HAUTE AUTORITÉ DE SANTÉ

DIABETOLOGY
Update
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

TRESIBA (insulin degludec), long-acting insulin analogue

Minor clinical added value in terms of safety compared to LANTUS, in adults with type 1 or 2 diabetes mellitus, at high risk of hypoglycaemia.

Main points

- TRESIBA has an MA for the treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.
- TRESIBA 100 units/ml induced fewer severe or symptomatic hypoglycaemic episodes than insulin glargine 100 units/ml (LANTUS) in one study in adults with type 1 diabetes and in another study in adults with type 2 diabetes.
- A cardiovascular safety study on a large population of patients with type 2 diabetes at cardiovascular risk demonstrated the non-inferiority of TRESIBA 100 units/ml compared to insulin glargine 100 units/ml on the rate of cardiovascular events and a lower frequency of hypoglycaemia with TRESIBA 100 units/ml compared to insulin glargine 100 units/ml.

Therapeutic strategy

- Patients with type 1 diabetes (T1D) require nutritional management and insulin treatment with systematic self-monitoring of blood glucose levels several times per day. The main objective of treatment is to control blood glucose levels in order to prevent long-term vascular complications and avoid acute metabolic complications. The objective of T1D treatment is to maintain glycated haemoglobin (HbA1c) levels at below 7 or 7.5%, being attentive to the risk of hypoglycaemia.
- An HbA1c target ≤ 7% is recommended for the majority of patients with type 2 diabetes (T2D). Generally, insulin therapy is recommended if the glucose target is not achieved with oral antidiabetic agents or in the event of intolerance or contraindications to these. When initiating insulin therapy, it is recommended to start with an intermediate-acting insulin (NPH) at bedtime or with a long-acting insulin analogue if the risk of nocturnal hypoglycaemia is a concern. If the blood glucose target is not achieved despite the introduction of insulin therapy, the latter should be intensified. GLP-1 analogues are an alternative to insulin in the event of a body mass index (BMI) ≥ 30 kg/m² or if weight gain under insulin treatment is a concern.
- **Role of the medicinal product in the therapeutic strategy**

  In type 1 diabetes, TRESIBA can be used as basal insulin in a basal-bolus regimen (in combination with a rapid-acting insulin or a rapid-acting analogue) in the same way as the other long-acting analogues, insulin glargine (LANTUS, ABASAGLAR, TOUJEO) and insulin detemir (LEVEMIR).

  In type 2 diabetes, intensified insulin regimens are no longer systematically recommended. TRESIBA, like other long-acting insulin analogues, can be used:

  - when initiating insulin therapy, as basal insulin (in combination with one or more oral antidiabetic agents). It is recommended to preferably start with an intermediate-acting insulin (NPH) at bedtime. The prescription of a long-acting insulin analogue, as an alternative to intermediate-acting insulin, should be discussed if the risk of severe nocturnal hypoglycaemia is a concern.
  - when initiating an intensified insulin regimen, as basal insulin in a basal-bolus regimen (in combination with an insulin or a rapid or ultra-rapid-acting insulin analogue).

  When it is not possible to administer the dose at the same time of the day, TRESIBA permits flexibility in the insulin administration time.

  In adult patients with type 1 or type 2 diabetes at high risk of hypoglycaemia, patient education plays a crucial role in the prevention of hypoglycaemia. TRESIBA is a long-acting basal insulin treatment suitable for adult diabetics at high risk of hypoglycaemia.

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Clinical data

- A randomised, crossover study was conducted in 501 T1D patients (1:1), with two treatment periods and two insulin administration times (half in the morning and the other half in the evening), with only 395 patients (78.8%) receiving the complete treatment over the 2 periods. The mean HbA1c level at inclusion was 7.6% [min 4.1; max 9.8]. Of the 5,898 confirmed severe or symptomatic hypoglycaemic episodes over the whole day during the two 16-week maintenance phases (primary endpoint), 2,772 were observed under TRESIBA 100 units/ml (i.e. 77.3% of patients) and 3,126 under insulin glargine 100 units/ml (i.e. 79.9% of patients). The relative rate (number of events divided by PYE (Patient Years Of Exposure) multiplied by 100) of confirmed severe or symptomatic hypoglycaemic episodes during the maintenance phase was 2,200.8 under TRESIBA versus 2,462.68 under insulin glargine, with an absolute difference of -130.31 [–193.5; –67.16]. The TRESIBA/insulin glargine ratio in terms of rate of confirmed severe or symptomatic hypoglycaemic episodes during the maintenance phase was 0.89 [0.85; 0.94], confirming the non-inferiority and superiority of TRESIBA compared to insulin glargine on the primary endpoint.
- A randomised, crossover study was conducted in 721 T2D patients (1:1), with two treatment periods and two insulin administration times (50.1% in the morning and 49.9% in the evening), with only 580 patients (80.4%) receiving the complete treatment over the 2 periods. The mean HbA1c level at inclusion was 7.6% [min 4.7; max 10.8]. Of the 849 confirmed severe or symptomatic hypoglycaemic episodes over the whole day during the two 16-week maintenance phases (primary endpoint), 353 were observed under TRESIBA 100 units/ml (i.e. 22.5% of patients) and 496 under insulin glargine 100 units/ml (i.e. 31.6% of patients). The relative rate of confirmed severe or symptomatic hypoglycaemic episodes was 185.6 under TRESIBA versus 265.36 under insulin glargine, i.e. an absolute difference of -23.66 95% CI
  [-33.98; -13.33]. The TRESIBA/insulin glargine ratio in terms of rate of episodes was 0.70 95% CI [0.61; 0.80] confirming the superiority of TRESIBA compared to insulin glargine.
- A cardiovascular safety study randomised 7,637 patients between the 2 groups: TRESIBA 100 units/ml (3,818 patients) or insulin glargine 100 units/ml (3,819 patients). The mean follow-up duration for patients was 2 years. Of the 7,637 patients randomised, 85.2% were over the age of 50 years with a diagnosis of cardiovascular disease or chronic kidney disease, while 14.5% were over the age of 60 years with cardiovascular risk factors at inclusion. The time to first occurrence of an adjudicated 3-component MACE event (primary endpoint) revealed 681 events, with 325 in the TRESIBA compared to 356 in the insulin glargine group. The hazard ratio was 0.91 95% CI [0.78; 1.06] (p<0.001) for TRESIBA compared to insulin glargine, confirming the non-inferiority of TRESIBA compared to insulin glargine on cardiovascular safety. Fewer episodes of severe hypoglycaemia (ranked secondary endpoint) were demonstrated with TRESIBA: 280 severe hypoglycaemic episodes occurring in 187 patients for the TRESIBA group versus 472 episodes occurring in 252 patients for the insulin glargine group, i.e. a relative risk of 0.60 95% CI [0.48; 0.76] (p<0.001) for TRESIBA compared to insulin glargine.

Benefit of the medicinal product

- TRESIBA provides a minor clinical added value* (Level IV CAV) in terms of safety compared to insulin glargine 100 units/ml, in adults with type 1 or 2 diabetes, at high risk of hypoglycaemia.

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This document was drafted on the basis of the Transparency Committee opinion dated 06 February 2019 (CT-17265) available at **www.has-sante.fr**

* The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".

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