TRANSARENCY COMMITTEE

Opinion

21 January 2009

Review of the dossier of the drugs included on the list of reimbursable products for a period of 5 years by the order of 8 July 2003 (OJ of 26 July 2003)

LANTUS 100 units/ml, solution for injection in vial
1 10-ml glass vial – CIP: 359 464-9

LANTUS 100 units/ml, solution for injection in cartridge
5 3-ml glass cartridges (for Optipen Pro pen) – CIP: 354 632-0
5 3-ml glass cartridges for OptiClick (reusable pen) – CIP: 365 149-4 (joint renewal)

LANTUS 100 units/ml, solution for injection in prefilled pens
5 3-ml glass cartridges in Optiset prefilled disposable pen – CIP: 356 519-7
5 3-ml glass cartridges in SoloStar prefilled disposable pen – CIP: 377 229-8 (joint renewal)

Applicant: SANOFI AVENTIS France

Insulin glargine

List II
ATC code: A10AE04

Marketing authorisation dates (centralised European procedure): 9 June 2000 (vial and cartridge) and 6 February 2001 (prefilled pens).

Request for renewal of inclusion on the list of medicines reimbursed by National Insurance

Medical, Economic and Public Health Assessment Division
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Insulin glargine

1.2. Indications

"Diabetes mellitus in adults, adolescents and children aged 6 and over requiring insulin treatment".

1.3. Dosage

"LANTUS must be administered once a day, at any time of day, but at the same time each day. The dosage and time of administration must be adjusted on a case-by-case basis. LANTUS can also be combined with oral antidiabetic agents (OADs) in patients suffering from type 2 diabetes.

Mode of administration: subcutaneous.

Children: the efficacy and safety of LANTUS have been demonstrated only when it is administered in the evening. As limited experience is available, it has not been possible to demonstrate the efficacy and safety of LANTUS in children under six years of age.

As limited experience is available, it has not been possible to assess the efficacy and tolerance of LANTUS in the following groups of patients: patients with liver failure and patients with moderate to severe kidney failure".

2. REMINDER OF THE COMMITTEE’S OPINION AND LISTING CONDITIONS

Listing opinion dated 22 January 2003

NB. Opinion given for LANTUS solution for injection 100 units/ml in 10-ml vials (box of 1), 3-ml cartridges (box of five) and LANTUS solution for injection OPTISET in 3-ml disposable prefilled pens (box of 5).

<table>
<thead>
<tr>
<th>- Actual benefit</th>
<th>E/AE ratio</th>
<th>Therapeutic use</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes</td>
<td>high</td>
<td>First-line medicine</td>
<td>substantial</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>high</td>
<td>Second-line medicine</td>
<td>substantial</td>
</tr>
</tbody>
</table>

- IAB: "level III compared to NPH insulins in terms of tolerance with fewer instances of nocturnal hypoglycaemia and in terms of ease of use (one injection per day, no need to put the product back into suspension)"

Opinion of 23 July 2003

NB. Opinion given following the change of indication to include a reference to the age of patients for whom LANTUS is suitable (adults, adolescents and children aged six or over).

- Actual benefit: substantial.

* The activity of insulin glargine is expressed in units. These units are specific to LANTUS and do not correspond to IUs or to units used for other insulin analogues.
- IAB: "No IAB can be suggested for the paediatric population in view of the available data showing no difference between insulin glargine and NPH insulin in terms of efficacy or tolerance".

Listing opinion dated 8 December 2004

NB. Opinion given for LANTUS solution for injection in 3-ml cartridges for OptiClick (box of 5).
- AB substantial.
- IAB V compared to the forms already available.

Listing opinion dated 15 November 2006

NB. Opinion given for LANTUS SoloStar solution for injection in 3-ml prefilled disposable pens (box of 5).
- AB substantial.
- IAB V (addition to the range).

3. SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2008)

A: Alimentary tract and metabolism
A10: Drugs used in diabetes
A10A: Insulins and analogues
A10AE: Insulins and analogues for injection, long-acting
A10AE04: Insulin glargine

3.2. Medicines in the same therapeutic category

Other long-acting insulin analogue (SC administration): LEVEMIR (insulin detemir), solution for injection in 3-ml cartridge (box of five) and in 3-ml prefilled pens (box of five).

3.3. Medicines with a similar therapeutic aim

1) Insulins and analogues
   - Human insulins:
     • NPH insulins used as basal insulin: INSULATARD, INSUMAN BASAL, UMULINE NPH
     • Rapid insulins (comparison in subcutaneous pump administration regimens): ACTRAPID, INSUMAN INFUSAT, INSUMAN RAPID, UMULINE RAPIDE, VELOSULIN
     • Mixed insulins: INSUMAN COMB 15, 25 et 50; MIXTARD 30, UMULINE PROFIL 30
   - Insulin analogues:
     • Rapid insulin analogues (comparison in subcutaneous pump administration regimens): API德拉 (insulin glulisine), HUMALOG (insulin lispro), NOVORAPID (insulin aspart)
     • Mixed intermediate-acting analogues used in comparable insulin treatment regimens: HUMALOG MIX 25 and 50 (insulin lispro), NOVOMIX 50, 50 and 70 (insulin aspart)

2) Other medicines that can be prescribed for type 2 diabetes:
   - Biguanides: metformin (GLUCOPHAGE and generics), metformin + glibenclamide (GLUCOVANCE); metformin + rosiglitazone (AVANDAMET); metformin + pioglitazone (COMPETACT)
   - Glucose-lowering sulfonamides (AMAREL; DAONIL, HEMI DAONIL, EUGLUCAN; GLIBENES, GLIPIZE, MINIDIAZ, OZIDIA; GLUCIDORAL; GLUTRIL)
   - Glinides (non-sulfonamide insulin secretors): repaglinide (NOVONORM)
   - Intestinal alpha-glucosidase inhibitors: acarbose (GLUCOR); miglitol (DIASTABOL)
   - Glitazones/thiazolidinediones: pioglitazone (ACTOS); rosiglitazone (AVANDIA)
   - Injectable incretin mimetic: exenatide (BYETTA solution for injection)
   - Dipeptidyl peptidase-4 inhibitors (DPP-4): sitagliptin (JANUVIA 100 mg).
   N.B. vildagliptin (GALVUS 50 mg): currently being assessed by the Transparency Committee.
4. UPDATING WITH DATA OBTAINED SINCE THE PREVIOUS OPINION

4.1. Efficacy

A1- In type 1 diabetes in adults

a- Comparison with insulin detemir (LEVEMIR)

Reminder:
- Insulin glargine (LANTUS) has been marketed in France since 2003, and insulin detemir (LEVEMIR) since 2005. Both substances are long-acting insulin analogues administered as basal insulin in a "basal-bolus" insulin treatment regimen: LANTUS is administered as one SC injection while LEVEMIR is normally administered as two SC injections.
- in its opinion dated 30 March 2005, the Committee stated that “LEVEMIR, like LANTUS, leads to fewer instances of nocturnal hypoglycaemia than NPH”, that “LANTUS can usually be administered as a single daily injection” and that “In clinical studies, patients on LEVEMIR had a smaller average weight fluctuation than patients taking NPH”. The Committee had decided that LEVEMIR should be classified as offering the same Improvement in Actual Benefit as LANTUS (level III versus NPH).

In one study (Pieber et al. 1), the efficacy of insulin detemir twice a day was compared with that of insulin glargine once a day, as basal insulins associated with insulin aspart for the bolus administrations. 320 patients with type 1 diabetes who had previously been treated with NPH insulin took part in this randomised, multi-centre study with an open-label follow-up period of 26 weeks. The primary endpoint was the blood glucose level (HbA1c) and the secondary endpoints were the incidence of hypoglycaemia and the total insulin dose.

Results:

<table>
<thead>
<tr>
<th>Study/protocol</th>
<th>Endpoints</th>
<th>glargine+aspart×3</th>
<th>detemir×2 aspart×3</th>
<th>+</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pieber (Europe) Multi-centre, randomised, open-label comparative 26 weeks</td>
<td>Initial HbA1c</td>
<td>8.8%</td>
<td>8.9%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Final HbA1c (26 weeks)</td>
<td>8.19%</td>
<td>8.16%</td>
<td>NS (Δ=0.03 [-0.25; 0.19])</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin doses</td>
<td>0.35 U/kg</td>
<td>0.47U/kg</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- basal</td>
<td>0.74 U/kg</td>
<td>0.83 U/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduction in the risk of severe and nocturnal hypoglycaemic events</td>
<td>32%</td>
<td>72%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After 26 weeks of treatment, no difference between detemir and glargine was observed in respect of blood glucose control (HbA1c): 0.030 [-0.25; 0.19].
b- Comparison with NPH insulins used as basal insulin:

- A randomised study (Fulcher et al.) of 125 patients with type 1 diabetes compared the efficacy in controlling blood glucose and the incidence of hypoglycaemia of an insulin lispro combined either with an NPH insulin (n = 63) or with an insulin glargine (n = 62). The drugs were administered in the context of a single-blind study design. The primary endpoint was the difference in HbA1c levels after 30 weeks of treatment.

Results:

<table>
<thead>
<tr>
<th>Study/protocol</th>
<th>Endpoints</th>
<th>Lispro+glargine</th>
<th>Lispro+NPH</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulcher (Australia) Multi-centre, 30 weeks</td>
<td>Initial HbA1c</td>
<td>9.2%</td>
<td>9.7%</td>
<td></td>
</tr>
<tr>
<td>125 patients Diabetic for = 17.5 years</td>
<td>Final HbA1c (30 weeks)</td>
<td>8.3%</td>
<td>9.1%</td>
<td>p&lt; 0.01 (Δ=0.53)</td>
</tr>
<tr>
<td></td>
<td>Nocturnal hypoglycaemia</td>
<td>81% (28 episodes)</td>
<td>86% (41 episodes)</td>
<td>NS (RR = 0.99 [-0.25; 0.19])</td>
</tr>
</tbody>
</table>

Comments:
- The difference observed in respect of the final HbA1c is of moderate clinical relevance given the initial difference in HbA1c levels, the size of the cohort and the duration of the study (26 weeks).
- There was no difference between the two arms in terms of the risk of experiencing symptomatic hypoglycaemia. There was also no difference between the two arms in respect of the risk of experiencing nocturnal hypoglycaemia (any degree of severity) (RR = 0.95 with 95% CI between 0.84 and 1.07). The risk of slight nocturnal hypoglycaemia was higher in the glargine arm, but the risk of moderate (p=0.04) or severe (p=0.02) hypoglycaemia was lower in the glargine arm than in the NPH arm.
- This study does not clearly show that insulin glargine achieves better glycaemic control or a reduction in the risk of hypoglycaemic events than NPH insulin as part of a basal-bolus regimen in these patients.

- No comments are made on the results of the following three studies for the following reasons:
  - The study conducted by McEwan et al. is a retrospective study; its results are presented in the form of an abstract.
  - Two studies (Ashwell et al., Chaterjee et al.) are randomised cross-over trials. In view of the short follow-up period (two sixteen-week treatment periods) and in particular the small cohort size (fewer than 60 patients in each study), these two studies offer little additional information to compare the efficacy of insulin glargine with NPH insulins.

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d- Data comparing different administration timetables for insulin glargine:

The company has submitted the results of three randomised clinical studies:

Comments:
- In one study (Grimaldi et al. 10), the efficacy of administration of insulin glargine as one daily injection taken with the evening meal was compared with that of one daily injection taken on retiring in patients with type 1 diabetes on a basal-bolus administration regimen (using either a rapid-acting analogue or a rapid-acting human insulin for the bolus). The aim of this study was to show the equivalence of these two insulin glargine administration times: the endpoint was HbA1c at 26 weeks, with an equivalence margin set at +/- 0.3% for a 90% CI (per protocol and intention to treat analyses); 1,178 patients were recruited and treated (589 in the "evening meal" arm and 589 in the "on retiring" arm). This study carried out in France showed insulin glargine to be equally effective irrespective of whether it was administered with the evening meal or on retiring.

- One study (Hamann et al. 11) performed on 378 patients with type 1 diabetes who had been undergoing treatment as a basal-bolus regimen for 24 weeks (bolus in the form of insulin lispro) found equivalent glycaemic control (HbA1c at the end of the study) irrespective of whether the insulin glargine was administered before breakfast, with the evening meal, or on retiring.

- One study (Ashwell et al. 12) was not taken into consideration because of the size of its cohort (23 patients).

A2- In type 1 diabetes in children aged over six and adolescents

The company has submitted the results of two randomised clinical studies, the results of which were taken into account despite the small cohort size as little data or studies with a satisfactory methodology are available in the context of paediatric medicine:

- In the study conducted by Murphy et al (13), the efficacy in terms of glycaemic control and the incidence of nocturnal hypoglycaemia of treatment with NPH insulin + rapid-acting human insulin (RAHI) was compared with that of treatment with insulin glargine + lispro over two successive periods of sixteen weeks (cross-over trial). The primary endpoint was the incidence of nocturnal hypoglycaemia on glycaemic profiles after 32 weeks.

Results:

<table>
<thead>
<tr>
<th>Study/ protocol</th>
<th>Endpoints</th>
<th>Glargine + lispro</th>
<th>NPH + RAHI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy (UK)</td>
<td>Initial HbA1c</td>
<td>9.3%</td>
<td>9.3%</td>
<td></td>
</tr>
<tr>
<td>Cross-over</td>
<td>Final HbA1c (16 weeks)</td>
<td>8.7%</td>
<td>9.1%</td>
<td>NS</td>
</tr>
<tr>
<td>28 patients</td>
<td>Total insulin doses</td>
<td>1.16 U/Kg</td>
<td>1.26 U/Kg</td>
<td>p&lt; 0.005</td>
</tr>
<tr>
<td>Average age = 14.8</td>
<td>Nocturnal</td>
<td>32% (8/25)</td>
<td>56% (14/25)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Diabetic for</td>
<td>hypoglycaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.3 years</td>
<td>(incidence)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments: these results must be interpreted prudently in view of the small size of the cohort in each arm (12 or 13 patients).
- One study (Doyle et al. 14) compared the efficacy of treatment with insulin glargine + aspart with that of insulin administered by subcutaneous pump in 32 children aged between 8 and 21 with type 1 diabetes. The primary endpoint was HbA1c at 16 weeks.

Results:

<table>
<thead>
<tr>
<th>Study/protocol</th>
<th>Endpoints</th>
<th>MDI*/glargine</th>
<th>Subcutaneous pump</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doyle (USA)</td>
<td>Initial HbA1c</td>
<td>8.2 ±1.1%</td>
<td>8.1 ±1.2%</td>
<td></td>
</tr>
<tr>
<td>16 weeks</td>
<td>Final HbA1c</td>
<td>8.1 ± 1.2%</td>
<td>7.2 ± 1.0%</td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>32 patients</td>
<td>Total insulin doses</td>
<td>1.2 IU/Kg/d</td>
<td>0.9 IU/Kg/d</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Average age = 13 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic for ≤ 6 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*MDI = Multiple-dose insulin

Comment: at the end of the study, 14/16 patients remained on the pump regimen and 12/16 in the glargine group transferred to a pump regimen.

N.B.: the company has submitted the results of five non-comparative studies (some of which were retrospective). No comments are made on their results in view of this methodology.

B- In type 2 diabetes in adults

The submission of the studies takes account of the insulin use strategy in patients with type 2 diabetes:

B1 - Patients in whom oral antidiabetics (OAD) have failed: addition of a basal insulin

a- Comparison with NPH insulin

The company has submitted the results of two randomised comparative studies (study carried out by LANMET, Yki-Jarvinen et al. 15; study carried out by Eliaschewitz et al. 16). These two studies were included in a Cochrane meta-analysis. The comments given relate only to the results:

- A Cochrane meta-analysis (Horvath et al., 2008) was conducted in order to compare the long-term effects of slow insulin analogues (with a long duration of action), insulin glargine and insulin detemir with those of NPH insulin in type 2 diabetics. The studies included had to be comparative, randomised and to have been conducted over at least 24 weeks (six months). In total, eight studies were taken into consideration, six of which compared insulin glargine (1,715 patients) with NPH insulin (1,463). The duration of these studies ranged from 24 to 52 weeks. Efficacy results: There was no difference between the different insulins in respect of glycaemic control measured by the endpoint HbA1c. The two slow insulin analogues were not found to confer any benefits in terms of mortality, morbidity or quality of life compared to NPH insulin.
b- Comparison with insulin detemir (LEVEMIR):

One non-inferiority study and the Cochrane meta-analysis were taken into consideration:

- One study (Rosenstock et al. 18) which was not included in the meta-analysis established non-inferiority in terms of glycaemic control between treatment with insulin detemir and insulin glargine prescribed in combination with an oral glucose-lowering treatment in 582 patients with type 2 diabetes who had never received insulin. Non-inferiority was determined on the basis of the requirement that the upper limit of the 95% confidence interval of the difference in HbA1c between the two arms after 52 weeks of treatment had to be less than 0.4%-units.

Results:

<table>
<thead>
<tr>
<th>Study/ protocol</th>
<th>Endpoints</th>
<th>glargine</th>
<th>detemir</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>52 weeks 582 patients</td>
<td>Initial HbA1c</td>
<td>8.66%</td>
<td>8.60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Final HbA1c (16 weeks)</td>
<td>7.1%</td>
<td>7.2%</td>
<td>NS (Δ=0.05% [-0.11; 0.21])</td>
</tr>
<tr>
<td></td>
<td>Proportion of patients achieving the objective of HbA1c≤7% without hypoglycaemia</td>
<td>35%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average insulin doses</td>
<td>0.44 U/Kg</td>
<td>0.78 U/Kg</td>
<td>p&lt; 0.05</td>
</tr>
</tbody>
</table>

Comments: there was no difference between the two arms with regard to the risk of hypoglycaemia (including nocturnal hypoglycaemia). The average dose of insulin detemir was higher (0.78 U/kg: 0.52 U/kg when taken as one injection per day and 1.00 U/kg when taken as two injections a day) than that of insulin glargine (0.44 IU/kg).

Insulin detemir (LEVEMIR) was prescribed in the form of 1 (45%) or 2 injections per day (55% of patients), with no difference in terms of the final HbA1c.

It should be noted that more patients in the insulin glargine arm than in the insulin detemir arm completed the study (87% versus 79%).

- In the Cochrane meta-analysis (Horvath et al, 2008) described above (a-), which assessed the long-term clinical effects of slow insulin analogues, no difference was found between insulin glargine and NPH insulin (1,715 patients, 6 studies) or between insulin detemir and NPH insulin (578 patients, 2 studies).

c- Comparison with premixed insulins

The company has submitted the results of three randomised clinical studies:

- In the LAPTOP study (Janka et al.19), 371 patients with type 2 diabetes poorly controlled by dual oral therapy with sulfonylurea and metformin received either one injection of insulin glargine combined with glimepiride 3 or 4mg + metformin ≥ 850 mg in the morning or a combination of human insulins (I30/70= premix of 30% rapid-acting insulin, 70% NPH) before breakfast and before dinner (and with no oral antidiabetic). The primary endpoint was the difference in HbA1c between the two arms after 24 weeks.
Results:

<table>
<thead>
<tr>
<th>Study/protocol</th>
<th>Endpoints</th>
<th>Glargine + glimepiride + metformin (G)</th>
<th>Premix NPH insulin / RAHI (I30/70)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janka LAPTOP (Europe)</td>
<td>Initial HbA1c</td>
<td>8.85%</td>
<td>8.83%</td>
<td>NS</td>
</tr>
<tr>
<td>24 weeks</td>
<td>Final HbA1c (24 weeks)</td>
<td>7.15%</td>
<td>7.49%</td>
<td>P = 0.0003 (Δ=0.34% [-0.52; -0.16])</td>
</tr>
<tr>
<td>371 patients</td>
<td>Average insulin doses</td>
<td>28 IU/d</td>
<td>64 ± 6 IU/d</td>
<td>(NC)</td>
</tr>
<tr>
<td>Average age = 60</td>
<td>Weight gain</td>
<td>1.4 kg</td>
<td>2.1 kg</td>
<td>(NC)</td>
</tr>
<tr>
<td>Diabetic for = 10 years</td>
<td>Hypoglycaemic events (incidence)</td>
<td>61.6%</td>
<td>67.2%</td>
<td>NS</td>
</tr>
<tr>
<td>BMI = 29.5 kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NB. A planned analysis in a sub-group of 130 patients aged over 65 (Janka study 20). After 24 weeks, HbA1c fell from 8.8 to 7.0% in the glargine + OADs arm (n = 67) and from 8.9 to 7.4% in the I30/70 arm (n = 63), a difference of - 0.34% [-0.52; -0.16] (p = 0.0003) in favour of the glargine + OADs arm. No conclusions can be drawn from this type of analysis (cohort size, sub-group analysis).

- In the INITIATE study (Raskin et al. 21), 233 patients with type 2 diabetes not controlled (HbA1c > 8%) by metformin (≥ 1 g/d) alone or in combination with other oral antidiabetics were treated by one injection of insulin glargine on retiring or by two injections (in the morning and before the evening meal) of premixed insulins (aspart 30% + NPH 70%) (BiAsp 30/70). The oral treatment was adjusted prior to randomisation; the metformin dose was titrated to achieve the optimum daily dose between 1.5 and 2.5 g per day. Insulin secretagogues were withdrawn and thiazolidinediones were continued. The primary endpoint was the difference in HbA1c between the two arms after 28 weeks.

Results:

<table>
<thead>
<tr>
<th>Study/protocol</th>
<th>Endpoints</th>
<th>Glargine + metformin</th>
<th>BiAsp 30/70 + metformin</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskin INITIATE (USA)</td>
<td>Initial HbA1c</td>
<td>9.8%</td>
<td>9.7%</td>
<td>NS</td>
</tr>
<tr>
<td>28 weeks</td>
<td>Final HbA1c (28 weeks)</td>
<td>7.41%</td>
<td>6.91%</td>
<td>p&lt; 0.01</td>
</tr>
<tr>
<td>263 patients</td>
<td>Hypoglycaemic events (number/patient/year)</td>
<td>0.7±2.0</td>
<td>3.4±6.6</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Average age = 52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI = 31.5 kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic for = 9 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A quality of life assessment was conducted on patients taking part in the INITIATE study, using the ITSQ (Insulin Treatment Satisfaction Questionnaire), and has been published 22. The three sets of parameters used to assess the treatment were efficacy, adverse effects and the burden imposed by the treatment. No difference between the arms was observed in terms of quality of life.

Comments: the treatment regimen of two premixed insulins (aspart 30% + NPH 70% (BiAsp 30/70)) administered by injection was more effective in terms of glycaemic control (HbA1c) than one injection of insulin glargine administered before retiring.
- A study (Kann et al. 23) compared the efficacy in respect of glycaemic control of two insulin introduction strategies for patients with type 2 diabetes poorly controlled by an OAD (sulfonamide at at least half the maximum dose, metformin > 2 g per day or a combination of sulfonamide + metformin). The 258 patients were randomised for treatment either with glargine (1 injection per day at a time chosen by the patient) + glimepiride (127 patients) or with BiAspart 30/70 morning and evening + metformin up to 2 g per day (128 patients). The primary endpoint was the difference in HbA1c between the two arms after 28 weeks.

Results:

<table>
<thead>
<tr>
<th>Study/protocol</th>
<th>Endpoints</th>
<th>BiAsp 30+ metformin</th>
<th>Glargine+glimepiride</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kann (Europe)</td>
<td>Initial HbA1c</td>
<td>9.2%</td>
<td>8.9 %</td>
<td>p = 0.07</td>
</tr>
<tr>
<td>258 patients</td>
<td>Final HbA1c (28 weeks)</td>
<td>7.5%</td>
<td>7.9%</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Average age = 61</td>
<td>Hypoglycaemic events (incidence)</td>
<td>20.3%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Diabetic for = 10 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI = 30 kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment: Treatment with insulin BiAsp 30/70 + metformin resulted in better glycaemic control than treatment with insulin glargine + glimepiride, but at the cost of an increase in hypoglycaemic events.

d- Comparison with rosiglitazone (AVANDIA)

- A study (Rosenstock et al. 24) conducted on patients with type 2 diabetes poorly controlled by metformin + sulfonamide compared the efficacy of adding insulin glargine or rosiglitazone to the regimen. The doses of metformin (2g/d) and sulfonamide were not changed.

Results:

<table>
<thead>
<tr>
<th>Study/protocol</th>
<th>Endpoints</th>
<th>Metformin+sulfonamide + glargine</th>
<th>Metformin+sulfonamide + rosiglitazone</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenstock (Europe)</td>
<td>Initial HbA1c</td>
<td>8.7%</td>
<td>8.8 %</td>
<td>NS</td>
</tr>
<tr>
<td>24 weeks</td>
<td>Change in HbA1c (24 weeks)</td>
<td>-1.51%</td>
<td>-1.66%</td>
<td>NS (Δ=1.66% [-0.52; -0.16])</td>
</tr>
<tr>
<td>217 patients</td>
<td>Weight gain</td>
<td>1.7 kg</td>
<td>3.0 kg</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Average age = 55</td>
<td>Confirmed symptomatic hypoglycaemic events</td>
<td>26 events</td>
<td>14 events</td>
<td>p&lt; 0.02</td>
</tr>
<tr>
<td>Diabetic for = 8 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI = 34 kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The initial insulin dose of 10 IU/d on retiring was adjusted in the light of the fasting glycaemia target of between 100 and 120 mg/dl, and the initial rosiglitazone dose of 4 mg/d was increased to 8 mg after 6 weeks of treatment if the fasting glycaemia level was > 5.5mmol/l. The primary endpoint was the change in HbA1c between inclusion and the end of the study (24 weeks).

Comment: These results do not clarify which strategy was better: addition of rosiglitazone or of an insulin glargine. It should be noted that the results in the sub-group of patients with an HbA1c > 9.5% on inclusion (not presented here) are of exploratory interest but that no conclusions can be drawn from them.
e- Comparison with injectable exenatide (BYETTA): no new data presented in addition to that submitted for the Committee's opinion on BYETTA issued on 28 February 2007.

B2- Patients in whom oral antidiabetics (OADs) combined with basal insulin have failed or in whom oral tritherapy has failed.

The company has submitted the results of four studies in this context:

- A randomised study (Rosenstock et al. 25) compared the efficacy and adverse effects of basal-bolus treatment with insulin glargine and insulin lispro (BBT) with those of a regimen involving three injections of premixed insulin (Humalog mix 50 (PPT)) in patients with type 2 diabetes poorly controlled by insulin glargine and OAD (in mono-, bi- or tritherapy). The purpose of this study was to demonstrate non-inferiority between the two insulin treatment regimens. The primary endpoint was the difference in HbA1c change between the two arms after 24 weeks of treatment, with a non-inferiority margin set at 0.3%.

Results:

<table>
<thead>
<tr>
<th>Study/protocol</th>
<th>Endpoints</th>
<th>PPT (premixed insulins administered as 3 inj/d)</th>
<th>BBT (basal bolus: glargine+lispro)</th>
<th>significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenstock (USA, Porto Rico) 24 weeks 374 patients Average age = 55 Diabetic for = 11 years On insulin for = 8 years BMI = 34 kg/m²</td>
<td>Initial HbA1c</td>
<td>8.83%</td>
<td>8.89 %</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Final HbA1c (24 weeks)</td>
<td>6.95%</td>
<td>6.78%</td>
<td>NS (Δ=-0.22% [-0.38; -0.07])</td>
</tr>
<tr>
<td></td>
<td>Total insulin doses</td>
<td>123 ± 69 U</td>
<td>146 ± 85 U</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Weight gain</td>
<td>4.5 kg</td>
<td>4.2 kg</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Severe hypoglycaemic events</td>
<td>0.10 ± 0.65 events/patient/year</td>
<td>0.05 ± 0.31 events/patient/year</td>
<td>NS</td>
</tr>
</tbody>
</table>

Comment: This study did not establish non-inferiority on the basis of the non-inferiority margin selected, although the HbA1c level was lower in the BBT arm than in the PPT arm. There was no difference between the two arms in the rate of hypoglycaemic events.

- No comment is made on the results of the study by Herman et al. 26 in view of the small size of the cohort assessed - 50 patients in the glargine arm and 48 patients in the pump arm - and since a randomisation bias existed (patient recruitment stopped before the number of subjects needed for statistical comparison was reached).

- No comments are made on the results of the randomised monocentre study (Yokoyama et al. 27 in view of the small size of the cohort: 62 patients with type 2 diabetes.

- No comments are made on the results of the OPAL randomised comparative study 28 as they were published in the form of an abstract.

C- Effects of insulin glargine on diabetic retinopathy

The HOE901/4016 study was conducted at the request of the FDA to assess the progress of diabetic retinopathy in patients with type 2 diabetes treated with insulin glargine compared to its progress in patients treated with NPH insulin. This study was conducted over a five-year period between 2001 and 2007 in the United States and Canada. The 1,024 subjects taking part were patients with type 2 diabetes, some of whom had previously been treated with insulin. They were randomised to receive insulin glargine (one injection per day) or NPH
insulin NPH (2 injections per day). The primary endpoint was the percentage of patients whose ETDRS (Early Treatment Diabetic Retinopathy Study) score increased by 3 points or more, measured by photographs of the fundus of the eye ("blind" reading; non-inferiority study, PP analysis).

The company submitted preliminary findings of this study: the average age of the patients was 55.1 years, their average BMI was 34.3 kg/m$^2$, they had been suffering from diabetes for an average of 10.7 years and had been taking insulin for 5.2 years. The HbA1c level on inclusion was 8.36%. The per-protocol population was 757 patients.

The percentage of patients with an increase of more than three points on the ETDRS score was 14.2% in the insulin glargine group versus 15.7% in the NPH insulin group: a non-significant difference of -1.98% [95%CI -7.02; 3.06]. This result was obtained from the ITT analysis.

The European Commission decided on 17/09/2008 to add the following information to section 5.1, Pharmacodynamic properties, of the SPC: “Effects of Lantus (once daily) on diabetic retinopathy were evaluated in an open-label 5-year NPH-controlled study (NPH given bid) in 1,024 type 2 diabetic patients in which progression of retinopathy by 3 or more steps on the ETDRS scale was investigated by fundus photography. No significant difference was seen in the progression of diabetic retinopathy when Lantus was compared to NPH insulin”.

4.2. Adverse effects

4.2.1. Clinical study data used to assess the risk of hypoglycaemic events:

- No comments are made on the results of a pooled analysis (Rosenstock et al$^{29}$) of four open-label randomised studies appearing in the LANTUS registration dossier in 2002 (2 phase III registration studies and 2 phase IIIb post registration studies lasting between 24 and 28 weeks, except for one study lasting 52 weeks). These studies were taken into consideration in the Cochrane meta-analysis of 2008, which is more comprehensive.

- The purpose of the Cochrane meta-analysis (Horvath et al, 2008) was to compare the long-term effects of two slow analogues (with a long duration of action), insulin glargine and insulin detemir, with those of NPH insulin in type 2 diabetes. The studies included had to be comparative, randomised and to have been conducted over at least 24 weeks (six months). In total, eight studies were taken into consideration, six of which compared insulin glargine (1,715 patients) with NPH insulin (1,463). The duration of these studies ranged from 24 to 52 weeks. Results in terms of hypoglycaemic risk: no difference in respect of the incidence of severe hypoglycaemic events was found between the various insulins. However, a statistical reduction in the risk of nocturnal hypoglycaemic events in favour of insulin glargine was observed. No beneficial impact on quality of life in favour of the two slow insulin analogues was observed.

- A meta-analysis using a binomial meta-regression model (Mullins et al.$^{30}$) was carried out to improve understanding of the results in terms of hypoglycaemic risk with NPH insulin and insulin glargine. The first step was the creation of a model of the interaction between the hypoglycaemic risk and HbA1c levels on the basis of clinical studies comparing insulin glargine and NPH insulin in patients with type 1 or type 2 diabetes. In total, 11 studies (5,074 patients), of which 6 (3,175 patients) involved type 2 diabetes were taken into consideration. According to the data from this meta-analysis:

  - in type 1 diabetes: the reduction in the rate of events (events/100 patients/day) among patients treated with glargine compared to patients treated with NPH was assessed at 16.8% for severe hypoglycaemic events ($p=0.06$), 20.1% for confirmed hypoglycaemic events ($p<0.05$) and 5.2% for symptomatic hypoglycaemic events ($p<0.05$). The reduction in the rate
of events (events/100 patients/day) adjusted according to the final HbA1c level among patients treated with glargine compared to patients treated with NPH was assessed at 21.5% for severe hypoglycaemic events, 21.6% for confirmed hypoglycaemic events (p<0.05) and 10.3% for symptomatic hypoglycaemic events (p<0.05).

- in type 2 diabetes: the reduction in the rate of events (events/100 patients/day) among patients treated with glargine compared to patients treated with NPH was assessed at 53.7% for severe hypoglycaemic events (p=0.06), 39.3% for confirmed hypoglycaemic events (p<0.05) and 13.7% for symptomatic hypoglycaemic events (p<0.05).

The reduction in the rate of events (events/100 patients/day) adjusted according to the final HbA1c level among patients treated with glargine compared to patients treated with NPH was assessed at 35% for severe hypoglycaemic events, 33.6% for confirmed hypoglycaemic events (p<0.05) and 7.0% for symptomatic hypoglycaemic events (p<0.05).

**Comments:**

It is difficult to interpret the results of these two meta-analyses, especially with regard to the hypoglycaemic risk, given the low level of evidence due to the actual characteristics of the studies:

- almost all the studies were carried out in an open-label design,
- randomisation of doubtful quality in respect of its unpredictability,
- no ad-hoc committee (blinded as to the treatment received) to validate events such as hypoglycaemic attacks,
- the meta-analyses include superiority studies, non-inferiority studies and equivalence studies; this could lead to disparities in the optimisation of treatment in the control groups and so in the quantitative effects observed.

The studies available therefore do not offer a sufficient level of evidence to confirm the superiority of LANTUS versus NPH insulin in terms of the incidence of hypoglycaemic events.

4.2. Data from pharmacovigilance reports (PSUR)

Following analysis of this tolerance data, myalgia and dysguesia were added to the "undesirable effects" section of the SPC (European Summary of Product Characteristics). This section divided lipodystrophy into lipohypertrrophy (common) and lipoatrophy (uncommon).

The "pregnancy and lactation" section was completed following analysis of post-marketing monitoring of pregnancies. *The use of Lantus during pregnancy can be considered if necessary.*
4.3. Conclusion

4.3.1 Clinical efficacy data

4.3.1.1. In type 1 diabetes

- In adults: LANTUS is prescribed in the context of a multi-injection basal-bolus insulin treatment regimen. New comparative data drawn from sources with a satisfactory methodology (study by Fulcher et al.) offer little additional information as to the efficacy of LANTUS compared with NPH insulins since the Committee's previous opinion. It confirms that the glycaemic control obtained (HbA1c) with insulin glargine in the context of a basal bolus regimen is comparable to that obtained with NPH insulin.

The two slow-acting insulin analogues, glargine (1 injection/d) and detemir (2 injections/d), have been compared in only one study (Pieber et al.). It cannot be concluded from the results that there is any difference between them, either in terms of glycaemic control (HbA1c) or hypoglycaemic risk.

- In children: there is still insufficient clinical data available for children aged over six and adolescents. The data is still insufficient to allow any conclusions to be drawn as to whether LANTUS offers greater benefits for this group than other insulin regimens. The efficacy and tolerance of LANTUS (and LEVEMIR) have not been studied in children under six.

4.3.1.2. In type 2 diabetes

Insulin treatment is considered after the failure of a combination of at least two blood glucose lowering agents in the form of one or two injections of an NPH insulin or a slow-acting insulin analogue. The glycaemic control obtained with slow-acting analogues or with NPH insulin is comparable in terms of reduction in HbA1c levels and the proportion of patients with HbA1c "normalised" at 7%. Little data is available on the long-term efficacy of insulin glargine (or insulin detemir). Slow-acting insulin analogues have not been shown to have any impact on morbidity and mortality or quality of life (Cochrane meta-analysis, 2008).

4.3.2. Adverse effects

- The risk of hypoglycaemia increases when glycaemic control is better, irrespective of the insulin used.

Comparisons between insulin glargine (LANTUS) and NPH insulin have not demonstrated any reduction in the risk of mild or severe symptomatic hypoglycaemic events, but several studies suggest that the risk of nocturnal hypoglycaemia is lower for insulin glargine. The size of this effect is difficult to estimate since hypoglycaemic events were assessed with variable definitions of the events and using various (secondary) assessment criteria (symptomatic hypoglycaemia, severe hypoglycaemia, diurnal hypoglycaemia, nocturnal hypoglycaemia). The size of this effect appears to be modest at best, and no impact on quality of life has been shown (Cochrane meta-analysis of 2008).

- Furthermore, the tolerance profile for LANTUS is not different from that mentioned in the Committee's opinion issued in January 2003.

- The data available for pregnant women and foetuses is reassuring (see change to SPC).

In conclusion,

- in type 1 diabetes, fast-acting and slow-acting insulin analogues, including insulin glargine, have helped to make the "basal-bolus" regimen the insulin treatment regimen of choice (expert consensus).
- in type 2 diabetes, where insulin treatment is indicated, there is no clinical argument justifying giving preference to slow-acting insulin analogues (the group to which insulin glargine belongs) over NPH insulins, whether in terms of glycaemic control or of tolerance.

The theoretical benefits of slow-acting insulin analogues are not reflected in a tangible additional medical benefit: long-term clinical data which would allow the risk/benefit ratio to be measured is not available. Patients' quality of life does not appear to be improved, despite a slight reduction in nocturnal hypoglycaemic events.

Nevertheless, the Committee notes that LANTUS can be administered as a single daily injection. This injection can be administered with the evening meal, at bedtime, or even in the morning.
5. DRUG USAGE DATA

5.1. Observational studies on the use of LANTUS

- Following a request for a study by the Directorate-General for Health (DGS), included in a CEPS agreement in June 2003, the company conducted an epidemiological study (the protocol of which was validated by the DGS) among patients treated with Lantus. The main purpose of the study was to ascertain the beneficial effect of Lantus on blood glucose (HbA1c) control under real conditions and, at the same time, on the reduction in the number of hypoglycaemic events.

Almost two-thirds of the 1,707 patients analysed had type 2 diabetes (T2D) and 35.7% had type 1 diabetes (T1D). 6-month and 12-month monitoring results were available for 1,404 patients; 148 had been monitored only at 6 months and 24 only at 12 months.

On starting treatment with Lantus, 63.8% of T2D patients and 54.0% of T1D patients had an HbA1c level above 8.

The conditions for use of Lantus were respected (one daily injection in almost all cases).

Glycaemic control improved following the introduction of Lantus treatment, with no increase in the number of severe hypoglycaemic events.

- in T1D patients: reduction of 0.6% in HbA1c between the start of Lantus treatment and inclusion, and stable level thereafter (-0.1%); increase in the proportion of patients whose glycaemia levels were under control (HbA1c < 7%) between the start of Lantus and the end of the follow-up period (17.2% to 29.5%) (the results are similar to those of the ENTRED study carried out in France between 2001 and 2003, in which 22% of patients had glycaemia levels which were under control);
- in T2D patients previously treated with insulin: reduction of 0.8% in HbA1c between the start of Lantus treatment and inclusion, followed by a reduction of 0.4% during the follow-up period, and an increase from 19.9% to 33.4% in the proportion of patients with glycaemia levels under control (HbA1c < 7%);
- in T2D patients not previously treated with insulin: reduction of 1.0% in HbA1c between the start of Lantus treatment and inclusion, followed by a reduction of 0.4% during the follow-up period, and an increase from 13.9% to 39.1% in the proportion of patients with glycaemia levels under control (HbA1c < 7%);
- in T1D patients, while the percentage of patients achieving target HbA1c levels during the follow-up period increased, the number of hypoglycaemic events reported as severe remained stable: 0.6 (+/-3.6) from D0 to M6 and 0.6 (+/-4.4) from M6 to M12. This figure rose from 0.04 (+/-0.41) to 0.07 (+/-0.57) among T2D patients.
- the percentage of patients with type 2 diabetes aged 75 or over with glycaemia levels under control was comparable to that obtained among younger patients, as was the incidence of severe hypoglycaemic events.

The results of this observational study confirm those produced by the clinical studies (effect on HbA1c and severe hypoglycaemic events). They clarify the contribution made by Lantus under actual conditions of use, especially among patients with elevated HbA1c and elderly people (see appendix, Observational study).

- Additional study: the company reported the results of an observational study conducted in the United Kingdom (study performed by Currie et al. 31) using the THIN database (approximately 300 general practitioners). The observation covered the nine months after patients were changed to a different treatment regimen, either insulin glargine or insulin detemir. The results relate to 2,808 patients with type 1 diabetes. Before the introduction of glargine, their HbA1c level was 9.2%, which improved by 0.5% by the end of the third quarter. The rate of hypoglycaemic events fell by 30%.
5.2. Other data:

Prescription data: IMS data (moving annual total for February 2008) shows that 790,000 prescriptions for LANTUS were issued (all forms and dosages). The average dose observed is 1.1 injections a day, which is in line with the SPC. LANTUS was prescribed for the indication "diabetes mellitus" in 97.7% of cases. LANTUS was most frequently co-prescribed with a fast-acting insulin (29%), metformin (29.8%) or glucose-lowering sulfonamides (23.8%).
6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Reassessment of Actual Benefit

Diabetes mellitus (type 1 or type 2) is a chronic, progressive disease with severe consequences in view of its complications (cardiovascular, nephropathy/renal dialysis, peripheral polyneuropathy, retinopathy, etc.).

LANTUS 100 units/ml is used in the context of symptomatic treatment. It is a first-line medicine for the management of patients suffering from type 1 diabetes and a second-line medicine for the management of patients suffering from type 2 diabetes.

There are therapeutic alternatives for type 1 diabetes (other insulins) and type 2 diabetes (in particular, starting patients on insulin detemir or NPH insulin as their first form of insulin).

Public health benefit.

*The public health burden of diabetes treated with insulin is high. Improving the therapeutic management of diabetics is a public health need. The data available, and in particular the results of the observational study, confirm the impact that LANTUS is expected to have in terms of glycaemic control and the frequency of severe hypoglycaemic events in patients with diabetes:*
- the conditions of use and the patient profile correspond to what would be expected (one daily injection in most cases, high percentage of patients with high glycaemia levels on inclusion)
- the improved glycaemic control in patients being treated with LANTUS was obtained without a rise in the number of severe hypoglycaemic events. This was particularly the cases with elderly people.

*Therefore, the proprietary drug LANTUS can be regarded as helping to meet the identified public health need.*

*Consequently, the proprietary drug LANTUS offers a public health benefit. It can be regarded as low.*

The efficacy/adverse effects ratio for LANTUS is high.

The actual benefit of LANTUS 100 units/ml (solution for injection in vials, cartridges and pens) is substantial in type 1 diabetes and type 2 diabetes.

6.2. Update of the improvement in actual benefit

In view of the results of the clinical studies available and of the observational study carried out, which confirmed the contribution made by LANTUS under actual conditions of use, the Committee considers that LANTUS offers a level IV (minor) improvement in actual benefit in terms of tolerance.
6.3. Therapeutic use

The aims of diabetes management are to reduce associated morbidity and mortality, maintain the patient's quality of life and avoid degenerative complications. Therapeutic education plays a vital role in this, while preserving the patient's independence. It is also very useful in reducing the hypoglycaemic risk.

6.3.1 The role of LANTUS in the management of patients with type 1 diabetes

Adult patients with type 1 diabetes require insulin treatment and dietary management. Their food intake (energy and carbohydrate content) must match their insulin action profile and exercise pattern.

The aims of treatment are: control of glycaemia in order to prevent long-term complications associated with diabetic microangiopathy (retinopathy, kidney failure, neurological, infectious and skin complications) and to prevent excessive height and weight gain and early puberty in children, to prevent hypoglycaemic events and acidoketosis.

Several insulin treatment regimens are available; the choice depends on the glycaemic target values, preferences and lifestyle of each patient:
- two injections a day: a mix of fast-acting insulin (or fast-acting analogue) and intermediate-acting insulin (before breakfast and the evening meal).
- 3, 4 or 5 injections a day: injections of a mix of fast-acting insulin (or fast-acting analogue) and intermediate-acting insulin (twice a day: before breakfast and the evening meal), and a fast-acting insulin (or fast-acting analogue) before the midday meal (once a day). In this regimen, the evening dose of the intermediate-acting insulin can be delayed until retiring in order to better cover the patient's nocturnal requirements (see expert consensus).
- "basal-bolus" regimen of 3, 4 or 5 injections a day: an intermediate-acting insulin (twice a day, morning and evening) or a slow analogue such as LANTUS (once a day) as the basal component plus a fast-acting insulin (or fast-acting analogue) or "prandial insulin" injected as the bolus component before each main meal (three times a day).
- SC administration via portable pump (continuous perfusion at a rate that can be fixed or varied according to the time of day or night, and bolus administration at mealtimes). Pump administration requires the use of fast-acting human insulin or a fast-acting analogue.

The basal-bolus and pump regimens match normal physiology most closely. Pump administration is the nearest option to the normal physiology of insulin secretion, but requires the patient to monitor his or her own glycaemic level and to adjust the dose of insulin at regular and repeated intervals.

A change in the insulin regimen can be considered for patients whose metabolism is poorly controlled after taking the other parameters of glycaemic equilibrium (diet, exercise, compliance) into account.

The expert consensus is that the availability of slow-acting insulin analogues (insulin glargine and insulin detemir) used in a basal-bolus regimen, particularly when used in combination with a fast-acting insulin analogue, has marked a step forward in the management of these patients.

Role and benefit of LANTUS in children:
Two injections of insulin per day are normally recommended for young children. LANTUS is not indicated for children aged under six, and the amount of data which would allow its clinical benefit in the management of children and adolescents to be assessed is limited.
6.3.2 Role of LANTUS in type 2 diabetes

The HbA1c level is not the only factor to be taken into consideration when deciding on insulin treatment for type 2 diabetes. According to the guideline “Medication for type 2 diabetes” published by Afssaps and HAS in November 2006, the initial treatment of type 2 diabetes is based on an assessment and realistic changes in lifestyle habits (diet and exercise). The adoption of an active lifestyle and nutritional planning are essential interventions at all stages of diabetes management. Oral antidiabetics should be prescribed when diet and lifestyle changes (DLC) are no longer sufficient to control blood glucose levels: HbA1c > 6%.

There are four therapeutic classes: metformin, intestinal alpha-glucosidase inhibitors (AGIs), insulin secretors (sulfonamides and glinides), glitazones.

NB: These recommendations on the management of patients with type 2 diabetes do not cover the therapeutic use of two antidiabetic treatments which received marketing authorisation following the publication of the recommendations: exenatide (BYETTA), an injectable incretin mimetic (marketing authorisation issued in November 2006) and two dipeptidyl peptidase-4 inhibitors/gliptins (sitagliptin (JANUVIA, marketing authorisation issued in March 2007) and vildagliptin (currently being assessed by the Committee).

The different stages of treatment are summarised in the table below.

**Treatment strategy (long-term condition 8 – Type 2 diabetes)†**

<table>
<thead>
<tr>
<th>HbA1c levels</th>
<th>Treatment</th>
<th>Target HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c between 6% and 6.5% despite DLC</td>
<td>Metformin monotherapy (or AGI in the case of intolerance or contraindication)</td>
<td>Maintain HbA1c &lt; 6.5%</td>
</tr>
<tr>
<td>HbA1c &gt; 6.5% despite DLC</td>
<td>Metformin monotherapy or Insulin secretor or AGI</td>
<td>Bring HbA1c down to &lt; 6.5%</td>
</tr>
<tr>
<td>HbA1c &gt; 6.5% despite monotherapy and DLC</td>
<td>Dual oral therapy</td>
<td>Bring HbA1c down to &lt; 6.5%</td>
</tr>
<tr>
<td>HbA1c &gt; 7% despite dual oral therapy and DLC</td>
<td>Triple oral therapy: metformin + insulin secretor + glitazone or insulin + metformin ± other OADs except glitazone</td>
<td>Bring HbA1c down to &lt; 7%</td>
</tr>
<tr>
<td>HbA1c &gt; 8% despite triple oral therapy and DLC</td>
<td>insulin + metformin ± other OAD except glitazone</td>
<td>Bring HbA1c down to &lt; 7%</td>
</tr>
</tbody>
</table>

DLC: diet and lifestyle changes; OADs: oral antidiabetics; AGI: intestinal alphaglucosidase inhibitors

According to these recommendations, insulin treatment can therefore be instigated when glycaemic control is inadequate, i.e. in adult patients found when tested to have an HbA1c > 7% despite being on dual oral therapy for at least six months (+ DLC) or an HbA1c > 8% despite being on triple oral therapy for at least six months (+ DLC); in the latter case, glitazones are contraindicated as a component.

The recommended first-line treatment is to add a single insulin injection to be taken on retiring to the dual oral therapy: this should be an intermediate-acting insulin (NPH) or a slow-acting analogue (insulin glargine or detemir).

In the case of failure, more intense insulin treatment (2 to 4 injections per day) must be implemented. At this stage, metformin can be continued (if it is tolerated and not contraindicated) to limit weight gain; insulin secretors must be suspended.

If glucose levels are still not under control after dual or triple oral therapy, LANTUS can be prescribed when insulin treatment is introduced (at one injection a day or under a more intense regimen) as an alternative to NPH insulin or injectable BYETTA (if the patient is overweight).

4.3. Reassessment of the target population

Methods for estimating the target population

In the light of the indications for which the product is used and its therapeutic use on the one hand and the data available on the other hand, the target population has been broken down into two sub-populations:

(1) diabetics already undergoing insulin treatment (presuming that the insulin treatment indications have been correctly established);

(2) type 2 diabetics (T2D) who are not on insulin but who might benefit from it according to HAS recommendations, i.e. those who are being treated with several OADs at a maximum dose and tolerate them well but whose glycaemia is not under control. This population is itself broken down into four sub-groups according to patients’ HbA1c level (≥7% to <8% and ≥8%) and the number of OADs they are taking (2 and ≥3) (see table 2). Our hypothesis is that most patients taking at least two OADs and with an HbA1c ≥8% could benefit from insulin treatment, but that only a minority of those with an HbA1c in the ≥7% to <8% would benefit from it, and we have performed a sensitivity analysis in which these proportions are varied (see below).

The estimate of the target population was drawn up for 2007. When temporal trends were noted for some parameters (such as the prevalence of diabetes), the values for these parameters were adjusted to take these trends into account. The estimates are rounded to the nearest thousandth.

Sensitivity analyses were performed. The parameters for which the data available was relatively uncertain and those which were most likely to influence the results were varied within a plausible range.

Results

The target population for Lantus for 2007 can be estimated at 796,000 people, i.e. the sum of the 588,000 diabetics (230,000 T1D and 358,000 T2D) already on insulin and the 208,000 type 2 diabetics taking at least two OADs whose HbA1c level is 7% or above who could in fact benefit from insulin treatment.

The figures for the parameters used and the estimates for each stage are given in table 1.

Sensitivity analysis

The parameter which has the most impact on the estimate of the target population for Lantus is the proportion of diabetics with an HbA1c level of 7% or more despite taking at least two OADs who could benefit from insulin treatment. This is also the parameter subject to the greatest degree of uncertainty. As mentioned above, it is unlikely that all these individuals are in fact benefiting from insulin treatment. Assuming that most people with an HbA1c of ≥8% benefit from insulin treatment, the proportion of those who are actually benefiting from such treatment was put at various levels from 70% to 95%, producing a population figure of between 173,000 and 235,000 individuals. Similarly, assuming that a minority of individuals with an HbA1c level in the ≥7% to <8% range are benefiting from insulin, the proportion actually benefiting from it was put at various levels from 10% to 20%, giving a population of between 34,000 and 86,000 individuals. The upper limit of the Lantus target population is therefore estimated at 910,000 people.
Conclusion
In conclusion, the target population for Lantus for 2007 is estimated at 796,000 people (230,000 T1D and 566,000 T2D) with a plausibility range from 588,000 (including 358,000 T2D) to 910,000 (including 679,000 T2D).
<table>
<thead>
<tr>
<th>Estimated figure</th>
<th>N</th>
<th>%</th>
<th>Ref.:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population of France (excluding overseas departments and territories)</td>
<td>61,707,672</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>Annual rate of increase in the prevalence of diabetes</td>
<td>4.5%</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Diabetics undergoing treatment</td>
<td>2,558,039</td>
<td>4.5% of the population</td>
<td></td>
</tr>
<tr>
<td>Type 1 (and other) diabetics undergoing treatment</td>
<td>230,223</td>
<td>9% of diabetics undergoing treatment</td>
<td>36</td>
</tr>
<tr>
<td>Diabetics already on insulin</td>
<td>588,349</td>
<td>23% of diabetics undergoing treatment</td>
<td></td>
</tr>
<tr>
<td>Diabetics undergoing treatment with OAD alone</td>
<td>1,969,690</td>
<td>76% of diabetics undergoing treatment</td>
<td></td>
</tr>
<tr>
<td>Diabetics undergoing treatment with multiple OADs alone</td>
<td>953,330</td>
<td>48.4% of diabetics undergoing treatment</td>
<td></td>
</tr>
<tr>
<td>Diabetics undergoing treatment with multiple OADs alone with an HbA1c ≥7%</td>
<td>591,440</td>
<td>62% of diabetics undergoing treatment</td>
<td>37</td>
</tr>
<tr>
<td>Diabetics undergoing treatment with multiple OADs alone with an HbA1c ≥8%</td>
<td>247,635</td>
<td>26% of diabetics undergoing treatment</td>
<td></td>
</tr>
<tr>
<td>Diabetics undergoing treatment with multiple OADs alone with an HbA1c ≥8% who could benefit from insulin treatment</td>
<td>173,345 235,254</td>
<td>Low-end assumption: 70% of diabetics undergoing treatment with multiple OADs alone have an HbA1c ≥8% High-end assumption: 95% of diabetics undergoing treatment with multiple OADs alone have an HbA1c ≥8%</td>
<td></td>
</tr>
<tr>
<td>Diabetics undergoing treatment with multiple OADs alone with an HbA1c ≥7% and &lt;8%</td>
<td>343,805</td>
<td>36% of diabetics undergoing treatment with multiple OADs alone</td>
<td></td>
</tr>
<tr>
<td>Diabetics undergoing treatment with multiple OADs alone with an HbA1c ≥7% and &lt;8% who could benefit from insulin treatment</td>
<td>34,380 85,951</td>
<td>Low-end assumption: 10% of diabetics undergoing treatment with multiple OADs alone have an HbA1c ≥7% and &lt;8% High-end assumption: 20% of diabetics undergoing treatment with multiple OADs alone have an HbA1c ≥7% and &lt;8%</td>
<td></td>
</tr>
<tr>
<td>Diabetics who could benefit from insulin treatment</td>
<td>796,074</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limit</td>
<td>588,349</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limit</td>
<td>909,554</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Parameters used and population estimates for 2007. The figures in this table have not been rounded. The percentages may not add up to 100% because the percentages were rounded.

<table>
<thead>
<tr>
<th>% HbA1c</th>
<th>No. OAD</th>
<th>2 OADs</th>
<th>≥ 3 OADs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥7% to &lt; 8%</td>
<td>254,563</td>
<td>89,242</td>
<td>343,805</td>
<td></td>
</tr>
<tr>
<td>≥8%</td>
<td>163,090</td>
<td>84,545</td>
<td>247,635</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>417,653</td>
<td>173,787</td>
<td>591,440</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Estimate of the number of diabetics being treated with at least 2 OADs whose glycaemia is not under control, according to HbA1c levels and number of OADs, 2007; figures not rounded.

6.4. Transparency Committee recommendations

The Transparency Committee recommends maintaining inclusion on the list of medicines reimbursed by National Insurance in the marketing authorisation’s indications and dosages.

4.3.1 Packaging: appropriate for the prescription conditions.
4.3.2 Reimbursement rate: 65%
36 A. Fagot-Campagna, Institut de veille sanitaire, communication personnelle, septembre 2008.
37 B. Detournay, communication personnelle, septembre 2008.