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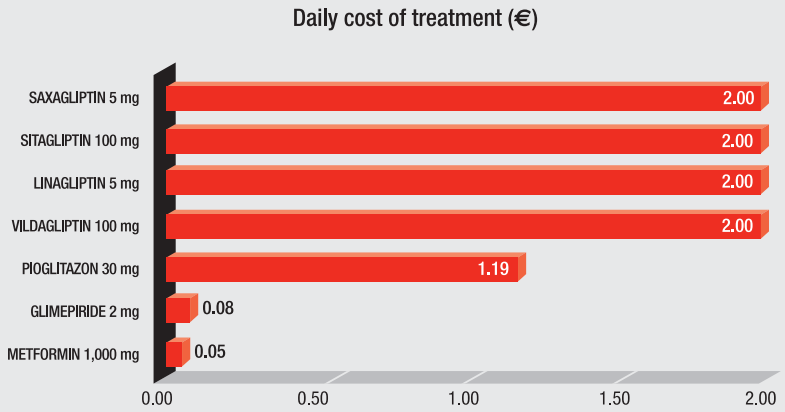
Linagliptin (▲Trajenta®) in type 2 diabetes

Another DPP-4 inhibitor... the fourth!



- Linagliptin is authorized for the treatment of type 2 diabetes in monotherapy only when metformin is not tolerated.
- Its use is approved in a two-drug combined therapy with metformin or insulin, and in triple therapy with metformin and sulphonylureas or with metformin and insulin.
- Regarding efficacy only a 0.6% reduction vs placebo in HbA1c was shown, which is of limited magnitude. Its effect on morbidity and mortality has not been evaluated.
- In one trial the combination of linagliptin + metformin was statistically inferior to glimepiride + metformin.
- There is no evidence that linagliptin offers significant advantages with respect to other gliptins in terms of efficacy and safety. No dose adjustments are required in renal impairment, unlike sitagliptin, saxagliptin and vildagliptin.
- There are no data on long term safety. The possible risks are related to the immune and cardiovascular system and the possibility of developing pancreatitis.

Indications[1,3]

In the management of type 2 diabetes as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment. In combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.

No improvement in efficacy and unknown long-term safety profile

Mechanism of action and pharmacokinetics[1]

This drug inhibits the DPP-4 enzyme which stimulates the secretion of insulin and reduces that of glucagon. It presents a bioavailability of 30% and metabolism is mainly through CYP3A4 cytochrome. The elimination half-life is 11.4 hours. Approximately 90% of the dose is excreted unaltered in faeces and 5% in urine.

Posology and administration[1]

The daily dose is 5 mg. It can be taken with or without food at any time of the day.

Clinical efficacy[1,2]

The EMA's assessment report[2] included 4 placebo-controlled pivotal trials of 6 months duration. Of these, one involved monotherapy[4], and three included linagliptin in combined therapy with metformin[5], metformin + sulphonylurea[6] and with pioglitazone[7] (an

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.

unapproved indication). Two unpublished trials evaluated the combination of linagliptin and insulin with or without metformin. In all trials the primary endpoint was the reduction in glycated hemoglobin (HbA1c) with respect to baseline values. Only surrogate endpoints were studied, and so the long term effects of treatment on type 2 diabetes complications remain unknown.

Trials versus placebo:

In monotherapy. In one trial[4] in which linagliptin was compared to placebo a significant improvement in HbA_{1c} levels was observed (-0.69%; 95%CI, -0.85 to -0.53).

In combination with metformin. In a trial[5] on patients inadequately controlled with metformin the effect of adding linagliptin or placebo was evaluated. The difference in the reduction of HbA_{1c} was -0.64% (95%CI, -0.78 to -0.50).

In combination with metformin + sulphonylurea. In one trial[6] on patients inadequately controlled with combined therapy (metformin + sulphonylurea) the addition of linaglilptin was evaluated compared to placebo. HbA_{1c} reduction in the linagliptin group was -0.62% (95%CI, -0.73 to -0.50).

In the main trials[4-7] different responses with regard to changes in HbA1c in the group under placebo have been observed in patients of Asian origin with respect to patients of Caucasian origin. The difference in % HbA_{1c} in Asian patients under linagliptin was higher (-0.80%) than in those of Caucasian/European origin (-0,50)/(-0.57%), at the limits of clinical relevance.[2] The percentage of patients included in these trials[4-6] that achieved a reduction of at least 0.5% in HbA_{1c} with linagliptin was between 47% and 58%.

Trial versus glimepiride:

In combination with metformin. One non-inferiority trial[14] included patients inadequately controlled with metformin to whom either linagliptin or glimepiride was added to their treatment. After two years, the difference between both groups was 0.20% (97.5%CI, 0.09 to 0.30) complying with the criteria of non-inferiority. However, linagliptin was statistically inferior to glimepiride. The EMA[2] considered that the non inferiority trial was not sufficiently well designed. Moreover, approximately 5% of the patients in the glimepiride group did not receive the maximum daily dose of 4 mg. In the linagliptin group, 24.7% of patients required rescue medication compared to 21.5% in the glimepiride group. There were more patients that abandoned treatment under linagliptin due to lack of efficacy with respect to glimepiride (5.8% vs 1.9%).

Safety

Adverse reactions[1]

Very frequent (≥1/10): hypoglycemia. **Infrequent (1/1.000 to <1/100):** nasopharyngitis, cough. **Unknown frequency:** hypersensitivity, pancreatitis. **Post-marketing reports:** angioedema and urticaria in some patients were observed though rarely.

Contraindications[1]

Hypersensitivity to the active substance or any of its excipients.

Warnings and precautions[1]

Do not employ in type 1 diabetes patients nor as treatment for ketoacidosis.

Risk of hypoglycemia when combined with sulphonylureas or insulin. Consider a reduction in dose of the sulphonylurea and insulin if combined.

Use in special situations[1]

Pregnancy and lactation: it should not be used. **Kidney impairment:** no dose adjustments required. **Liver impairment:** no dose adjustments required, though clinical experience is limited. **Children:** no data available. **Elderly:** no dose adjustments required, though clinical experience is limited in patients over 80 years.

Interactions[1]

Rifampicin reduces the maximum concentration of linagliptin (43.8%), and thus it is foreseeable that the combination of linagliptin with potent inducers of gp-P do not reach complete efficacy, especially those administered in the long term.

Risk Management Plan of the European Medicines Agency (EMA)[2]

This includes the study of patients with severe renal impairment, liver impairment, elderly patients with high cardiovascular risk, patients over 80 years, and the possibility of producing pancreatitis, cancer, skin lesions and hypersensitivity reactions and infections.

Place in therapeutics

In the management of type 2 diabetes, metformin is considered the first choice when glycemic control is inadequate under diet and exercise. A sulphonylurea can be added to improve glycemic control.[22,23] Gliptins[24] can be considered as second or third line options in combined therapy. In two-drug[23] combinations, gliptins are an alternative to sulphonylureas when these are contraindicated, not tolerated, or when there is a risk of hypoglycemia or important weight gain. In triple therapy, they can be indicated in addition to the combination of metformin + sulphonylurea if weight gain is relevant.[23] The NICE guidelines[22] recommend 6 months treatment to evaluate continuity, and if the reduction in HbA_{1c} is <0.5 then the gliptin should be suspended.

In placebo-controlled trials on the effects of linagliptin in monotherapy o in combined therapy, a 0.6% reduction in HbA_{1c} vs placebo was observed[2,20], less than in other trials with metformin, sulphonylureas and pioglitazone (1%)[8,9] and similar to sitagliptin (0.7%)[10,21], saxagliptin (0.6%) and vildagliptin (0.6%).[21] There is only one trial with an active comparator, in which the combination of linagliptin + metformin was shown to be statistically inferior to glimepiride + metformin.

Linagliptin does not require dose adjustments in moderate or severe renal impairment, unlike sitagliptin, saxagliptin and vildagliptin which do require dose adjustments. This possible benefit is not as such when combined with metformin, as this is contraindicated when creatine clearance is <60 mL/min. Currently there is no evidence that linagliptin offers statistically significant advantages compared to other gliptins in terms of efficacy and safety.

Linagliptin's long term safety profile is still not sufficiently established. It is necessary to establish a relationship with the effects derived from the inhibition of DPP-4 enzyme, especially those affecting the immune system (infections, skin lesions, etc). The effects on cardiovascular risk and the risk of pancreatitis are yet to be known.

Presentations

Trajenta® (linagliptin) (Boehringer Ingelheim Pharma GmbH) 5 mg 30 tablets (59.95 €)
Jentadueto® (metformin + linagliptin) (Boehringer Ingelheim Pharma GmbH) 850 mg / 2.5 mg 60 tablets (65.57€); 1000 mg / 2.5 mg 60 comp (65.57€)

References

A complete report on linagliptin can be consulted at: http://www.dtb.navarra.es

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