin is insufficient, then the elective option would be combining metformin with a sulfonylurea.

Combinations like metformin+pioglitazone or metformin+DPP-4 inhibitors or gliptins should be reserved when sulphonylureas are contraindicated or not tolerated by patients (risk of hypoglycaemia and its consequences). The addition of a DPP-4 inhibitor should only continue if there is a favourable metabolic response (HbA1c reduction of at least 0.5% after 6 months of treatment)[9,10].

Currently there is no evidence that saxagliptin offers significant advantages with respect to efficacy and safety when compared to the other available DPP-4 inhibitors (sitagliptin and vildagliptin). Moreover, the data from long-term clinical trials of all the DPP-4 inhibitors is limited, and thus the risk-benefit relationship is not currently established[2,11]. The studies evaluating saxagliptin lasted only between 24 and 52 weeks. It is necessary to establish the long-term safety profile with respect to the effects of inhibiting the DPP-4 enzyme, especially those affecting the immune system (infections, skin eruptions, etc). The efficacy and cardiovascular safety profile is yet to be established. The use of saxagliptin in monotherapy and in combination with other antidiabetic drugs as initial therapy is not authorized.

There is no trial available that evaluates the clinical relevance of the results obtained from the use of saxagliptin. It is necessary to know the effects of saxagliptin on the cadiovascular system, the incidence of micro and macrovascular complications related to diabetes, and ultimately on mortality. For all these reasons, it is recommended to employ the metformin+sulfonylurea combination which is the elective option when combined therapy with two drugs is required in the management of type 2 diabetes.

Presentations

Onglyza® (Bristol-Myers Squibb Pharmaceuticals) 5 mg 28 tablets (55.95 €), 5 mg 56 tablets (83.92 €). Prescription medicine only.

References

A complete report on saxagliptin can be found at: http://www.dtb.navarra.es

Servicio Navarro de Salud
Osasunbidea

INFORMATION:
Servicio de Prestaciones Farmacéuticas Plaza de la Paz s/n, 4ª planta - 31002 Pamplona **T** 848429047 **F** 848429010