HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

2 April 2014

TRESIBA 100 U/ml, solution for injection in prefilled pen

B/5 pre-filled pens of 3 ml (CIP: 34 009 268 531-5 0)

TRESIBA 100 U/ml, solution for injection in cartridge

B/5 cartridges of 3 ml (CIP: 34 009 268 533-8 9)

Applicant: NOVO NORDISK

INN	insulin degludec
ATC code (2013)	Not yet assigned
Reason for the review	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"Treatment of diabetes mellitus in adults."**

Actual Benefit	**The actual benefit of TRESIBA is substantial in the treatment of type 1 and type 2 diabetes in adults.**
Improvement in Actual Benefit	**In view of:** - **the glycaemic control achieved with TRESIBA (insulin degludec) which is comparable to that observed with insulin glargine (LANTUS) in type 1 and type 2 diabetes and insulin detemir (LEVEMIR) in type 1 diabetes,** - **the difficulty in assessing the clinical relevance of any advantage in terms of a reduction in the occurrence of hypoglycaemic episodes, particularly at night in view of the very small differences observed by comparison with other long-acting analogues, despite the use of rigorous assessment methods,** - **the non-demonstration of any impact in terms of morbidity and mortality, particularly cardiovascular,** - **the absence of any robust data that allow the preferential recommendation of one long-acting insulin analogue,** **the Committee considers that TRESIBA does not provide any improvement in actual benefit (level V, nonexistent) in the management, with long-acting insulin analogues (LANTUS and LEVEMIR), of adult patients with type 1 or type 2 diabetes.**
Therapeutic use	**<u>In type 1 diabetes</u>, TRESIBA can be used as a basal insulin in a basal-bolus regimen (in combination with a rapid-acting insulin or analogue) in the same way as other long-acting analogues.** **<u>In type 2 diabetes</u>, TRESIBA, like other long-acting analogues, can be used:** **- when initiating insulin therapy, as basal insulin (in combination with one or more oral antidiabetics)** **- when initiating an intensified insulin regimen, as basal insulin in a basal-bolus regimen (in combination with a rapid- or ultra-rapid-acting insulin or analogue).**
Recommendations	**-**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date (centralised procedure): 21 January 2013
Prescribing and dispensing conditions/ special status	List II

ATC Classification	2013 *Not yet assigned*

02 BACKGROUND

This is an application for inclusion of a new basal insulin, a long-acting insulin analogue, in the treatment of diabetes mellitus in adults.

03 THERAPEUTIC INDICATIONS

“Treatment of diabetes mellitus in adults.”

04 DOSAGE

“Tresiba is a basal insulin for once-daily subcutaneous administration at any time of the day, preferably at the same time every day.

The potency of insulin analogues, including insulin degludec, is expressed in units (U). One (1) unit (U) of insulin degludec corresponds to 1 international unit (IU) of human insulin, 1 unit of insulin glargine or 1 unit of insulin detemir.

In patients with type 2 diabetes mellitus, Tresiba can be administered alone or in any combination with oral anti-diabetic medicinal products or bolus insulin (see section 5.1).

In patients with type 1 diabetes mellitus, Tresiba must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements.

Tresiba is to be dosed in accordance with the individual patient’s needs. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose.
As with all insulin products adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.
[…]
With Tresiba 100 units/ml a dose of 1-80 units per injection, in steps of 1 unit, can be administered. The dose counter shows the number of units regardless of strength and **no** dose conversion should be done when transferring a patient to a new strength.

Flexibility in dosing time
On occasions when administration at the same time of the day is not possible, TRESIBA allows for flexibility in the timing of insulin administration (see section 5.1). A minimum of 8 hours between injections should always be ensured.

Patients who forget a dose are advised to take it upon discovery and then resume their usual once-daily dosing schedule.

Initiation
Patients with type 2 diabetes mellitus
The recommended daily starting dose is 10 units followed by individual dosage adjustments.

Patients with type 1 diabetes mellitus
Tresiba is to be used once-daily with meal-time insulin and requires subsequent individual dosage adjustments.

Transfer from other insulin medicinal products
Close glucose monitoring is recommended during the transfer and in the following weeks. Doses and timing of concurrent rapid-acting or short-acting insulin products or other concomitant anti-diabetic treatment may need to be adjusted.

Patients with type 2 diabetes mellitus
For patients with type 2 diabetes taking basal, basal-bolus, premix or self-mixed insulin therapy, changing the basal insulin to Tresiba can be done unit-to-unit based on the previous daily basal insulin dose followed by individual dosage adjustments.

Patients with type 1 diabetes mellitus
For most patients with type 1 diabetes, changing the basal insulin to Tresiba can be done unit-to-unit based on the previous daily basal insulin dose with subsequent individual dosage adjustments. For patients with type 1 diabetes transferring from twice-daily basal insulin or having HbA_{1c} < 8.0% at the time of transfer, the dose of Tresiba will be determined on an individual basis. Dose reduction needs to be considered followed by individual dosage adjustment based on the glycaemic response.

Special populations
Elderly patients (≥ 65 years old):
TRESIBA can be used in elderly patients. Glucose-monitoring is to be intensified and the insulin dose adjusted on an individual basis (see section 5.2).

Renal and hepatic impairment
TRESIBA can be used in renal and hepatic impaired patients. Glucose-monitoring is to be intensified and the insulin dose adjusted on an individual basis (see section 5.2).

Paediatric population
The safety and efficacy of TRESIBA in children and adolescents below 18 years of age have not been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.

Method of administration
Tresiba is for subcutaneous use only.
Tresiba must not be administered intravenously as it may result in severe hypoglycaemia. Tresiba must not be administered intramuscularly as it may change the absorption. Tresiba must not be used in insulin infusion pumps.

Tresiba is administered subcutaneously by injection in the thigh, the upper arm or the abdominal wall. Injection sites are always to be rotated within the same region in order to reduce the risk of lipodystrophy.

Tresiba comes in a pre-filled pen (FlexTouch) designed to be used with NovoFine or NovoTwist injection needles. The 100 units/ml pre-filled pen delivers 1 - 80 units in steps of 1 unit."

05 THERAPEUTIC NEED [1,2,3,4]

05.1. Therapeutic strategy for the management of type 1 diabetes

Adult patients with type 1 diabetes must receive insulin therapy and nutritional management. The amount of energy and carbohydrates in the food intake must be matched to the action profile of the insulin and the physical exercise taken.
The objectives of treatment are: to control blood glucose so as to prevent long-term complications linked to diabetic microangiopathy (retinopathy, renal failure, neurological, infectious and cutaneous complications) and the prevention of normal height and weight development and pubertal development in children, and the prevention of hypoglycaemic episodes and ketoacidosis.

There are several possible insulin therapy regimens; the choice depends on the glycaemic targets of each patient, his/her preferences and his/her way of life:

- treatment with two injections/day: a mixture of rapid-acting insulin (or rapid-acting analogue) and intermediate-acting insulin (before breakfast and the evening meal).
- treatment with three, four or five injections/day: injections of a mixture of rapid-acting insulin (or rapid-acting analogue) and intermediate-acting insulin (2 times/day: before breakfast and the evening meal), and a rapid-acting insulin (or rapid-acting analogue) before the midday meal (1 x/day). In this regimen, the intermediate-acting insulin in the evening can be postponed until bedtime to better cover the insulin needs of the night (see "with the experts").
- "basal-bolus" treatment with three, four or five injections/day: an intermediate-acting "basal insulin" (2x/day, morning and evening) or a long-acting insulin analogue (1 to 2x/day) is combined with a rapid-acting injected "prandial insulin" (or rapid-acting analogue) injected as a bolus before each of the main meals (3 times/day).
- treatment with a portable SC pump (continuous infusion with a basic flow rate which is fixed or variable according to day or night schedules and a bolus at mealtimes). Administration with a pump requires the use of a rapid-acting insulin (or a rapid-acting analogue).

Regimens with basal-bolus or pump administration are those which best reproduce normal physiology. Administration by pump gets closest to the normal physiology of insulin secretion, but at the price of blood-glucose self-monitoring and regular and repeated adjustments to the insulin.

In patients with poor metabolic control, a change in the insulin regimen can be considered after account has been taken of other parameters influencing glycaemic control: diet, physical exercise and compliance.

[1]NICE (National Institute for Health and Clinical Excellence). NICE and diabetes: a summary of relevant guidelines. November 2009.
[2]SIGN (Scottish Intercollegiate Guidelines Network). Management of diabetes - A national clinical guideline. Guideline 116. Mars 2010.
[3]ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes). Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35: 1364-79.
[4]Stratégie médicamenteuse du contrôle glycémique du diabète de type 2. Recommandations de bonne pratique de la HAS. [Drug strategy for glycaemic control in type 2 diabetes. HAS good practice guidelines]. January 2013.

Place of long-acting analogues in the therapeutic strategy for the management of type 1 diabetes:
Long-acting analogues, insulin glargine (LANTUS) and detemir (LEVEMIR) are used as basal insulin in a basal-bolus regimen (in combination with a rapid-acting insulin or a rapid-acting analogue).

05.2. Therapeutic strategy for the management of type 2 diabetes

Treatment objective: to reduce morbidity and mortality particularly by means of proper glycaemic control. The short-term objective is to improve the symptoms (thirst, polyuria, asthenia, weight loss and blurred vision) and to prevent acute complications (infectious conditions and hyperglycaemic coma). The longer-term objective is to prevent chronic microvascular complications (retinopathy, nephropathy and neuropathy), macrovascular complications (myocardial infarction, strokes and obliterating arteriopathy of the lower limbs) and to reduce mortality.

Glycaemic target: according to the HAS guidelines (2013), this must be individually tailored to the patients' profile and may thus change over time. Diabetes is progressive and all aspects of its treatment must be reassessed regularly: hygiene and dietary measures, health education and drug treatment. The literature data do not allow a lower limit for the target HbA1c to be defined. Once the target has been achieved, treatment should be adjusted case by case. For most type 2 diabetes patients, a target HbA1c of ≤ 7% is recommended. Drug treatment must be initiated or reassessed if the HbA1c is greater than 7%.
Special cases: for patients with newly diagnosed diabetes who have a life expectancy of more than 15 years and no history of cardiovascular disease, a target of ≤ 6.5% is recommended, on condition that it is achieved by the initiation or reinforcement of hygiene and dietary measures then, if those fail, by means of oral monotherapy.
There are a number of special cases for which the glycaemic target is less strict: age > 75 years; history of macrovascular complications; chronic renal failure; proven serious comorbidity; limited life expectancy (< 5 years); long duration of diabetes (> 10 years) and for whom the target of 7% proves difficult to achieve since the intensification of drug therapy causes severe hypoglycaemia.
The initiation of effective hygiene and dietary measures is an essential prerequisite for drug treatment for glycaemic control.

Drug strategy:
According to the recent HAS guidelines, the recommended strategy for the initiation of antidiabetics is generally as follows:
- metformin monotherapy
- then dual therapy with metformin + sulfonylurea if the deviation from the target is < 1% HbA1c.
- then triple therapy with metformin + sulfonylurea + alpha-glucosidase inhibitors or with DPP-4 inhibitors if the deviation from the target is < 1% HbA1c.
- then, if the hypoglycaemic target has not been met, insulin is started in combination with metformin + sulfonylurea. Possible alternative to insulin: GLP-1 analogues if BMI ≥ 30 or if weight gain on insulin gives cause for concern.

Insulin therapy can also be considered in the following special situations:

At the triple therapy stage
Insulin can be combined with metformin + sulfonylurea if the deviation from the target is > 1% HbA1c with dual therapy.
Alternative: combination of metformin + sulfonylurea + GLP-1 analogues if BMI ≥ 30 or if weight gain on insulin gives cause for concern.

At the dual therapy stage in the event of intolerance of or contraindication to sulfonylureas or metformin

Insulin can be combined with metformin (or with a sulfonylurea) if the deviation from the target is > 1% HbA1c on monotherapy, and if oral dual therapy fails.
Alternative: combination of metformin (sulfonylureas) + GLP-1 analogues if BMI ≥ 30 or if weight gain on insulin or the occurrence of hypoglycaemic episodes give cause for concern.

At the monotherapy stage
Insulin therapy is not recommended outside special situations (pregnancy). In addition, it is recommended to start insulin therapy if the glycaemic target has not been achieved despite monotherapy with repaglinide, an alpha-glucosidase inhibitor or a DPP-4 inhibitor and if metformin and sulfonylurea are not tolerated or are contraindicated.

The role of insulin therapy
The choice of an insulin therapy regimen depends on several parameters, such as:
- the patient's choice: does the patient accept the treatment? The number of injections?
- the glycaemic targets and the patient's ability to achieve them;
- the patient's independence: can they manage their treatment? If he cannot, can their family and friends help or is a visit by a nurse required?
- glycaemic profiles: has fasting hyperglycaemia occurred in isolation or together with one or more post-prandial hyperglycaemic episodes?
- the patient's way of life: are the type of diet (times of meals and their carbohydrate content) and physical exercise constant or erratic?

Consequently, the choice of insulin treatment is based on the expert opinion of the nursing staff which should be passed on to the patient or the person will be in charge of that treatment. Referral to an endocrinologist should be considered for the initiation or optimisation of the insulin regimen if there is any difficulty in achieving the specified glycaemic targets.

When initiating insulin therapy, it is recommended, in addition to monotherapy or dual therapy, to start:
- preferably an intermediate-acting insulin (NPH) at bedtime;
- or a long-acting analogue if the risk of night-time hypoglycaemia is a concern.

If the glycaemic target is not achieved despite the initiation of insulin therapy, the therapy will be intensified. The various possible regimens are:
- the basal-bolus regimen: a long-acting insulin or a long-acting analogue and a rapid-acting or ultra-rapid-acting insulin or analogue before one or more meals during the day;
- regimen with 1-3 injections a day of biphasic insulin (mixture of rapid-acting or ultra-rapid-acting insulin and intermediate-acting or long-acting insulin).

In patients with very poorly controlled diabetes, with repeated blood glucose levels over 3 g/l and/or an HbA1c > 10%, an intensified insulin regimen can be initiated from the outset on the advice of an endocrinologist.

06 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators of the medicinal product assessed are medicinal products available at the same stage of therapeutic use and intended for the same population, on the date of the assessment.

In this case, these are long-acting human insulin analogues.

06.1. Medicinal products

In type 1 diabetes:
The clinically relevant comparators of insulin degludec (TRESIBA) are:

- insulins used as basal insulin in a basal-bolus regimen or in a regimen of two to five injections a day (NPH intermediate-acting insulin or insulin glargine, LANTUS, insulin detemir, LEVEMIR), in combination with a rapid-acting or ultra-rapid-acting insulin or analogue.
- insulins administered as basal insulin by portable subcutaneous pump (rapid-acting insulin or analogue).

In type 2 diabetes:
The clinically relevant comparators of insulin degludec are:

- when initiating insulin therapy: insulins used as basal insulin at a rate of one injection a day (NPH intermediate-acting insulin or insulin glargine, LANTUS, insulin detemir, LEVEMIR) or two injections a day (LEVEMIR), and in combination with at least one oral antidiabetic;
- when initiating an intensified insulin regimen:
  - insulins used as basal insulin in a basal-bolus regimen (NPH intermediate-acting insulin or insulin glargine, LANTUS, insulin detemir, LEVEMIR), in combination with a rapid-acting or ultra-rapid-acting insulin or analogue*,
  - mixed (or pre-mixed) insulins administered in one to three injections a day.

*NPH intermediate-acting insulins or insulin detemir LEVEMIR

INN	Same TC*	Name (Company)	Date of opinion	AB	IAB	Reimbursement
NPH insulin Human insulin	Yes	INSUMAN BASAL (Sanofi-Aventis France)	12 September 2007 (RI)**	Substantial	Not applicable	Yes
NPH insulin Human insulin	Yes	INSULATARD (Novo Nordisk)	18 July 2012 (RI)**	Substantial	Not applicable	Yes
NPH insulin Human insulin	Yes	UMULINE NPH (Lilly France)	20 February 2013 (RI)**	Substantial	Not applicable	Yes
Insulin glargine Recombinant analogue	Yes	LANTUS (Sanofi-Aventis France)	25 May 2011 (re-assessment) RI** being assessed	Substantial	V versus other insulins	Yes
Insulin detemir Recombinant analogue	Yes	LEVEMIR (Novo Nordisk)	18 December 2013 (RI)**	Substantial	IACB V (nonexistent)	Yes

*TC = therapeutic category
**Renewal of inclusion

06.2. Other health technologies

Not applicable

Conclusion

All the comparators listed are clinically relevant. The most relevant are other insulins used as basal insulin: NPH insulin, insulin glargine and insulin detemir.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

TRESIBA has obtained Marketing Authorisation in the following countries: Japan (28 September 2012), Mexico (18 December 2012), Norway (12 February 2013).
TRESIBA is currently reimbursed in Japan.
The assessment of reimbursement by the health insurance system in the United Kingdom is in progress.

In the USA, the Marketing Authorisation is being assessed by the FDA which has not approved TRESIBA because of fears about the increased risk of major cardiovascular events.

08 ANALYSIS OF AVAILABLE DATA

The company has submitted the following in support of its application:

- **Three phase III studies in the treatment of type 1 diabetes:**

- Two studies with similar methods: study 3583, comparing insulin degludec with insulin glargine over 52 weeks; study 3585, comparing insulin degludec with insulin detemir over 26 weeks in patients treated with insulin. The insulins were administered in a basal/bolus regimen in combination with insulin aspart. Both studies were followed up, at 104 weeks for study 3583 and at 52 weeks study 3585. The main purpose of follow-up extensions studies was to evaluate safety.
- One study (3770) comparing two dosage regimens of insulin degludec (fixed and flexible schedules) with insulin glargine. This study will not be described, firstly because its objective is not to assess clinical benefit and secondly because it compares dosage regimens validated by the SPCs of insulins degludec and glargine.[5]

- **Five phase III studies in the treatment of type 2 diabetes:**

- Two studies with comparable methods: study 3579, lasting 52 weeks, versus insulin glargine in combination with oral antidiabetics (OAD); study 3582, lasting 26 weeks, versus insulin glargine whether or not in combination with OADs and insulin aspart. These two studies were extended, to 104 weeks for study 3579 and to 78 weeks for study 3582.
- One study (3580), lasting 26 weeks, versus sitagliptin, not used because at this stage in the management of type 2 diabetic patients, sitagliptin is not a clinically relevant comparator. In fact, gliptins must be stopped when insulin therapy is initiated, according to the latest HAS guidelines.
- One study (3668) comparing two dosage regimens of insulin degludec (fixed and flexible schedules) with insulin glargine, which is not described for the same reasons as study 3770 in type 1 diabetes.
- One study (3846) comparing two titration algorithms for TRESIBA, not used because it does not allow the clinical benefit to patients to be assessed.

- **Two meta-analyses:[6]**

- One meta-analysis assessed the occurrence of hypoglycaemic episodes on insulin degludec by comparison with insulin glargine.
- The other had the objective of assessing the cardiovascular profile of insulin degludec in terms of the occurrence of major cardiovascular events by comparison with other comparators used in trials of the phase III clinical development plan.

[5]In fact, according to its SPC, insulin glargine must be administered once a day at any time of the day but at the same time each day, i.e. with a fixed schedule. For TRESIBA, the SPC recommends preferential administration at the same time every day. When the dose cannot be administered at the same time of the day, TRESIBA offers flexibility in the time of administration. The administration intervals for TRESIBA in the flexible arms of these studies correspond to flexibility conditions pushed to the extreme which do not reflect recommended use in clinical practice.

[6]Provided for in the clinical development plan for TRESIBA.

08.1 Efficacy

8.1.1 Studies in type 1 diabetes: studies 3583[7] and 3585 (currently being published)

	Study 3583	Study 3585
Primary objective of the study	To evaluate the efficacy and safety of insulin degludec compared with those of a basal insulin, insulin glargine (study 3583) or insulin detemir (study 3585), in forced titration, in accordance with a basal bolus regimen combined with insulin aspart in type 1 diabetic patients	
Method	Open-label, non-inferiority, phase III study randomised 3:1 in study 3583, 2:1 in study 3585, versus insulin glargine or detemir, in combination with insulin aspart	
Study duration:	52 weeks	26 weeks
Inclusion criteria	- Type 1 diabetic patients, aged ≥ 18 years, treated with insulin in accordance with a basal-bolus regimen for at least 12 months - HbA1c ≤ 10.0% - BMI ≤ 35.0 kg/m²	
Non-inclusion criteria	- cardiovascular disease within 6 months before the study, defined as myocardial infarction; heart failure (NYHA) class III or IV; unstable angina; coronary artery bypass; angioplasty - severe, uncontrolled arterial hypertension, whether or not treated (SBP ≥ 180 mmHg and/or DBP ≥ 100 mmHg) - impaired hepatic function (ALAT ≥ 2.5 times the upper limit of normal) - impaired renal function (blood creatinine ≥ 180 µmol/l). - recent major hypoglycaemia (more than one severe hypoglycaemic episode within the last 12 months); hypoglycaemic coma or diabetic ketoacidosis within the last 6 months - proliferative retinopathy or maculopathy necessitating acute treatment - treatment with an antidiabetic other than insulin within 3 months before the study.	
Treatment groups	Insulin degludec + insulin aspart versus insulin glargine + insulin aspart	Insulin degludec + insulin aspart versus insulin detemir + insulin aspart
Course of the study	In the two studies, during the first 26 weeks of treatment strict forced titration (weekly follow-up by the investigator, see attached titration algorithm) was applied in order to achieve the glycaemic objectives. Whereas the period of treatment in study 3585 stopped in that 26th week, in study 3583, from the 26th week to the 52nd week less intensive follow-up was carried out (follow-up every 2 weeks by the investigator).	
Primary efficacy endpoint	Mean change in the HbA1c level at 52 weeks of treatment for study 3583 and 26 weeks for study 3585 by comparison with baseline	
Secondary endpoints	- Number of confirmed night-time hypoglycaemic episodes - Number of confirmed hypoglycaemic episodes (minor and severe hypoglycaemic episodes, both daytime and night-time) - Change in fasting blood glucose at the end of the study.	
Calculation of the number of subjects required	The calculation of the number of subjects to be included was based on the following assumptions: a standard deviation of 1.1% (based on experience in phase III studies in type 1 diabetic patients treated with insulin); a single-sided significance level of 2.5%; a mean difference of 0% between the two treatments; a power of 95%; a non-inferiority threshold of 0.4%. The number of patients to be included was 468 patients in the degludec group and 156 patients in the glargine group for study 3583; 284 patients in the	

[7]Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L, Renard E, Russell-Jones D, Philotheou A, Francisco AMO, Pei H, Bode B. Insulin degludec versus insulin glargine in basal bolus therapy with mealtime insulin aspart in type 1 diabetes: a 52 week, phase 3, randomised, open-label, multicentre, treat-to-target trial. Lancet 2012; 379: 1489–1497.

	degludec group and 142 patients in the detemir group for study 3585.
Statistical analysis	Insulin degludec was to be regarded as not inferior to insulin glargine or insulin detemir if the upper limit of the 95% confidence interval for the difference in the endpoint of the HbA1c level variation between the two treatments (degludec - glargine and degludec - detemir) was less than 0.4%. If non-inferiority was established, an analysis of superiority was scheduled for this endpoint (superiority established if the upper limit of the 95% confidence interval was less than 0). If non-inferiority was demonstrated for the primary endpoint, the secondary endpoints were tested using a sequential hierarchical procedure (to prepare for the risk of an increase in the significance level), in the following order: 1. Confirmed night-time hypoglycaemic episodes: *Superiority was confirmed if the 95% confidence interval for the relative risk (insulin degludec/insulin detemir or glargine) was strictly less than 1.* 2. Confirmed hypoglycaemic episodes: *Superiority was confirmed if the 95% confidence interval for the relative risk (insulin degludec/insulin detemir or glargine) was strictly less than 1.* 3. Change in fasting blood glucose at the end of the study: *Superiority was confirmed if the 95% confidence interval for the difference between the two treatments (insulin degludec - insulin detemir or glargine) was strictly less than 0.* When no difference was demonstrated for one of the secondary endpoints, no conclusion could be drawn from the results of the secondary endpoints that were ranked lower in the predefined hierarchical sequence.

Results of study 3583:

A total of 629 patients were randomised: 472 patients to the insulin degludec group and 157 to the insulin glargine group.[8]

Characteristics of patients on inclusion (Table 1)

	TRESIBA insulin degludec n=472	**LANTUS insulin glargine n=157**
Mean age (years) (SD)	42.8 (13.7)	43.7 (13.3)
Duration of diabetes (years) (SD)	19.1 (12.2)	18.2 (11.4)
Mean HbA1c (%) (SD)	7.7 (0.9)	7.7 (1.0)
Fasting blood glucose (mmol/l) (SD)	9.1 (4.0)	9.7 (4.4)
Mean BMI (kg/m^2) (SD)	26.3 (3.7)	26.4 (4.2)
Mean weight (kg) (SD)	78.9 (14.3)	78.3 (16.2)

The patients' characteristics were similar between the two treatment groups: patients had a mean age of 43 years, an age of diabetes of 18.9 years, an HbA1c level of 7.7% and a BMI of 26.3 kg/m².

The most commonly observed ongoing diabetes treatment (in 70.4% of the randomised patients) was treatment with basal insulin 1 time/day + rapid-acting insulin 3 times/day. In the two treatment groups, the basal-bolus insulin therapy regimen was followed by 99% of the randomised patients.

[8]Most patients (626 patients i.e. 99.5%) were exposed to the study products: only three patients in the glargine group were randomised but not exposed.

Primary efficacy endpoint:

Table 2: Change in the HbA1c level at 52 weeks (PP population)

Treatment group	N	Mean final HbA1c level (SD)	Mean change (SD) at week 52 compared with baseline
degludec + aspart glargine + aspart	448 147	7.32 (0.05) 7.33 (0.07)	-0.37 (0.05) -0.36 (0.07)
Estimated difference degludec *versus* glargine			Difference between the means (95% CI): **-0.01 [-0.14; 0.12]**

After 52 weeks of treatment, in the per protocol population, the difference between insulin degludec and insulin glargine in terms of the reduction in the HbA1c level was -0.01%, 95% CI [-0.14; 0.12]. Since the upper limit of the confidence interval for this difference was less than the fixed threshold (0.4%), the non-inferiority of insulin degludec with respect to insulin glargine was demonstrated.
The superiority of insulin degludec with respect to insulin glargine has not been established.
These results are found in the ITT population.

It should be noted that the reduction in the HbA1c level was greatest with degludec and with glargine up to the 26th week of treatment. HbA1c levels rose after that.

Change in HbA1c at the end of the study:
Study 3644 (extension of study 3583):
After 104 weeks of treatment, the HbA1c was 7.4 ± 1.0% in the degludec group and 7.5 ± 1.1% in the insulin glargine group.

Secondary endpoints:

- *confirmed night-time hypoglycaemic episodes:*
The number of night-time hypoglycaemic episodes was comparable in the two groups of treatment up to the 6th week of treatment. After that, the number of night-time hypoglycaemic episodes was smaller in the degludec group.
At the end of treatment, a difference was reported in favour of insulin degludec (413.66 episodes per 100 patient-years n=472) compared with insulin glargine (548.20 episodes per 100 patient-years n=154), RR for insulin degludec/glargine = 0.75, 95% CI [0.59; 0.96], p=0.011).

- confirmed hypoglycaemic episodes (daytime + night-time):
No difference was observed between the two treatment groups.
The procedure for the analysis of secondary endpoints was therefore stopped.[9]

[9]For information, there was no difference between the two treatment groups in terms of the occurrence of severe hypoglycaemic episodes.

Results of study 3585:

A total of 455 patients were randomised: 302 patients to the insulin degludec group and 157 to the insulin detemir group.[10]

Characteristics of patients on inclusion (Table 3)

	TRESIBA insulin degludec n=302	**LEVEMIR insulin detemir n=157**
Mean age (years) (SD) Adults (18-65 years) > 65 years	41.1 (14.9) 277 (91.7) 25 (8.3)	41.7 (14.4) 141 (92.2) 12 (7.8)
Duration of diabetes (years) (SD)	13.7 (10.6)	14.4 (9.7)
Mean HbA1c (%) (SD)	8.0 (1.0)	8.0 (0.9)
Mean fasting blood glucose (mmol/l) (SD)	9.9 (4.0)	9.5 (4.0)
Mean BMI (kg/m^2) (SD)	24.0 (3.5)	23.7 (3.4)
Mean weight (kg) (SD)	66.5 (14.9)	66.7 (13.4)

The patients' characteristics were similar between the two treatment groups: patients had a mean age of 41.3 years, a BMI of 23.9 kg/m², a mean HbA1c level of 8.0% and a duration of type 1 diabetes of 13.9 years. The mean fasting blood glucose level was 9.8 mmol/l. In the two treatment groups, the basal-bolus insulin therapy regimen was followed by more than 99% of the randomised patients.

Primary efficacy endpoint:

Table 4: Change in the HbA1c level at 26 weeks (PP population)

Treatment group	N	Mean final HbA1c level (SD)	Mean change (SD) at week 26 compared with baseline
degludec + aspart detemir + aspart	291 144	7.29 (0.06) 7.37 (0.07)	-0.71 (0.06) -0.62 (0.07)
Estimated difference degludec *versus* detemir			Difference between the means (95% CI): **-0.08 [-0.23; 0.06]**

After 26 weeks of treatment, in the per protocol population, the difference between insulin degludec and insulin detemir in terms of the reduction in the HbA1c level was -0.08%, 95% CI [-0.23; 0.06]. Since the upper limit of the confidence interval for this difference was less than the fixed threshold (0.4%), the non-inferiority of insulin degludec with respect to insulin detemir was demonstrated.
The superiority of insulin degludec with respect to insulin detemir has not been established.
These results are found in the ITT population.

Change in HbA1c at the end of the study:
Study 3725 (extension of study 3585):

[10]Most patients (453 patients i.e. 99.5%) were exposed to the study products: only three patients were randomised but not exposed to the study products (two patients in the degludec group, one patient in the detemir group).

In both treatment groups, the mean HbA1c fell during the first 26 weeks. Thereafter, the HbA1c increased slightly until the 39th week (12th week of the extension period), then remained stable until the end of the study. After 52 weeks of treatment, the HbA1c was 7.5 ± 1.1% in the degludec group and 7.5 ± 0.9% in the insulin detemir group.

Secondary endpoints:

- confirmed night-time hypoglycaemic episodes:
Confirmed night-time hypoglycaemic episodes were reported in 58.5% of patients on degludec and 58.6% of patients on detemir. The number of night-time hypoglycaemic episodes was comparable in the two groups of treatment up to the 4th week of treatment.
At the end of treatment, a difference was reported in favour of insulin degludec (390.72 episodes per 100 patient-years n=301) compared with insulin detemir (591.59 episodes per 100 patient-years n=152), RR for insulin degludec/detemir = 0.66, 95% CI [0.49; 0.88], p<0.05).

- confirmed hypoglycaemic episodes (daytime + night-time):
No difference was observed between the 2 treatment groups.
The procedure for the analysis of secondary endpoints was therefore stopped.[11]

[11]For information, there was no difference between the two treatment groups in terms of the occurrence of severe hypoglycaemic episodes.

8.1.2 Studies In type 2 diabetes: studies 3579[12] and 3582[13]

	Study 3579	Study 3582
Primary objective of the study	To evaluate the efficacy and safety of insulin degludec compared with those of insulin glargine in patients with inadequately controlled type 2 diabetes who are already being treated with OADs (oral antidiabetics)	
Method	Open-label, non-inferiority phase III study, randomised 3 :1, versus insulin glargine, with forced titration	
	In combination with OADs	In combination with OADs + insulin aspart according to a basal/bolus regimen
Study duration:	52 weeks	
Inclusion criteria	- Patients over 18 years of age, with type 2 diabetes for more than 6 months, treated with OADs (metformin in monotherapy or in combination with a sulfonylurea or a gliptin in stable doses for at least 3 months) and naive to all insulin treatment only in study 3579 - 7.0% ≤ HbA1c ≤ 10.0% - BMI ≤ 40.0 kg/m²	
Non-inclusion criteria	- cardiovascular disease within 6 months before the study, defined as myocardial infarction; heart failure (NYHA) class III or IV; unstable angina; coronary artery bypass; angioplasty - severe, uncontrolled arterial hypertension, whether or not treated (SBP ≥ 180 mmHg and/or DBP ≥ 100 mmHg) - deterioration of hepatic function (ALAT ≥ 2.5 times the upper limit of normal) - impaired renal function (blood creatinine ≥ 180 µmol/l). - recent major hypoglycaemia (more than one severe hypoglycaemic episode within the last 12 months); hypoglycaemic coma or diabetic ketoacidosis within the last 6 months - proliferative retinopathy or maculopathy necessitating acute treatment - treatment with a GLP-1 antagonist (exenatide or liraglutide) and/or with glitazone (only rosiglitazone for study 3582) within 3 months before the study	
Treatment groups	Degludec + metformin ± gliptin versus glargine + metformin ± gliptin	Degludec + aspart (1 injection at each meal) ± metformin ± pioglitazone versus glargine + aspart ± metformin ± pioglitazone
Course of the study	On randomisation, OADs were stopped, except: - For study 3579: metformin and the gliptins. Throughout the study, no other antidiabetic could be used. - For study 3582: metformin and pioglitazone if the combination was permissible under the regulations in each participating country. During the study, the doses of metformin and pioglitazone could not be changed, except for safety reasons. Throughout the study, no other antidiabetic could be used. The dose of basal insulin (insulin degludec or insulin glargine) was adjusted by the investigator in accordance with the enclosed detailed titration algorithm.	
Primary efficacy endpoint	Mean change in the HbA1c level at 52 weeks of treatment compared with the baseline value.	
Secondary endpoints	- Number of confirmed hypoglycaemic episodes (daytime and night-time) - Change in fasting blood glucose	

[12]Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, Endahl L, Mathieu C; on behalf of the NN1250-3579. Once Long Trial: Insulin degludec, an ultra-long-acting basal insulin, compared with insulin glargine in insulin-naïve patients with type 2 diabetes in a 1-year, phase 3, randomised, parallel-group, multinational, treat-to-target trial. Once Long Trial Investigators. Diabetes Care 2012; 35: 2464-2471.

[13]Garber A, King AB, Del Prato S, Sreenan S, Rosenstock J, Endahl LA, Francisco AMO, Hollander P; on behalf of the NN1250-3582. Trial Investigators. Insulin degludec versus insulin glargine in basal-bolus therapy with mealtime insulin aspart in type 2 diabetes: a 52-week, phase 3, randomised, parallel-group, multinational, treat-to-target trial. Lancet 2012; 379: 1498–1507.

	- Number of responder patients (HbA1c < 7.0%) with no confirmed hypoglycaemic episode (severe or minor) during the last 12 weeks of treatment.
Calculation of the number of subjects required	The calculation of the number of subjects to be included was based on the following assumptions: a standard deviation of 1.3%; a single-sided significance level of 2.5%; a mean difference of 0% between the two treatments; a power of 95%; a non-inferiority threshold of 0.4%. The number of patients to be included was 984 patients in total, i.e. 738 patients for insulin degludec and 246 patients for insulin glargine.
Statistical analysis	Insulin degludec was to be regarded as not inferior to insulin glargine if the upper limit of the 95% confidence interval for the difference in the endpoint of the HbA1c level variation between the two treatments (degludec - glargine) was less than 0.4%. If non-inferiority was established, an analysis of superiority was scheduled for this endpoint (superiority established if the upper limit of the 95% confidence interval was less than 0). If non-inferiority was demonstrated for the primary endpoint, the secondary endpoints were tested using a sequential hierarchical procedure (to prepare for the risk of an increase in the significance level), in the following order: 1. Confirmed hypoglycaemic episodes: Superiority was confirmed if the 95% confidence interval for the relative risk (insulin degludec/insulin glargine) was strictly less than 1. 2. Change in fasting blood glucose at the end of the study: Superiority was confirmed if the 95% confidence interval for the difference between the two treatments (degludec - insulin glargine) was strictly less than 0. 3. Number of responder patients with no confirmed hypoglycaemic episode during the last 12 weeks of treatment: Superiority was confirmed if the 95% confidence interval for the odds ratio for degludec/glargine was strictly more than 1. When no difference was demonstrated for one of the secondary endpoints, no conclusion could be drawn from the results for the secondary endpoints that were ranked lower in the predefined hierarchical sequence.

Results of study 3579:

A total of 1030 patients were randomised: 773 patients to the insulin degludec group and 257 to the insulin glargine group.

Characteristics of patients on inclusion (Table 5)

	TRESIBA insulin degludec n=773	**LANTUS insulin glargine n=257**
Mean age (years) (SD)	59.3 (9.7)	58.7 (9.9)
Duration of diabetes (years) (SD)	9.4 (6.3)	8.6 (5.7)
Mean HbA1c (%) (SD)	8.2 (0.8)	8.2 (0.8)
Mean fasting blood glucose (mmol/l) (SD)	9.6 (2.6)	9.7 (2.6)
Mean BMI (kg/m^2) (SD)	30.9 (4.8)	31.6 (4.4)

On inclusion, the characteristics of the patients in the two treatment groups were similar: patients had a mean age of 59.1 years, a BMI of 31.1 kg/m², a duration of diabetes of 9.2 years. About 28% of the patients were more than 65 years of age. The HbA1c and fasting blood glucose levels were comparable on inclusion, with an HbA1c level of 8.2% and a fasting blood glucose level of 9.7 mmol/L.
Monotherapy with metformin was being used by 27.3% of the patients included in the degludec group and 34.2% of the patients included in the glargine group. 70.9% of the patients were receiving two OADs before inclusion in the study.[14]

Primary efficacy endpoint:

Table 6: Change in the HbA1c level at 52 weeks (PP population)

Treatment group	N	Mean final HbA1c level (SD)	Mean change (SD) at week 52 compared with baseline
Degludec + OAD Glargine + OAD	665 221	7.04 (0.04) 6.91 (0.06)	-1.14 (0.04) -1.27 (0.06)
Estimated difference degludec *versus* glargine			Difference between the means (95% CI): **0.13 [-0.01; 0.26]**

After 52 weeks of treatment, in the per protocol population, the difference between insulin degludec and insulin glargine in terms of the reduction in the HbA1c level was 0.13%, 95% CI [-0.01; 0.26]. Since the upper limit of the confidence interval for this difference was less than the fixed threshold (0.4%), the non-inferiority of insulin degludec with respect to insulin glargine was demonstrated.
The superiority of insulin degludec with respect to insulin glargine has not been established.
These results are found in the ITT population. It should be noted that the reduction in the HbA1c level was greater with insulin glargine than with insulin degludec.

It should be noted that the reduction in the HbA1c level was greatest with degludec and with glargine up to the 40th week of treatment. Thereafter, the HbA1c levels remained stable.

[14]Only metformin and the gliptins were continued during the study. No other OAD or injectable antidiabetic could be used throughout the study.

Change in HbA1c at the end of the study:
Study 3643 (extension of study 3579):
There was no difference between the two treatment groups.

Secondary endpoints:

- confirmed hypoglycaemic episodes:
No difference was observed between the two treatment groups.
The procedure for the analysis of secondary endpoints was therefore stopped.[15]

Results of study 3582:

A total of 1006 patients were randomised: 755 patients to the insulin degludec group and 251 to the insulin glargine group.[16]

Characteristics of patients on inclusion (Table 7)

	TRESIBA insulin degludec n=755	**LANTUS insulin glargine n=251**
Mean age (years) (SD)	59.2 (9.1)	58.1 (10.0)
Duration of diabetes (years) (SD)	13.6 (7.4)	13.4 (6.9)
Mean HbA1c (%) (SD)	8.3 (0.8)	8.4 (0.9)
Mean fasting blood glucose (mmol/l) (SD)	9.2 (3.0)	9.2 (3.2)
Mean BMI (kg/m^2) (SD)	32.3 (4.7)	31.9 (4.5)

On inclusion, the characteristics of the patients in the two treatment groups were similar: patients had a mean age of 58.9 years, a BMI of 32.2 kg/m², a duration of diabetes of 13.5 years. On inclusion, patients on average had an HbA1c level of 8.3 ± 0.8% and fasting blood glucose of 9.2 ± 3.1 mmol/l.

Before inclusion in the study, the basal/bolus ± OAD regimen was most common (49% of patients), followed by regimens using premix insulins ± OAD (24.4% of patients) then basal insulin ± OAD (21.2%).[17]
Of the basal insulins used before randomisation, the commonest used was insulin glargine (42.7%) followed by insulin detemir (16.1%). For prandial insulins, the most commonly used was insulin aspart (28.8%) followed by insulin lispro (12.2%).
As regards OADs, before randomisation, those most commonly prescribed were metformin (58.2% of patients in the degludec group, 60.9% of patients in the glargine group), and sulfonylureas (15.7% of patients on degludec and 14.1% of patients on glargine).[18]

[15]For information, a post-hoc analysis that could not be accepted by the Committee was made of the endpoint severe hypoglycaemic episodes.
[16]Only two patients in the degludec group were randomised but not exposed to the product.
[17]Since randomisation was stratified according to the different insulin therapy regimens, the different regimens were represented in equivalent manner in the two treatment groups.
[18]The use of other OADs (alpha-glucosidase inhibitors, glinides, glitazones, gliptins) was low, of the order of 0.4 to 4.8% of all patients included in the study.

Primary efficacy endpoint:

Table 8: Change in the HbA1c level at 52 weeks (PP population)

Treatment group	N	Mean final HbA1c level (SD)	Mean change (SD) at week 52 compared with baseline
Degludec + aspart + OAD Glargine + aspart + OAD	694 233	7.11 (0.06) 7.06 (0.08)	-1.18 (0.06) -1.22 (0.08)
Estimated difference degludec *versus* glargine			Difference between the means (95% CI): **0.05 [-0.08; 0.18]**

After 52 weeks of treatment, in the per protocol population, the difference between insulin degludec and insulin glargine in terms of the reduction in the HbA1c level was 0.05%, 95% CI [-0.08; 0.18]. Since the upper limit of the confidence interval for this difference was less than the fixed threshold (0.4%), the non-inferiority of insulin degludec with respect to insulin glargine was demonstrated.
The superiority of insulin degludec with respect to insulin detemir has not been established.
These results are found in the ITT population. It should be noted that the reduction in the HbA1c level was slightly larger with insulin glargine than with insulin degludec.

It should be noted that the reduction in the HbA1c level was greatest with degludec and with glargine up to the 26th week of treatment. Thereafter, the HbA1c levels rise.

Change in HbA1c at the end of the study:
Study 3667 (extension of study 3582):
The HbA1c level remained stable during the extension phase. After 78 weeks of treatment, the HbA1c was 7.3 ± 1.1% in the degludec group and 7.2 ± 1.0% in the insulin glargine group.

Secondary endpoints:

- confirmed hypoglycaemic episodes (daytime + night-time):
The percentage of patients with confirmed hypoglycaemic episodes was 80.9% in the degludec group and 82.1% in the glargine group. Thus, at the end of treatment, a difference was reported in favour of insulin degludec (728.90 episodes per 100 patient-years) compared with insulin glargine (886.07 episodes per 100 patient-years), RR = 0.82, 95% CI [0.69; 0.99]).

- Change in fasting blood glucose after 52 weeks of treatment:
No difference was observed between the two treatment groups.
The procedure for the analysis of secondary endpoints was therefore stopped.

08.2. Safety/Adverse effects

8.2.1 Data from all studies in type 1 and type 2 diabetics

Adverse events were observed in 3018/4275 patients (70.6%) in the insulin degludec group and 1530/2269 patients (67.4%) in the comparator groups. These events were serious in 7.9% of the patients in the degludec group and 6.5% of the patients in the comparator groups. They were regarded as linked to treatment in 646 patients on degludec (15.1%) and 305 on the comparators (13.4%).
These events led to the discontinuation of treatment in 2.3% of the patients on degludec and 1.3% of patients on the comparators.
In terms of events, the main ones were nasopharyngitis (15% of patients on insulin degludec, 12.3% of patients on comparators), headaches on account of hypoglycaemia (9.5% of patients on insulin degludec, 7.5% of patients on comparators), upper airway infections (8.7% of patients on insulin degludec, 7.7% of patients on comparators), gastrointestinal complaints, mainly diarrhoea (in 5.7% of patients on insulin degludec, 6.7% of the patients on comparators).

In type 1 diabetic patients, adverse events were observed in 77.3% of patients on insulin degludec (852/1102) and 76.2% of patients on comparators (356/467). These events were linked to the treatment for 21.2% of patients in the degludec group and 17.1% of patients in the comparator groups and led to the discontinuation of treatment in 24 patients on degludec and 4 on comparators.

In type 2 diabetic patients, adverse events were observed in 68.3% of patients on insulin degludec (2166/3173) and 65.1% of patients on comparators (1174/1802). These events were linked to the treatment for 13.0% of patients in the degludec group and 12.5% of patients in the comparator groups and led to the discontinuation of treatment in 74 patients on degludec and 26 on comparators.
Serious adverse events affected, all patients combined (type 1 and 2 diabetics), 7.9% of patients on degludec (337/4275) and 6.5% of patients on comparators (147/2269). The commonest serious adverse event was hypoglycaemia in the two groups.

Adverse events of specific interest:
Neoplasia:
Neoplasia were analysed on the basis of all the studies carried out for Tresiba and for Ryzodeg *(mixture of insulin aspart/insulin degludec, not affected by the present application)*. The cases of neoplasia identified were reviewed and classified, blind, by an independent committee (45 malignant, 128 benign, 25 unclassifiable).
The number of malignant neoplasia reported in the Tresiba/Ryzodeg group was small and similar to that observed in the comparator groups (0.9 events/100 patient-years versus 0.8 events/100 patient-years respectively).
The most commonly reported malignant neoplasia were:
- cutaneous neoplasia (n=13), mainly basal cell carcinomas or squamous cell carcinomas, of which 11 with insulin degludec. Most of the events (n=9) were diagnosed within 3 months after the start of the study. In five cases of the Tresiba/Ryzodeg group, the cutaneous lesion was present before the initiation of treatment and/or the patient had a history of skin cancer.
- Gastrointestinal neoplasia (n=11), of which 8 with degludec; 7 were colon cancers in type 2 diabetic patients, most of them obese. One case was diagnosed just after the initiation of treatment. The other cases were diagnosed within 6-7 months after the initiation of treatment.
- breast cancers (n=5), neoplasia of the thyroid (n=4) and the bladder (n=3).
The cutaneous, gastrointestinal and breast neoplasia were more common in the Tresiba/Ryzodeg group. The neoplasia of the thyroid and the bladder were most common in the comparator group.

Retinopathy:
The retinopathy rates were comparable in the two groups (5.1 events per 100 patient-years in the degludec group and 5.6 events per 100 patient-years in the comparator group). In type 1 diabetic

patients, the rate of events in the degludec group was higher than in the comparator group (6.2 versus 4.4 events per 100 patient-years), but in type 2 diabetic patients the rate of events in the degludec group was lower than in the comparator group (4.7 versus 5.9 events per 100 patient-years). No difference was reported between the groups in terms of the time to the occurrence of the event or the duration of the event. Most of the cases occurred after 6 months of treatment. The event had not resolved in 71% of subjects in the degludec group and 80% of those in the comparator group after the end of the studies.

Antibodies:
The administration of insulin may induce the formation of antibodies. In rare cases, the presence of anti-insulin antibodies may necessitate an adjustment in the insulin dose so as to correct any tendency to hyperglycaemia or hypoglycaemia.
The mean level of crossed antibodies was low on inclusion in all the studies. Overall, the specific antibodies of insulin degludec, insulin glargine and insulin aspart remained at very low and comparable levels throughout the studies.

Weight changes:
Weight gain was:

- in the overall population, 2.0 kg with degludec (n=3746) and 1.4 kg with comparators (n=1998) after 26 weeks of treatment and 2.7 kg with degludec (n=1991) and comparators (n=662) after 52 weeks of treatment
- in the population of type 1 diabetics, 1.5 kg with degludec (n=985) and 1.3 kg with comparators (n=429) after 26 weeks of treatment and 1.8 kg with degludec (n=472) and 1.6 kg with comparators (n=154) after 52 weeks of treatment
- in the population of type 2 diabetics, 2.1 kg with degludec (n=2761) and 1.5 kg with comparators (n=1569) after 26 weeks of treatment and 3.0 kg with degludec (n=1519) and with comparators (n=508) after 52 weeks of treatment

8.2.2 Data from long-term extension phases

The main objective of these extension phases was to evaluate the long-term safety of insulin degludec.

Summary of the results of extension studies in type 1 diabetes:
Study 3644 (52-week extension of study 3583):
A total of 629 patients were randomised in the main study (3583): 472 patients in the degludec group and 157 in the insulin glargine group. A total of 469 patients were recruited to the extension study: 351 (74.4%) in the degludec group and 118 (75.2%) in the insulin glargine group. The number of patients who did not complete the follow-on study was 21 (of which 3 on account of adverse events, and 5 dropped out) in the degludec group and 5 patients (of which 2 on account of adverse events), in the insulin glargine group.

No difference was observed between the two groups in terms of confirmed hypoglycaemic episodes and severe hypoglycaemic episodes.
Confirmed night-time hypoglycaemic episodes were reported in 77.5% of patients in the degludec group and 79.2% of the patients in the insulin glargine group. The number of night-time hypoglycaemic episodes was comparable in the two treatment groups up to the 6th week of treatment. There were 381.42 events/100 patient-years in the degludec group (n=472) and 508.49 events/100 patient-years in the glargine group (n=154), so RR=0.75 95% CI [0.59; 0.95].

Study 3725 (26-week extension of study 3585):
Three hundred and seventy patients were recruited to the extension study: 248 (81.8%) in the degludec group and 122 (79.7%) in the insulin detemir group. A total of 13 patients (6 on degludec, 7 on detemir) dropped out of the study, 1 from each group, on account of an adverse event.

No difference was observed between the two groups in terms of confirmed hypoglycaemic episodes and severe hypoglycaemic episodes.
Confirmed night-time hypoglycaemic episodes were reported in 68.1% of patients in the degludec group and 64.5% of the patients in the insulin detemir group. The number of confirmed night-time hypoglycaemic episodes was comparable in the two treatment groups up to the 4th week of treatment. There were 333.0 events/100 patient-years in the degludec group (n=301) and 497.06 events/100 patient-years in the detemir group (n=152), so RR=0.67 95% CI [0.51; 0.88].

Summary of the results of extension studies in type 2 diabetes:
Study 3643 (52-week extension of study 3579):
A total of 1030 patients were randomised in the main study. Of these patients, 725 were recruited to the extension study: 551 patients in the insulin degludec group and 174 in the insulin glargine group. Of these patients, 659 completed the extension phase, with 505 patients in the degludec group and 154 patients in the insulin glargine group. Twelve patients on degludec, 5 on glargine dropped out on account of adverse events.

No difference was observed between the two groups in terms of confirmed hypoglycaemic episodes.
The percentage of patients with confirmed night-time hypoglycaemic episodes during the 104 weeks was 20.6% in the degludec group and 23.7% in the insulin glargine group. The relative risk for degludec/glargine of the onset of night-time hypoglycaemic episodes was 0.57 95% CI [0.40; 0.81].
The percentage of patients who had severe hypoglycaemic episodes was small in the two groups during the 104 weeks: 0.8% in the degludec group and 2.7% in the insulin glargine group. The relative risk for degludec/glargine was 0.305 95% CI [0.110; 0.849].

Study 3667 (52-week extension of study 3582):
A total of 1006 patients were randomised in the main study. Of these patients, 757 were recruited to the extension study: 566 patients to the insulin degludec group and 191 in the insulin glargine group. Of these patients, 722 completed the extension phase, with 539 patients in the degludec group and 183 patients in the insulin glargine group. Only 4 patients on degludec dropped out on account of adverse events.

No difference was reported between the two groups in terms of confirmed hypoglycaemic episodes, confirmed night-time hypoglycaemic episodes or severe hypoglycaemic episodes.

8.2.3 SPC data

“The most frequently reported adverse reaction during treatment is hypoglycaemia.
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitations.
[…]
With insulin preparations, allergic reactions may occur. Immediate-type allergic reactions to either insulin itself or the excipients may potentially be life-threatening.
With TRESIBA, hypersensitivity (manifested with swelling of tongue and lips, diarrhoea, nausea, tiredness and itching) and urticaria were reported rarely.

Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

Injection site reactions (including injection site haematoma, pain, haemorrhage, erythema, nodules, swelling, discolouration, pruritus, warmth and injection site mass) occurred in patients treated with TRESIBA. These reactions are usually mild and transitory and they normally disappear during continued treatment."

8.2.4 Prespecified meta-analysis of hypoglycaemic events[19]

The studies used for this meta-analysis were all studies scheduled by the development plan and had insulin glargine in the comparator group.[20]

The main aim of this meta-analysis was to compare the effect of insulin degludec in relation to insulin glargine on the occurrence of confirmed hypoglycaemic episodes.
The primary efficacy endpoint was the number of confirmed hypoglycaemic episodes.
The secondary endpoints were the number of confirmed night-time hypoglycaemic episodes, the number of severe hypoglycaemic episodes, the number of confirmed hypoglycaemic episodes and the number of confirmed night-time hypoglycaemic episodes in patients over 65 years of age (this subgroup contained only 20% of the patients, so its results will not be presented).

The statistical analysis was carried out with a hierarchical test to avoid inflation of the significance level because of the wide variety of tests. A selection bias in the studies cannot be ruled out. No heterogeneity test was carried out, so the results must be interpreted with caution.[21]

A total of 4330 patients were included (2899 in the degludec group, 1431 in the glargine groups). These were patients aged 55.1 ± 12.2 years; of these, 3426 patients (79.1%) were aged ≤ 65 years. The mean BMI was 29.7 ± 5.2 kg/m² and the duration of diabetes was 12.6 ± 9.0 years, with an HbA1c level of 8.2 ± 0.9% and a fasting blood glucose level of 9.3 ± 3.1 mmol/l. The percentage of patients with type 1 diabetes was 22% (i.e. 952 patients).

The relative risk of the occurrence of confirmed hypoglycaemic episodes (primary efficacy endpoint) on degludec compared with insulin glargine was 0.91 95% CI [0.83; 0.99]. There were 829.4 events per 100 patient-years in the degludec group (n=2886) and 914.1 events in the glargine group (n=1421).
In the subpopulation of type 1 diabetic patients, no difference was observed. In the subpopulation of type 2 diabetic patients, this relative risk is 0.84 95% CI [0.76; 0.93]. There were 6346 events per 100 patient-years on degludec (n=637) and 5719 on glargine (n=316).

As regards the secondary endpoints:
- there were 100.7 confirmed night-time hypoglycaemic events in the degludec group (n=2866) and 135.2 in the glargine group (n=1421), i.e. an RR for degludec/glargine of 0.74 95% CI [0.65; 0.85]
- no difference in severe hypoglycaemic episodes was reported.

Post-hoc analyses were carried out at the request of the FDA; they cannot be taken into account by HAS.

[19]Ratner RE, Gough SC, Mathieu C, Del Prato S, Bode B, Mersebach H, Endahl L, Zinman B. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. Diabetes Obes Metab. 2013 ;15:175-84.
[20]Hypoglycaemic episodes reported in the extension phases of the studies were not included because these extension studies were still in progress when the database was frozen.
[21]The influence of potential heterogeneity was assessed in a sensitivity analysis which assessed the interaction of treatment in studies as a random effect. There are differences between the populations included according to the type of diabetes.

8.2.5 Meta-analysis of cardiovascular events

The cardiovascular safety of insulin degludec was assessed on the basis of a predefined meta-analysis of major cardiovascular events.
This meta-analysis was based on the data from 16 studies from the clinical development programmes for Tresiba and Ryzodeg. The analysis population comprised 8941 patients, 5631 exposed to treatment with Tresiba or Ryzodeg and 3306 patients exposed to the comparator(s).
No difference was observed between the degludec group and the comparator group(s) in terms of cardiovascular events (cardiac and vascular disorders).

At the request of the CHMP [Committee for Medicinal Products for Human Use], a new analysis was made on the basis of new data available on 1 May 2012. That new analysis included nine additional studies: six extension studies (five for TRESIBA and one for RYZODEG), one phase IIIa study for RYZODEG in Japanese patients and two new phase IIIb studies for TRESIBA. These new data included 742 additional patients treated with degludec and 149 additional patients in the comparator groups.

The main aim of the meta-analysis was to define the cardiovascular profile of insulin degludec in terms of the occurrence of major cardiovascular events by comparison with the other comparators used in trials in the phase III clinical development plan.
These studies evaluated different populations at different stages in their management. In the absence of a heterogeneity test, the results of this meta-analysis must be interpreted with caution, since no formal conclusion can be drawn from it.

The primary efficacy endpoint was the time to the occurrence (number of days) of the first major cardiovascular event (MACE) defined as acute coronary syndromes, including unstable angina, myocardial infarctions with ST segment elevation, myocardial infarctions without ST segment elevation, strokes and deaths of cardiovascular origin.[22]
It was planned to carry out sensitivity analyses with stratification by type of diabetes, treatment, sex and taking age as a co-variable.

Main results:
A total of 8959 patients were included (5647 in the TRESIBA/RYZODEG group, 3312 in the comparator groups).
The patients were aged 54.3 ± 12.7 years, of which 7152 patients (79.8%) were aged ≤ 65 years. The mean BMI was 29.3 ± 5.3 kg/m² and the duration of diabetes was 12.3 ± 8.8 years, with an HbA1c level of 8.3 ± 0.9% and a fasting blood glucose level of 9.3 ± 3.2 mmol/L. The number of patients with type 1 diabetes was 2125 patients, i.e. 23.7%. In addition, 18.8% of patients with type 2 diabetes and 5.5% of patients with type 1 diabetes had a history of cardiovascular disease (ischaemic stroke, myocardial infarction, haemorrhagic stroke, other ischaemic heart disease).

As regards the overall incidence of major cardiovascular events, 83 events were reported in 80 of the 8959 patients. Fifty three patients reported at least one event in the degludec group, i.e. 1.48 events per 100 patient-years. In the comparator group, 27 patients were reported as having at least one major cardiovascular event, i.e. 1.44 events per 100 patient-years.
Fifty type 2 diabetic patients on insulin degludec and 26 on comparators reported at least one major cardiovascular event. Four type 1 diabetic patients, 3 of them on degludec, reported at least one event.

[22] All cardiovascular events of interest or suspected cardiovascular events collected during clinical studies were reassessed by an independent assessment committee so as to validate their inclusion in the meta-analysis. The definitions of the events and the procedures for adjudication on the events were referred up to the FDA.

In both groups, most of the major cardiovascular events reported were acute coronary syndromes.
The incidence of events per 100 patient-years was greater in type 2 diabetes patients (1.96 in the degludec group and 1.81 in the comparator group) than in the patients with type 1 diabetes (0.29 in the degludec group and 0.23 in the comparator group).

No difference was reported between the two groups as regards the time to the occurrence of the first major cardiovascular event. The analysis according to type of diabetes did not show any difference between the two treatment groups. The various sensitivity analyses carried out confirmed these results.
Post-hoc analyses were carried out at the request of the FDA. These analyses will not be described in detail for methodological reasons. However, it should be remembered that the FDA has not validated the Marketing Authorisation for TRESIBA because of doubts about the cardiovascular safety of insulin degludec.

09 SUMMARY & DISCUSSION

1/ Efficacy
In type 1 diabetes
The efficacy of insulin degludec was evaluated in two randomised, open-label, non-inferiority studies versus insulin glargine (study 3583 which included 629 patients) and versus insulin detemir (study 3585 which included 455 patients), administered by forced titration in accordance with a basal/bolus increasing-dose regimen in combination with insulin aspart.
In study 3583, on inclusion the patients were overweight, had a mean age of 43 years and an HbA1c level of 7.7%, i.e. an HbA1c level poor enough to justify intensive insulin therapy. After 52 weeks of treatment in the per-protocol population, the non-inferiority of insulin degludec by comparison with insulin glargine was demonstrated, but not its superiority in the primary efficacy endpoint, the change in the HbA1c level.
In study 3585, the mean age of the patients was 41.3 years and the mean HbA1c level was 8.0%. After 26 weeks of treatment in the per-protocol population, the non-inferiority of insulin degludec by comparison with insulin detemir was demonstrated in terms of the change in the HbA1c level, but not its superiority.

At 26 weeks, the reduction in the HbA1c level was greater than at 52 weeks but these reductions are small, <1%, lying between 0.4% and 0.6%.
These studies included a small number of patients.

In type 2 diabetes
The efficacy of insulin degludec was evaluated in two randomised, open-label, non-inferiority studies lasting 52 weeks, versus insulin glargine, with forced titration, in patients who were inadequately controlled with OADs and naive to any insulin treatment.
In study 3579 in which insulin therapy was initiated, the patients included (1030) were obese, had a mean age of 59.1 years, with an HbA1c level of 8.2%, and were in most cases (70%) receiving OAD treatment consisting of metformin either with or without a gliptin.
In study 3582 which included 1006 patients, aged about 59 years and obese, with an HbA1c level of 8.3%, insulin therapy was in most cases administered in a basal/bolus regimen, combined or not combined with OADs (metformin + sulfonylurea).
After 52 weeks of treatment in the per-protocol population, the non-inferiority of insulin degludec by comparison with insulin glargine was demonstrated in the two studies in terms of the change in the HbA1c level. The superiority of insulin degludec in relation to insulin glargine has not been established.
The reduction in the HbA1c level was greater with glargine than with degludec.

There is no responder rate and thus no response to the treatment objectives.
The relevance of the treatment strategy used in study 3579 is debatable. Firstly, the metformin/gliptin/insulin triple therapy used in this study was not mentioned in the good practice

guidelines updated by HAS in January 2013 on glycaemic control in type 2 diabetes; secondly, gliptins must be stopped when insulin therapy is initiated. Finally, only 60% of patients were on metformin, and yet that is the OAD of reference. Also, in this study the patients were naive to any insulin treatment, whereas usually an increasing-dose regimen is put in place if the glycaemic aims have not been achieved despite prior insulin therapy.

None of the studies (in type 1 and type 2 diabetics) included patients at cardiovascular risk or those who had previously had major hypoglycaemic episodes whereas, with intensive insulin therapy, hypoglycaemic episodes are increased.

2/ Adverse effects

In all the studies carried out in type 1 and type 2 diabetics, adverse events were observed in 3018/4275 patients (70.6%) in the insulin degludec group and 1530/2269 patients (67.4%) in the comparator groups. They were regarded as linked to treatment in 646 patients on degludec (15.1%) and 305 on the comparators (13.4%). These events led to the discontinuation of treatment in 2.3% of the patients on degludec and 1.3% of patients on comparators. The main adverse events were nasopharyngitis, headaches linked to hypoglycaemia, upper airways infections and gastrointestinal disorders, mainly diarrhoea.

In the phase III studies at 26 and 52 weeks, the secondary endpoints linked to the evaluation of the occurrence of hypoglycaemia were analysed rigorously (using a hierarchical sequential procedure limiting the overestimation of effect). Their results can therefore be taken into account.

In type 1 diabetics, a difference in terms of night-time hypoglycaemic episodes was reported in favour of insulin degludec by comparison with insulin glargine at 52 and 104 weeks (study 3583 and its extension phase) of treatment and by comparison with insulin detemir at 26 and 52 weeks (study 3585 and its follow-up).

On the other hand, no difference was observed in the occurrence of confirmed hypoglycaemic episodes (both minor and severe, and daytime and night-time) and severe hypoglycaemic episodes in each of the studies and their extension phases.

In type 2 diabetic patients in study 3579, there was no difference in confirmed hypoglycaemic episodes at 52 and 104 weeks between insulin degludec and insulin glargine. In study 3582, a difference was observed in this endpoint at 52 weeks in favour of insulin degludec but not at 104 weeks.

At 104 weeks, in the insulin therapy initiation study (3579), a difference was observed in favour of insulin degludec in terms of severe and night-time hypoglycaemic episodes. In the dose intensification study, there was no difference.

Overall, with equivalent glycaemic control,

- the short-term results, despite being evaluated using proper methods, do not allow any conclusion to be drawn on the advantage of one insulin over another in terms of the risk of occurrence of hypoglycaemic episodes, since the differences in absolute terms between the treatments are very small
- the long-term results must be interpreted with caution, given the multiple tests carried out when analysing the different hypoglycaemic episodes.

A prospective meta-analysis provided for in the clinical development plan for insulin degludec had the aim of comparing insulin degludec with insulin glargine in terms of the occurrence of confirmed hypoglycaemic episodes (primary efficacy endpoint). Its results must be interpreted with caution because of methodological bias. It analysed 4330 patients with a mean age of 55 years who were overweight, with an HbA1c level of 8.2%, most of whom had type 2 diabetes. A difference in favour of insulin degludec was observed by comparison with glargine in the primary efficacy endpoint in the overall population of diabetics. This same result is found only in the population of type 2 diabetics. As regards the (exploratory) secondary endpoints, a difference was observed in the night-time hypoglycaemic episodes. There was no difference in the severe episodes.

The level of evidence of the insubstantial proof does not allow any conclusion to be drawn about the possible clinical relevance of the risk reductions observed.

In a meta-analysis of cardiovascular safety in terms of the occurrence of major cardiovascular events with insulin degludec by comparison with the comparators used in all the studies, no difference was reported between the treatment groups in terms of the time of occurrence of the 1st major event (primary efficacy endpoint). No conclusion can be drawn from this result which must be interpreted with caution in view of the methodological bias inherent in this meta-analysis and the increase in major cardiovascular events on insulin degludec shown in post-hoc analyses carried out by the FDA. Consequently, the FDA asked for a study to be carried out specifically to evaluate cardiovascular safety.
There are no long-term data on microvascular and macrovascular complications, nor any data on quality of life.

010 PLANNED STUDIES

The risk management plan contains mainly follow-up measures on:
- certain adverse events such as: hypoglycaemic episodes, allergic reactions, medication errors confusing basal and bolus insulins and the different concentrations of TRESIBA (100 U/ml and 200 U/ml[23]), and the formation of neutralising antibodies.
- certain special populations: pregnant or lactating women, children and adolescents < 18 years, patients with hepatic impairment, patients with moderate to severe renal impairment, elderly patients (>75 years), and patients receiving GLP-1 inhibitors.

Among the studies currently in progress, one study is evaluating the efficacy (in terms of the change in the HbA1c level) and safety (hypoglycaemic episodes) of the addition of liraglutide or insulin aspart to TRESIBA, after 26 weeks of treatment, in type 2 diabetic patients treated with metformin.

011 THE MEDICINE'S THERAPEUTIC USE

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

When initiating insulin treatment in type 2 diabetes, the glycaemic objective should take into account the benefit and potential risks of intensification, particularly in the elderly and/or patients with comorbidities, especially cardiovascular and renal ones.
The current guidelines no longer systematically favour intensified insulin regimens.
TRESIBA, like other long-acting analogues, can be used:

- when initiating insulin therapy, as basal insulin (in combination with one or more oral antidiabetics). According to the recent HAS guideline, it is advisable to start, for preference, 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 considered if the risk of severe night-time hypoglycaemic episodes is worrying.
- when initiating an intensified insulin regimen, as basal insulin in a basal-bolus regimen (in combination with an insulin or a rapid-acting or an ultra-rapid-acting analogue).[24]

Where administration at the same time of the day is not possible, TRESIBA allows for flexibility in the timing of insulin administration (see section 5.1 of the SPC).

[23]For information, the 200 U/ml formulation is not affected by this application for inclusion.
[24]When intensification of treatment is necessary in order to achieve the HbA1c objective.

012 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

012.1. Actual Benefit

◗ Diabetes (type 1 and type 2) is a chronic disease with potentially serious complications, especially cardiovascular ones.
TRESIBA would be used in the context of treatment for hyperglycaemia.
◗ It is intended as curative treatment.
The efficacy/adverse effects ratio for this medicinal product is high. However, the long-term risks are poorly defined, particularly in relation to cardiovascular adverse events.
◗ Alternative medicinal products exist.

◗ *Public health benefit:*
The public health burden of insulin-treated diabetes is substantial.
Improving the therapeutic management of diabetics is a public health need.
On the basis of the available data, both for type 1 and for type 2 diabetes, TRESIBA has no additional impact on glycaemic equilibrium than the comparators. Compared with insulin glargine and insulin detemir, TRESIBA is not expected to have any additional impact on the occurrence of hypoglycaemic episodes, particularly night-time ones. TRESIBA has no additional impact on morbidity and mortality, particularly cardiovascular. The impact which TRESIBA could be expected to have on treated patients' quality of life cannot be quantified, in the absence of any data. A small impact might be expected on the organisation of healthcare through the reduction in the number of cases of self-monitoring but, in the absence of any data, that impact cannot be quantified.
The transferability of the data to current practice is questionable because of the exclusion of patients with cardiovascular problems from the studies presented.
Therefore TRESIBA provides only a partial response to the identified public health need.
Overall, it is not expected that TRESIBA will benefit public health in the treatment of diabetes in adults.

Consequently, the Committee considers that the actual benefit of TRESIBA is substantial in the treatment of diabetes in adults.

012.2. Improvement in actual benefit (IAB)

In view of:
- the glycaemic control achieved with TRESIBA (insulin degludec) which is comparable to that observed with insulin glargine (LANTUS) in type 1 and type 2 diabetes and insulin detemir (LEVEMIR) in type 1 diabetes,
- the difficulty in assessing the clinical relevance of any advantage in terms of the reduction in the occurrence of hypoglycaemic episodes, particularly at night in view of the very small differences observed by comparison with other long-acting analogues, despite the use of rigorous methods of assessment,
- the failure to demonstrate any impact in terms of morbidity and mortality, particularly cardiovascular,
- the absence of any robust data that allow the preferential recommendation of one long-acting insulin analogue,

the Committee considers that TRESIBA does not provide any improvement in actual benefit (level V, nonexistent) in the management, with long-acting insulin analogues (LANTUS and LEVEMIR), of adult patients with type 1 or type 2 diabetes.

013 TARGET POPULATION

Definition:
The patients eligible for insulin therapy are:

- all patients with type 1 diabetes (T1D);
- some patients with type 2 diabetes (T2D), mainly those with failure of triple oral therapy (metformin + sulfonylurea + other AOD) and those with failure of dual oral therapy (metformin + sulfonylurea) with a deviation from the glycaemic objective ≥ 1% HbA1c.

The target population consists of all diabetic patients already treated with insulin (T1D and T2D patients) and T2D patients treated with OADs alone, who are uncontrolled and eligible for insulin therapy.
The hypotheses used are:

- 70% of T2D patients treated with OADs alone, who are uncontrolled with an HbA1c ≥ 8% are eligible for insulin therapy (sensitivity analysis: lower limit 0%; upper limit 95%);
- 10% of T2D patients treated with OADs alone, who are uncontrolled, with 7% ≥ HbA1c < 8% are eligible for insulin therapy (sensitivity analysis: lower limit 0%; upper limit 25%).

On the basis of recent epidemiological data (French population,[25] percentage of diabetic patients treated,[26] percentages of T1D and T2D patients treated,[26] percentages of T2D patients treated with OAD alone who are well controlled, treated with OAD alone and not controlled, and already treated with insulin),[27] the number of diabetic patients treated in France can be estimated at 2,886,196, of which 141,424 T1D patients treated with insulin and 2,741,700 T2D patients treated.
Among the T2D patients, 1,724,202 are treated with OAD alone and well controlled, 537,700 are treated with OADs alone, but are uncontrolled, and 479,798 are already being treated with insulin. Among the T2D patients treated with OAD alone who are uncontrolled, 157,707 with an HbA1c ≥ 8% are eligible for insulin therapy and 31,240 with an HbA1c level ≥ 7% and < 8% are eligible for insulin therapy.

Overall, the target population of TRESIBA can be estimated at about 810,000 diabetic patients (T1D and T2D), i.e. a total of 620,000 diabetic patients already treated with insulin (of which 140,000 T1D patients and 480,000 T2D patients) and 190,000 T2D patients treated with OAD alone, who are not controlled and are eligible for insulin therapy, with a plausibility interval between 620,000 patients (lower limit) and 915,000 patients (upper limit).

014 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the indication "treatment of diabetes mellitus in adults" and at the dosage in the Marketing Authorisation.

Proposed reimbursement rate: 65%

Packaging
Appropriate for the prescribing conditions.

[25] INSEE (Institut National de la Statistique et des Études Économiques [National Institute of Statistics and Economic Studies]). French population in 2011 (metropolitan France, 1 January 2012).
[26] Health insurance. Database of the EGB (representative sample of individuals covered by national health insurance) 2011.
[27] Cegedim Strategic Data. LPD database (Longitudinal Patient Databases) 2011.

APPENDIX

Titration algorithm for basal insulin (insulin degludec or insulin glargine or insulin detemir) common to all studies

Fasting blood glucose (mean of last three days)	Adjustment to the dose of basal insulin (TRESIBA or insulin glargine)
< 3.1 mmol/l (56 mg/dl)	- 4 U (for a dose > 45 U, dose reduction of 10%)
< 3.9 mmol/l (70 mg/dl)	- 2 U (for a dose > 45 U, dose reduction of 5%)
< 5 mmol/l (90 mg/dl)	No adjustment
< 7 mmol/l (126 mg/dl)	+ 2 U
< 8 mmol/l (144 mg/dl)	+ 4 U
< 9 mmol/l (162 mg/dl)	+ 6 U
≥ 9 mmol/l (162 mg/dl)	+ 8 U

Titration algorithm for insulin aspart during the study:

Insulin aspart was to be injected just before the three main meals (breakfast, lunch, dinner) and titrated according the preprandial blood glucose levels measured just before lunch, just before dinner and on going to bed.

On randomisation, the switch from the earlier rapid-acting insulin to insulin aspart was made dose for dose.

After 8 weeks, it was expected that the dose of basal insulin should be optimised. At this time, the investigator could then decide whether the dose of rapid-acting insulin should be optimised according to the following algorithm:

Preprandial blood glucose level (mean of the last three days)	Adjustment in the dose of rapid-acting insulin (insulin aspart)
< 5 mmol/l (90 mg/dl)	No adjustment
< 8 mmol/l (144 mg/dl)	+ 2 U
< 10 mmol/l (180 mg/dl)	+ 3 U
≥ 15 mmol/l (180 mg/dl)	+ 4 U

Initiation of a second dose of insulin detemir (study 3585 only):

In the event of inadequate blood glucose control at visit 10 (i.e. after 8 weeks of treatment and dose optimisation), the investigator could consider adding a second dose of insulin detemir only if all three of the following criteria were met:

- Lack of improvement in glycaemic control (for subjects with an HbA1c level <8.0% on inclusion: a deterioration in HbA1c and for subjects with an HbA1c level between 8.0% and 10% on inclusion : an improvement in HbA1c <0.5%);
- Mean preprandial blood glucose level before dinner > 6.0 mmol/l (108 mg/dl);
- No treatable disease causing hyperglycaemia diagnosed.

The starting dose for the second dose of insulin detemir was to be 4 U, administered before breakfast. If one morning dose was initiated, it was important to monitor the fasting blood glucose level and adjust it accordingly in the evening. The increase in the morning dose of insulin detemir was based on the mean of the preprandial blood glucose level measured just before dinner in the preceding 3 days, using the following titration algorithm.

Preprandial blood glucose level (pre-dinner)	Adjustment of the dose of insulin detemir
< 5 mmol/l (90 mg/dl)	No adjustment
< 10 mmol/l (180 mg/dl)	+ 2 U
< 15 mmol/l (270 mg/dl)	+ 4 U
≥ 15 mmol/l (270 mg/dl)	+ 6 U

Definition of hypoglycaemic episodes used in all studies:

- minor episodes were symptomatic episodes with a blood glucose measurement of < 3.1 mmol/l (56 mg/dl) not requiring the assistance of a third party for the administration of carbohydrate, glucagon or any other resuscitation action, or any asymptomatic episode with a blood glucose measurement of < 3.1 mmol/l (56 mg/dl);
- severe episodes are symptomatic episodes necessitating the assistance of a third party because of a severe disorder of consciousness or behaviour, with a blood glucose level of < 3.1 mmol/l and rapid recovery after administration of glucose or glucagon**;**
- night-time episodes were those occurring between 0:00 and 5:59 in the morning;
- confirmed hypoglycaemic episodes were minor episodes and severe episodes.