HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

7 May 2014

LANTUS 100 units/ml, solution for injection in a vial

B/1 vial of 10 ml (CIP: 34009 359 464 9 2)

LANTUS 100 units/ml, solution for injection in cartridge

B/5 cartridges of 3 ml (CIP: 34009 354 632 0 3)

LANTUS OptiSet 100 units/ml, solution for injection in pre-filled pen

B/5 pre-filled pens of 3 ml (CIP: 34009 356 519 7 6)

LANTUS SoloStar 100 units/ml, solution for injection in pre-filled pen

B/5 pre-filled pens of 3 ml (CIP: 34009 377 229 8 8)

APPLICANT: SANOFI-AVENTIS FRANCE

INN	insulin glargine
ATC code	A10AE04 (insulins and analogues for injection, long-acting)
Reasons for the review	**Re-assessment at the Committee's initiative following the opinion of 25 May 2011** **Renewal of inclusion**
List concerned	**National Health Insurance** (French Social Security Code L.162-17)
Indication concerned	**"Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above. "** **NB: the review of the indication extension in children aged between 2 and 5 years old is the subject of a separate opinion.**

Actual Benefit	**Remains substantial in type 1 and type 2 diabetes.**
Improvement in Actual Benefit	**Given, on the one hand:** **- the glycaemic control obtained with LANTUS (insulin glargine) compared with that observed with NPH insulin and insulin detemir (LEVEMIR),** **- the absence of a difference between insulin glargine, insulin detemir and NPH insulin in terms of the occurrence of severe hypoglycaemia and between insulin glargine and insulin detemir in terms of overall and nocturnal hypoglycaemia,** **- the opinion of experts who do not recognise any benefit in their daily practice of using LANTUS compared with another long acting insulin analogue,** **And, on the other hand,** **- current recommendations which no longer favour treatment intensification for type 2 diabetes, which reduces the risk of hypoglycaemia,** **the Transparency Committee cannot confirm the previously recognised benefit of LANTUS (minor IAB in terms of safety) in type 1 and type 2 diabetes.** **Thus, the Committee considers that LANTUS (insulin glargine) does not provide an improvement in actual benefit (level V, non-existent) in the management of adult or adolescent patients and children aged 2 and above with type 1 or type 2 diabetes.**
Therapeutic use	**LANTUS is a 1st-line medicinal product in the management of patients with type 1 diabetes and a 2nd-line medicinal product in the management of patients with type 2 diabetes**
Transparency Committee recommendations	**The Committee will reassess LANTUS in the light of scientific developments and the data on recombinant analogues of human long-acting insulin, particularly in terms of the risk of cancer.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (European)	Initial date (centralised procedure): - 9 June 2000 (LANTUS) - 6 February 2001 (LANTUS OPTISET and LANTUS SOLOSTAR)
Prescribing and dispensing conditions/special status	List II

ATC Classification (2012)	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

02 BACKGROUND AND HISTORY OF THE REASSESSMENT

2.1 Background

The Committee shall reassess the AB and IAB of LANTUS following the provision of the results of pharmacoepidemiology studies requested by the EMA to evaluate the existence of a possible link between insulin glargine and the occurrence of breast cancer of which it asked to be the recipient in its opinion of 25 May 2011. Indeed, in this opinion, the Committee reported that the AB of LANTUS remained substantial in type 2 diabetes, but, given the uncertainties about its efficacy/adverse effects ratio, it was awaiting the results of the studies requested by the EMA before confirming or refuting the existence of an increased risk of cancer with insulin glargine. It also stated that: "Pending the results of the studies requested by the EMA, the Committee considers that it cannot confirm the benefit that it had recognised in LANTUS in terms of its safety. The Committee considers, in the current state of affairs, that insulin glargine does not provide an improvement in actual benefit (level V) compared with other insulins. "

In this opinion, the Committee shall also review the request for renewal of inclusion of LANTUS, reinstated on the list of medicines refundable by National Health Insurance for a period of 5 years from 26 July 2008 by notice published in the JO [- Official Gazette] of 12 May 2009.

The review of the indication extension in children aged between 2 and 5 years old is the subject of a separate opinion.

2.2 History

Date of opinion	**22 January 2003**
Reason	**Inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.**
Indication	"Diabetes mellitus requiring insulin treatment"
Actual Benefit	"substantial"
Improvement in Actual Benefit	"IAB level III compared with NPH insulins in terms of safety with fewer episodes of nocturnal hypoglycaemia and in terms of ease of use (1 injection a day without having to resuspend the insulin). "

Date of opinion	**23 July 2003**
Reason	**Changes in inclusion requirements: inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in adolescents and children aged 6 years and above who require insulin treatment.**
Indication	"Diabetes mellitus in adults, adolescents and children aged 6 years and above who require insulin treatment"
Actual Benefit	"substantial"
Improvement in Actual Benefit	"In the paediatric population, the available data according to which insulin glargine does not stand out, neither in terms of efficacy, nor in terms of safety, from NPH insulin, cannot result in an IAB being offered. "

Date of opinion	**15 November 2006**
Reason	**Inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use of LANTUS SoloStar 100 IU/ml in a pre-filled pen (3 ml)**
Indication	"Diabetes mellitus in adults, adolescents and children aged 6 years and above who require insulin treatment."
Actual Benefit	"substantial"
Improvement in Actual Benefit	"This proprietary medicinal product is an addition to the range which does not provide an improvement in actual benefit "

Date of opinion	**21 January 2009**
Reason	**Renewal of inclusion.**
Indication	"Diabetes mellitus in adults, adolescents and children aged 6 years and above who require insulin treatment"
Actual Benefit	"The actual benefit of LANTUS 100 units/ml (solution for injection in a vial, cartridge and pen) is substantial in type 1 and type 2 diabetes. "
Improvement in Actual Benefit	"Given the results of clinical studies available and the observational study performed which confirmed the contribution of LANTUS in real conditions of use, the Committee considers that LANTUS provides an improvement in actual benefit level IV (minor) in terms of safety. "

Date of opinion	**25 May 2011**
Reason	**Re-assessment of the AB, IAB in the therapeutic use and the target population of LANTUS following a DGS [General Directorate for Health] referral.**
Indication	"Diabetes mellitus in adults, adolescents and children aged 6 years and above who require insulin treatment."
Actual Benefit	"The actual benefit of LANTUS remains substantial in type 1 diabetes. " "The actual benefit of LANTUS remains substantial in type 2 diabetes, but, given the uncertainties about its efficacy/adverse effects ratio, the Committee is awaiting the results of the studies requested by the EMA before confirming or refuting the existence of an increased risk of cancer with insulin glargine. "
Improvement in Actual Benefit	"Pending the results of the studies requested by the EMA, the Committee considers that it cannot confirm the benefit that it had recognised in LANTUS in terms of its safety. The Committee considers, in the current state of affairs, that insulin glargine does not provide an improvement in actual benefit (level V) compared with other insulins. "

03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

3.1 Therapeutic indications

"Diabetes mellitus in adults, adolescents and children aged 6 years and above who require insulin treatment. "

3.2 Dosage

“LANTUS should be administered once daily at any time but at the same time each day.
The Lantus dose regimen (dose and timing) should be individually adjusted. "

04 CLINICALLY RELEVANT COMPARATORS

In type 1 diabetes:
In type 1 diabetes, the clinically relevant comparators of insulin glargine (LANTUS) are:
- insulins used as basal insulin in a basal-bolus regimen or in a regimen of two to five injections a day (Intermediate-acting NPH insulin or 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:
In type 2 diabetes, the clinically relevant comparators of insulin glargine (LANTUS) are:
- when insulin therapy is implemented: insulins used as basal insulin for one injection a day (Intermediate-acting NPH insulin or insulin detemir, LEVEMIR) or two injections a day (LEVEMIR), and in combination with at least one oral antidiabetic;
- when an intensified insulin regimen is implemented:
  - insulins used as basal insulin in a basal-bolus regimen (Intermediate acting NPH insulin or 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 two injections a day.

*Intermediate-acting NPH insulin or insulin detemir, LEVEMIR:

Name (Company)	INN	Date of opinion	AB	IAB
INSULATARD (Novo Nordisk)	Human NPH insulin (intermediate-acting insulin)	18 July 2012 (renewal of inclusion)	Substantial	Not applicable
UMULINE NPH (Lilly)	Human NPH insulin (intermediate-acting insulin)	20 February 2013 (renewal of inclusion)	Substantial	Not applicable
LEVEMIR (Novo Nordisk)	Insulin detemir (long-acting insulin analogue)	29 May 2013 (notice of renewal of inclusion during the phase when it can be contested (phase contradictoire)	Substantial	IAB V (non-existent) compared with other insulins

◗ **Conclusion**
The most relevant comparators are other insulins used as basal insulin: NPH insulin and insulin detemir.

NB: a new long-acting insulin analogue (insulin degludec, TRESIBA) has just obtained a Marketing Authorisation in the treatment of diabetes mellitus.

05 CLINICAL EFFICACY DATA

The company has provided new efficacy data: One clinical morbidity and mortality study and one literature review on efficacy in terms of glycaemic control, evaluated in terms of the HbA1c level, comprising 16 controlled, randomised studies, which included at least 100 patients, including 2 studies in type 1 diabetes and 14 studies in type 2 diabetes (see Appendix I).

5.1 Efficacy data in terms of morbidity and mortality

ORIGIN trial[1,2]
This is a controlled, randomised, open-label study. Its objective was to evaluate the effect of insulin glargine on the occurrence of cardiovascular events in patients with cardiovascular risk factors associated with type 2 diabetes or pre-diabetes (impaired fasting blood glucose or intolerance to glucose).

The two co-primary efficacy endpoints were the incidence of cardiovascular events (non-fatal myocardial infarction, non-fatal stroke and death) and the incidence of these same cardiovascular events associated with a revascularisation procedure or a hospitalisation linked to heart failure.

The 12,537 patients included in the study were randomised into two groups: the insulin glargine group (6264 patients) and the standard care group (6273 patients). The patients, mostly men (65%), had a mean age of 63.5 years at baseline and most had type 2 diabetes (82.3% of patients previously diagnosed, 6.1% of patients newly diagnosed and 11.6% of patients pre-diabetic). Among the patients with type 2 diabetes previously diagnosed, 33.3% were treated with metformin.

The median duration of follow-up was 6.2 years. The incidence of co-primary efficacy endpoints did not differ between the two groups (insulin glargine versus standard care): 2.94 versus 2.85 per 100 patient-years (HR=1.02; 95% CI: [0.94; 1.11]; p=0.63) for the first co-primary efficacy endpoint and 5.52 versus 5.28 per 100 patient-years (HR=1.04; 95% CI: [0.97; 1.11]; p=0.27) for the second co-primary efficacy endpoint.

5.2 Efficacy data in terms of glycaemic control

Review of the literature
The reduction in glycated haemoglobin (HbA1c) is the main primary endpoint concerning efficacy in terms of glycaemic control frequently used in the clinical trials included.

In type 1 diabetes (2 studies):
Comparison of insulin glargine with NPH insulin (one study):
- Chase et al:.[3] the non-inferiority of insulin glargine compared with NPH insulin was demonstrated after 24 weeks of treatment.

Comparison of insulin glargine with insulin detemir (one study):
- Heller et al.:[4] the non-inferiority of insulin detemir compared with insulin glargine was demonstrated after 52 weeks of treatment.

1 ORIGIN Trial Investigators. Gerstein H, Yusuf S, Riddle MC, *et al*. Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). Am Heart J. 2008; 155(1): 26-32, 32.e1-6. Trial funded by the company).

2 ORIGIN Trial Investigators. Gerstein HC, Bosch J, Dagenais GR, *et al*. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012; 367(4): 319-28.

3 Chase HP, Arslanian S, White NH, *et al*. Insulin glargine versus intermediate-acting insulin as the basal component of multiple daily injection regimens for adolescents with type 1 diabetes mellitus. J Pediatr. 2008; 153(4): 547-53.

In type 2 diabetes (14 studies):

Comparison of insulin glargine with NPH insulin (two studies):

- Rosenstock et al. 2009[5] (study on diabetic retinopathy): a significant difference between insulin glargine and NPH insulin was reported on a secondary endpoint after 5 years of treatment. This difference is in favour of NPH insulin in two injections/d: reduction in HbA1c of -0.55% versus -0.76%; difference +0.21%; 95% CI [0.06%; 0.35%]; p=0.0053).
- Lee et al.[6] (pooled analysis of 5 studies): no difference between insulin glargine and NPH insulin one injection/d was demonstrated after 24 to 28 weeks of treatment.

Comparison of insulin glargine with insulin detemir (four studies):

- Swinnen et al.:[7] no difference between insulin glargine and detemir was demonstrated after 24 weeks of treatment, knowing that it was a secondary endpoint (the primary efficacy endpoint being the proportion of patients with an HbA1c <7% without symptomatic hypoglycaemia).
- Raskin et al.;[8] Hollander et al.:[9] the non-inferiority of insulin detemir compared with insulin glargine was demonstrated after 26 to 52 weeks of treatment.
- Meneghini et al.:[10] the non-inferiority of insulin detemir compared with insulin glargine was not demonstrated, after 26 weeks of treatment, with a non inferiority hypothesis set at 0.4% (detemir versus glargine: reduction in HbA1c of -0.48% versus -0.74%; adjusted difference +0.30%; 95% CI [0.14%; 0.46%])

Comparison of insulin glargine with mixed insulins (aspart and lispro) (seven studies):

- Fritsche et al.:[11] a significant difference between insulin glargine and mixed insulins was reported, after 52 weeks of treatment, in favour of insulin glargine: reduction in HbA1c of -1.31% versus -0.80%; adjusted difference -0.476%; 95% CI [-0.71%; -0.24%]; p=0.0001).
- Buse et al.:[12] a significant difference between insulin glargine and insulin lispro was reported after 24 weeks of treatment in favour of mixed insulins: reduction of HbA1c of -1.7% versus -1.8%; difference +0.1%; p=0.005.

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4 Heller S, Koenen C, Bode B. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. Clin Ther. 2009; 31(10): 2086-97.

5 Rosenstock J, Fonseca V, McGill JB, *et al*. Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: a long-term, randomised, open-label study. Diabetologia. 2009; 52(9): 1778-88.

6 **Lee P, Chang A, Blaum C, *et al*. Comparison of safety and efficacy of insulin glargine and neutral protamine hagedorn insulin in older adults with type 2 diabetes mellitus: results from a pooled analysis. J** Am Geriatr Soc. 2012; 60(1): 51-9.

7 Swinnen SG, Dain MP, Aronson R, *et al*. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. Diabetes Care. 2010; 33(6): 1176-8.

8 Raskin P, Gylvin T, Weng W, *et al*. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. Diabetes Metab Res Rev. 2009; 25(6): 542-8.

9 Hollander P, Cooper J, Bregnhoj J, *et al*. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. Clin Ther. 2008; 30(11): 1976-87.

10 Meneghini L, Kesavadev J, Demissie M, *et al*. Once-daily initiation of basal insulin as add-on to metformin: a 26 week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes. Diabetes Obes Metab. 2013 Feb 19. [Epub ahead of print].

11 Fritsche A, Larbig M, Owens D *et al*. Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes-results of the GINGER study. Diabetes Obes Metab 2010; 12: 115-23.

- Ligthelm et al.:[13] no difference was demonstrated between insulin glargine and insulin aspart after 24 weeks of treatment.
- Bretzel et al.;[14] Strojek et al. 2009;[15] Strojek et al. 2010:[16] the non-inferiority of mixed insulins (aspart and lispro) compared with insulin glargine was demonstrated after 24 to 44 weeks of treatment.
- Rosenstock et al. 2008:[17] the non-inferiority of insulin lispro compared with insulin glargine was not demonstrated, after 24 weeks of treatment, with a non-inferiority hypothesis set at 0.3% (lispro versus glargine: reduction in HbA1c of -1.87% versus -2.09%; difference +0.22%; 95% CI [0.07%; 0.38%])

Guidelines from HAS and ANSM [National Medicines and Health Products Safety Agency][18]
According to the guidelines from HAS and ANSM of January 2013 on the therapeutic strategy for glycaemic control in type 2 diabetes, no difference in terms of variation in HbA1c was observed between insulin glargine and NPH insulin on the one hand, and between insulin glargine and detemir on the other hand.

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[12] Buse JB, Wolffenbuttel BH, Herman WH, *et al*. DURAbility of basal versus lispro mix 75/25 insulin efficacy (DURABLE) trial 24-week results: safety and efficacy of insulin lispro mix 75/25 versus insulin glargine added to oral antihyperglycemic drugs in patients with type 2 diabetes. Diabetes Care. 2009; 32(6): 1007-13.

[13] Ligthelm RJ, Gylvin T, DeLuzio T, *et al*. A comparison of twice-daily biphasic insulin aspart 70/30 and once daily insulin glargine in persons with type 2 diabetes mellitus inadequately controlled on basal insulin and oral therapy: a randomized, open-label study. Endocr Pract. 2011; 17(1): 41-50.

[14] Bretzel RG, Nuber U, Landgraf W, *et al*. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet. 2008; 371(9618): 1073-84.

[15] Strojek K, Bebakar WM, Khutsoane DT, *et al*. Once-daily initiation with biphasic insulin aspart 30 versus insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs: an open-label, multinational RCT. Curr Med Res Opin. 2009; 25(12): 2887-94.

[16] Strojek K, Shi C, Carey MA*, et al*. Addition of insulin lispro protamine suspension or insulin glargine to oral type 2 diabetes regimens: a randomized trial. Diabetes Obes Metab. 2010; 12(10): 916-22.

[17] Rosenstock J, Ahmann AJ, Colon G, *et al*. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. Diabetes Care. 2008; 31(1): 20-5.

[18] HAS (Haute Autorité de Santé) et ANSM (Agence Nationale de Sécurité du Médicament et des produits de santé). Stratégie médicamenteuse du contrôle glycémique du diabète de type 2. Good practice guidelines. January 2013.

06 CLINICAL SAFETY DATA

6.1 General safety

6.1.1 Safety data in terms of hypoglycaemia

The most commonly reported adverse effect is hypoglycaemia.

ORIGIN trial[1,2] (DT2)
Hypoglycaemia incidence was one of the secondary endpoints of this study. Overall hypoglycaemia was more common in the insulin glargine group (57.1% of patients) than in the standard care group (25.2% of patients, p<0.001) and severe hypoglycaemia was more common in the insulin glargine group (1.00/100 patient-years with at least one episode) than in the standard care group (0.31/ 100 patient-years with at least one episode, p<0.001), over a median follow-up of 6.2 years.

Review of the literature
The results in terms of hypoglycaemia (overall hypoglycaemia, severe or major hypoglycaemia and nocturnal hypoglycaemia) are presented below, when they are available.

The definition of hypoglycaemia and character of severity varies from one study to another and are to be interpreted with caution in terms of the fixed glycaemic targets in each study.

In type 1 diabetes (2 studies):
No difference in overall, severe and nocturnal hypoglycaemia was demonstrated between insulin glargine, NPH insulin and insulin detemir after 24 to 52 weeks of treatment.

In type 2 diabetes (14 studies):
Comparison of insulin glargine with NPH insulin (three studies)[5,6,19]:

- overall hypoglycaemia: none of the three studies used this endpoint for the comparison
- severe or major hypoglycaemia: two of the three studies used this endpoint for the comparison:
  - Rosenstock et al.[5] (study on diabetic retinopathy): a significant difference (but of questionable clinical relevance) in favour of insulin glargine was reported after 5 weeks of treatment in terms of percentage of patients who had at least one episode (glargine versus NPH: 7.6% versus 11.1% of patients; p=0.0439) but not in terms of the number of episodes/year/patient.
  - Home et al.[19] (meta-snalysis of five studies on safety data): no difference was demonstrated after 24 to 52 weeks of treatment.
  - Lee et al[6]: no difference was demonstrated after 24 to 28 weeks of treatment.
- nocturnal hypoglycaemia: two of the three studies used this endpoint for the comparison
  - Lee et al.[6] (pooled analysis of five studies): a significant difference between insulin glargine and NPH insulin was reported after 24 to 28 weeks of treatment in favour of insulin glargine: 0.8% versus 2.2% of patients and 0.03 versus 0.08 episodes/patient/year, p<0.05.
  - Home et al.[19] (meta-analysis of 5 studies on safety data): a significant difference between insulin glargine and NPH insulin was reported after 24 to 52 weeks of treatment in favour of insulin glargine: OR=0.52; 95%CI [0.27; 1.00], p=0.0498, but only affects severe nocturnal hypoglycaemia in one or two pooled analyses.

[19] Home PD, Fritsche A, Schinzel S, *et al*. Meta-analysis of individual patient data to assess the risk of hypoglycaemia in people with type 2 diabetes using NPH insulin or insulin glargine. Diabetes Obes Metab. 2010; 12(9): 772-9.

- Rosenstock et al. 2009[5] (study on diabetic retinopathy): no difference was demonstrated after 5 years of treatment.

Comparison of insulin glargine with insulin detemir (four studies):

- overall hypoglycaemia: three of the four studies used this endpoint for the comparison
  - Meneghini et al.:[10] a significant difference between insulin glargine and insulin detemir was reported after 26 weeks of treatment in favour of insulin detemir: RR=0.73 95% CI [0.54; 0.98]; p=0.034.
  - Raskin et al.,[8] Hollander et al.:[9] no difference was demonstrated after 26 to 52 weeks of treatment.
- severe or major hypoglycaemia: the four studies used this endpoint for the comparison
  - Meneghini et al.:[10] a significant difference between insulin glargine and insulin detemir was reported after 26 weeks of treatment in favour of insulin detemir: 0% versus 1% of patients and 0.00 versus 0.02 episodes/patient/year.
  - Swinnen et al.,[7] Raskin et al.,[8] Hollander et al.:[9] no difference was demonstrated after 26 to 52 weeks of treatment.
- nocturnal hypoglycaemia: the four studies used this endpoint for the comparison
  - Swinnen et al.,[7] Raskin et al.,[8] Hollander et al.,[9] Meneghini et al.:[10] no difference was demonstrated after 26 to 52 weeks of treatment.

Comparison of insulin glargine with mixed insulins (aspart and lispro) (seven studies):

- overall hypoglycaemia: the seven studies used this endpoint for the comparison
  - Buse et al.:[12] a significant difference between insulin glargine and mixed insulins was reported after 24 weeks of treatment in favour of insulin glargine: 51.8% versus 57.1% of patients, p=0.016 and 23.1 versus 28.0 episodes/patient/year; p<0.05.
  - Ligthelm et al.:[13] a significant difference between insulin glargine and aspart was reported after 24 weeks of treatment in favour of insulin glargine: RR=1.47; 95% CI [1.01; 2.12]; p<0.05.
  - Bretzel et al.:[14] a significant difference between insulin glargine and insulin lispro was reported after 44 weeks of treatment in favour of insulin glargine: 66% versus 89% of patients and 5.21 versus 24.00 episodes/patient/year, p<0.0001.
  - Strojek et al. 2009:[15] a significant difference between insulin glargine and aspart was reported after 26 weeks of treatment in favour of insulin glargine: RR=1.41 (95% CI [1.03; 1.93]; p=0.034.
  - Fritsche et al.,[11] Strojek et al. 2010,[16] Rosenstock et al. 2008:[17] no difference was demonstrated after 24 to 52 weeks of treatment.
- severe or major hypoglycaemia: the seven studies used this endpoint for the comparison
  - Fritsche et al.,[11] Buse et al.,[12] Ligthelm et al.,[13] Bretzel et al.,[14] Strojek et al. 2009,[15] Rosenstock et al. 2008:[17] no difference between insulin glargine and mixed insulins was demonstrated after 24 to 52 weeks of treatment.
  - Strojek et al, 2010:[16] two patients had an episode of severe or major hypoglycaemia in the glargine group versus nine in the insulin aspart group, p=0.04 but with no difference between the two groups in terms of number of episodes/patient/year.
- nocturnal hypoglycaemia: the seven studies used this endpoint for the comparison
  - Strojek et al. 2009:[15] a significant difference between insulin glargine and aspart was reported after 26 weeks in favour of insulin glargine: RR=2.41; 95% CI [1.34; 4.34]; p=0.003.
  - Strojek et al. 2010:[16] a significant difference between insulin glargine and insulin lispro was reported after 24 weeks in favour of insulin glargine: 38.2% versus 50.2% of patients, p=0.01 and 4.1 versus 6.1 episodes/patient/year; p<0.001.
  - Buse et al.:[12] a significant difference between insulin glargine and insulin lispro was reported after 24 weeks of treatment in favour of insulin lispro: 11.4 versus 8.9 episodes/patient/year; p=0.009.
  - Fritsche et al.,[11] Ligthelm et al.,[13] Bretzel et al.,[14] Rosenstock et al. 2008:[17] no difference was demonstrated after 24 to 52 weeks of treatment.

Reminder of SPC data

The "Undesirable effects" section of the SPC specifies that hypoglycaemia is a very common undesirable effect (higher than or equal to 1 case in 10), as well as the following:

"Hypoglycaemia, in general, the most frequent adverse effect of any insulin therapy, may occur if the insulin dose is higher than is necessary. […]
Severe hypoglycaemic episodes, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life threatening.
In many patients, the signs and symptoms of neuroglycopaenia are preceded by signs of adrenergic compensatory response. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of adrenergic compensatory response and its symptoms. "

The "Special warnings and precautions for use" section of the SPC specifies the following:

The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed. Due to more sustained basal insulin supply with Lantus, less nocturnal but more early morning hypoglycaemia can be expected.
Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients
with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).
Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups [...].
Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.
The prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycaemia.
If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.
Adherence of the patient to the dose and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment [...]. "

6.1.2 Pharmacovigilance data

The compnay has submitted the ten most recent periodic safety update reports (PSURs) covering the period from 22 October 2007 to 21 October 2012. Exposure to insulin glargine throughout this period was estimated to be 36,566,959 patient-years worldwide. Exposure since its marketing was estimated to be 51,857,914 patient years worldwide. During this period, 54,879 cases were reported, 11,635 (21.2%) of these by healthcare professionals. Among these 54,879 cases, 12,184 (22.2%) were serious cases. Among these 54,879 cases, 7774 (14.2%) were serious unexpected cases and 1828 (15.0%) of them were confirmed by healthcare professionals.

The quantitative analyses of all the effects show an increase in the number of spontaneous notifications from 2009, the time at which the articles on the supposed linked between cancer and insulin glargine were published in the journal *Diabetologia*. The cumulative analyses focus on the serious and unexpected effects (analysis of the cases and literature) and also include the analyses requested by the EMA as part of its Risk Management Plan (RMP). These analyses did not reveal any new safety signal for insulin glargine.

6.1.3 Changes to the SPC

Since the previous renewal of inclusion (opinion of 21 January 2009), changes to the SPC have been carried out and mainly cover the sections "Therapeutic indications", "Posology and method of administration", "Special warnings and precautions for use", "Fertility, pregnancy and lactation", "Undesirable effects", "Pharmacodynamic properties" and "Pharmacokinetic properties" (see Appendix II).

6.2 Specific safety: carcinogenicity

6.2.1 Carcinogenicity

Insulin generally has a mitogenic effect in vitro. The mitogenic effect of insulin may be induced by extended activity of the insulin receptor (IR) and/or excessive stimulation of the IGF-1 receptor, IGF-1R (interference between IR and IGF-1R). Expression of IR and IGF-1R may vary among different tissues. Moreover, inter-individual differences in protein levels in the IGF-1R system might be critical in the mitogenic effect of insulin analogues. Insulin stimulates and regulates the growth and proliferation of certain types of somatic cells. Insulin resistance and hyperinsulinaemia may be major risk factors for cancer in diabetics. Some insulin analogues, including insulin glargine and insulin detemir, have been suspected of having a greater mitogenic effect than human insulin.

Epidemiological[20] studies indicate that diabetes is a risk factor for breast, colon, bladder, pancreas and endometrial cancer and that insulin may contribute to the growth of tumour cells.

The "Preclinical safety data" section of the SPC specifies the following: *"Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. "*

[20] ADA (American Diabetes Association) and ACS (American Cancer Society). Giovannucci E, Harlan DM, Archer MC, *et al*. Diabetes and cancer: a consensus report. Diabetes Care. 2010; 33(7): 1674-85.

6.2.2 Risk of cancer under insulin glargine

Data from the post-marketing ORIGIN trial[1,2]

Cancer incidence was a secondary endpoint. All-cause cancer incidence (breast, lung, colon, prostate, melanoma, other) did not differ between the two groups (insulin glargine versus standard care: HR=1.00 (95% CI [0.88; 1.13]; p=0.97). The mortality rate linked to all cancers did not differ between the two groups (insulin glargine versus standard care: HR=0.94 (95% CI [0.77; 1.15]; p=0.52). Cancer incidence, localisation by localisation, did not differ between the two groups (insulin glargine versus standard care: HR between 0.88 and 1.21; p between 0.27 and 0.95), particularly with regards to breast cancer (insuline glargine versus standard care: HR=1.01; 95% CI [0.60; 1.71]; p=0.95).

These results should be interpreted with caution for the following reasons:

- almost 12% of the 12,537 patients included were pre-diabetic,
- almost 27% of the patients included and almost 60% of patients at the end of the study were also treated with metformin. However, metformin is considered likely to have a protective effect with respect to the occurrence of cancer in these patients.

Moreover, we note that in its report dated 16 May 2013 (EMA/PRAC/295408/2013), the PRAC has decided not to show the results of this study concerning cancer in section 5.1 *Pharmacodynamic properties* of the SPC. This decision was based on the fact that the study was not designed to evaluate this risk.

Data from pharmacoepidemiology studies (see Appendix III)

In July 2009, following the publication of the results of four epidemiological studies,[21,22,23,24] the CHMP [Committee for Medicinal Products for Human Use] evaluated the existence of a possible link between exposure to insulin analogues, particularly insulin glargine, and the occurrence of cancer, particularly breast cancer given these data.[25] The EMA has therefore concluded that, especially given the existence of considerable methodological bias and contradictory results, these studies do not allow any conclusions to be made about a link between taking insulin glargine and the increased risk of cancer. The registration authorities have asked SANOFI to provide additional data, in particular pharmacoepidemiological studies.

In May 2013, following submission of the results of three pharmacoepidemiology studies,[26,27,28] the CHMP re-assessed the possible link between exposure to insulin glargine and the occurrence of cancer.[29] Two of these three studies are studies on retrospective cohorts, conducted in Northern Europe[26] and the United States[27] which investigated the appearance of breast, colorectal and prostate cancers associated with different insulins. The third study is a case-control study,

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21 Hemkens LG, Grouven U, Bender R, *et al*. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia. 2009; 52(9): 1732-44.

22 Jonasson JM, Ljung R, Talbäck M, *et al*. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. Diabetologia. 2009; 52(9): 1745-54.

23 SDRN (Scottish Diabetes Research Network) Epidemiology Group. Colhoun HM. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. Diabetologia. 2009; 52(9): 1755-65.

24 Currie CJ, Poole CD, Gale EA, *et al*. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia. 2009; 52(9): 1766-77.

25 EMEA (European Medicines Agency). European Medicines Agency update on safety of insulin glargine. EMEA/408474/2009. June 2009.

26 Northern European Database Study of Insulin and Cancer Risk. Boyle P, Boffetta P, Autier P, *et al*. [Unpublished].

27 Cohort Study of Insulin Glargine and Cancer Risk among Patients with Diabetes Mellitus - Kaiser Permanente, Northern and Southern California Regions. Habel LA, Ferrara A, Danforth KN, *et al*. [Unpublished].

28 ISICA (International Study of Insuline and CAncer) - Insulin glargine and the risk of breast cancer. ISICA Research Group. [Unpublished].

29 EMA (European Medicines Agency). Outcome of review of new safety data on insulin glargine - Data from population-based studies and the scientific literature do not indicate an increased risk of cancer. EMA/329790/2013 - EMEA/H/C/000309. May 2013.

conducted in France, Great Britain and Canada,[28] which compared diabetic patients with breast cancer with a control group (diabetic patients with no breast cancer), treated with different insulins. Based on all these data and a review of the literature, the EMA concluded that there was no increased risk established for cancer due to insulin glargine. However, in the report on the discussions of the PRAC of May 2013, some of the rapporteur countries estimated that this increased risk could not be ruled out.
Moreover, the ANSM has made a referral to the CNAMTS [French National Health Insurance Fund for Salaried Workers] for them to carry out an observational study from the data collected in France by National Health Insurance.

Summary of the studies:

After the publication in Diabetologia of four retrospective studies, databases, three of which suggested a possible link between taking insulin analogues (especially insulin glargine) and the risk of cancer, the CHMP (EMA), in its opinion of 18 February 2010, stipulated that the benefit/risk balance remained positive, renewed the Marketing Authorisation of Lantus for 5 years and combined this opinion with the implementation of a European RMP which included the following:

- Amendments to the protocol of the ORIGIN trial (on cardiovascular events) to integrate cancer cases (results expected in Q4 2012).
- Completion of three epidemiological studies (protocols approved by EMA)
  - Cohort study "breast, prostate and colorectal cancer and antidiabetics" from prescription databases in Sweden, Norway, Denmark, Finland and Scotland (final results initially planned for Q2 2011 and announced at the end of Q1 2012).
  - "Cancer and insulins" cohort study from Californian Kaiser Permanente database on around 160,000 patients monitored for 9 years (final results initially planned in Q3 2011, recently announced in Q1 2012)
  - ISICA "breast cancer and insulin" case-control study on 750 patients with breast cancer and 3000 controls (final results initially planned in Q2 2012, announced in Q4 2012).

The results below are for the three epidemiological studies cited above, and a study carried out by the CNAM-TS at the request of the ANSM from the SNIIRAM [National Information System Inter Plans Health Insurance] database and an additional study provided by the company, carried out by the University of North Carolina from the American database MedAssurant.

- **Northern European cohort study, based on a database analysis (Sweden, Norway, Denmark, Finland and Scotland)**

For breast cancer, the meta-analyses carried out as part of this study show:
- in the total study population: no statistically significant increased risk in women using glargine compared with all female users of insulins (RR=1.15 [0.97; 1.34]) and compared with all female users of human insulins (RR=1.14 [0.96; 1.36]);
- in the subpopulation of new female users of insulin: a statistically significant increased risk in new female users of glargine compared with all other insulins (RR = 1.45 [1.10; 1.90]).
The dose-response analyses showed that this increase appeared early, in the first year that glargine was used.
For colorectal cancer, there was no increased risk associated with the use of insulin glargine. For prostate cancer, the results of the meta-analysis cannot be considered because of the screening differences between the countries studied.
For the other cancer localisations (all localisations, lung and pancreatic), the meta-analyses do not show any increased risk associated with the use of glargine.

- **"Insulin glargine and risk of cancer among diabetic patients" cohort study - Kaiser Permanente (USA)**

Among all patients, this study does not show any association between insulin glargine and breast cancer (HR=1.0 [0.9; 1.3]), prostate cancer (HR=0.7 [0.6; 0.9]), or colorectal cancer (HR=1.0 [0.8; 1.2]).
Moreover, there is no association between insulin glargine and the risk of "all localisation" cancer (HR = 0.9 [0.9; 1.0]).

In contrast, there is an association between insulin glargine and breast cancer in new users of insulin (HR=1.3 [1.0; 1.8]), especially in those who initiated insulin glargine over 2 years ago (HR=1.6 [1.0; 2.8]) taking into account the time elapsed between the prescriptions and HR=2.2 [1.2; 4.2] taking into account the duration of prescription).

- **ISICA study**

This study did not show any increased risk of breast cancer among users of glargine compared with non-users or compared with users of human insulin.

- **CNAMTS study**

The CNAMTS study did not show an increased risk of "all localisation" cancer linked to insulin glargine in the first analysis.
For breast cancer, although the data presented do not show statistically significant increased risk (study power), the fact that the RR increase according to cumulative dose (dose effect), prompts caution.
A new analysis was conducted with an additional year of follow-up: a statistically significant increased risk is found in 40-79 year-olds for breast cancer with insulin glargine (HR=1.86 [1.29; 2.68] for model 1 and HR=2.10 [1.42; 3.12] for model 2) and insulin detemir (HR=1.95 [1.05; 2.05] for model 1 and HR=1.50 [1.03; 2.19] for model 2), for cumulative doses >=37,000 IU versus <18,000 for glargine and >= 34,000 IU versus <15,000 for detemir. Equally statistically significant results were found with the mean dose for both types of insulin. No statistically significant result was found with cumulative duration.
For colorectal cancer, an increased risk is found for glargine only in the analysis relating to mean dose (HR=1.39 [1.03; 1.88] for model 1 and HR=1.55 [1.12; 2.14] for model 2 in 40-79 year-olds) and for detemir in the analysis relating to cumulative dose (HR=2.62 [1.55; 4.45] for model 1 and HR=2.84 [1.62; 4.99] for model 2 in 40-79 year-olds) and the mean dose (HR=2.06 [1.21; 3.48] for model 1 and HR=2.39 [1.36; 4.20] for model 2 in 40-79 year-olds).
However, no increased risk was found with human insulin, regardless of the type of cancer considered, the type of analysis conducted or the population considered.

In this study, the results of analyses by duration and by cumulative dose do not agree. Remember, no adjustment was made for BMI, HbA1c and insulin resistance.

- **Study conducted from MedAssurant**

This study for which we only have very patchy results, in which the median duration of follow-up is very short (less than one year) and the number of events low (122 cases of breast cancer whatever the insulin considered), indicates a non-adjusted HR of the same order of magnitude as, presented in the other studies between use of glargine and breast cancer, but not statistically significant (HR=1.517 [0.976; 2.358]) and an adjusted HR[30] of 1.05 [0.830; 2.050].

07 USAGE AND PRESCRIPTION DATA

According to the IMS-EPPM [IMS Permanent Study of Medical Prescription] (moving annual total summer 2012), the proprietary medicinal products LANTUS were prescribed 1,345,000 times, 56% of them as a vial and 44% as a pre-filled syringe. Almost 33% of prescriptions were made for patients with type 1 diabetes, 23% for patients with type 2 diabetes and the information is not available for 43% of prescriptions. Over 98% of prescriptions were made for patients aged 25 years and above (around 91% for patients aged 45 years and above, 61% for patients aged 65 years and above and 33% for patients aged 75 years and above). The mean dose was one daily application, and the mean number of months for which prescriptions were issued was 2.

[30] Propensity score including the following factors: age, sex, year of entry into the cohort, comorbidities, associated drug treatments, participation in screening tests, use of healthcare services.

08 SUMMARY & DISCUSSION

8.1 Summary

8.1.1 Efficacy data in terms of morbidity and mortality in diabetes

Type 1 diabetes

No new clinical data.

Type 2 diabetes

The ORIGIN trial[1,2] compared the effect of insulin glargine on the occurrence of cardiovascular events in patients with cardiovascular risk factors associated with type 2 diabetes or pre-diabetes with that of a standard treatment without insulin. The two co-primary efficacy endpoints were the incidence of cardiovascular events (non-fatal myocardial infarction, non-fatal stroke and death) and the incidence of these same cardiovascular events associated with a revascularisation procedure or a hospitalisation linked to heart failure. The incidence of the two co-primary endpoints did not differ between the two groups (insulin glargine versus standard care) in 12,537 patients and with a median duration of follow-up of 6.2 years. Given these results, the efficacy of insulin glargine expected in terms of morbidity and mortality is not different from that of other insulins in type 2 diabetes.

8.1.2 Efficacy data in terms of glycaemic control

A review of the literature allowed an evaluation to be made about the efficacy of insulin glargine in terms of glycaemic control. The reduction in glycated haemoglobin (HbA1c) was the primary endpoint concerning efficacy in terms of glycaemic control.

Type 1 diabetes
During its previous review in 2009, the Committee had concluded that:
- In adults: LANTUS is prescribed as part of an insulin therapy regimen with multiple basal bolus injections. The new comparative data of satisfactory methodological quality (Fulcher et al study) provides little additional information on the efficacy of LANTUS in comparison with NPH insulins since the Committee's previous opinion. They confirm that the glycaemic control obtained (HbA1c) with insulin glargine as part of a basal-bolus regimen is similar to that obtained with NPH insulin.
The two long-acting insulin analogues, glargine (one injection/d) and detemir (two injections/d) were compared in one single study (Pieber et al.). The results do not support any conclusions that there is any difference between them, whether it's in terms of glycaemic control (HbA1c) or hypoglycaemia risk.
- In children: the clinical data available in children aged 6 years and above and in adolescents remain insufficient. They are insufficient to assess the benefit of LANTUS in these patients compared with other insulin regimens. The efficacy and safety of LANTUS (and LEVEMIR) have not been studied in children below 6 years of age.

The new data presented by the company confirms the non-inferiority of insulin glargine compared with NPH insulin after 24 weeks in children aged 9 to 17 years (Chase et al study) and compared with insulin detemir after 52 weeks of treatment in children (Heller et al study). In children under 6 years of age, the data remain very limited (see opinion for LANTUS in the indication extension in children aged 2 to 5 years).

Type 2 diabetes
During its previous review in 2009, the Committee had concluded that:
Insulin therapy is considered after failure of a combination of at least two hypoglycaemic agents as one or two injections of NPH insulin or a long acting insulin analogue. The glycaemic control obtained with the long-acting analogues or with NPH insulin is similar in terms of reduction in the

HbA1c level and proportion of patients with a "normalised" HbA1c of 7%. The long-term efficacy of insulin glargine (and insulin detemir) remains poorly documented. Long-acting insulin analogues have not demonstrated an impact on morbidity or mortality or on quality of life (Cochrane meta-analysis, 2008).

The new data presented by the company:
Comparison of insulin glargine with NPH insulin (three studies):

- two studies (including one pooled analysis of five studies) did not demonstrate any difference in favour of insulin glargine after 24 weeks to 5 years of treatment.
- one study (Rosenstock *et al.* 2009[5]) reported a difference to the disadvantage of insulin glargine in terms of a secondary endpoint (study on diabetic retinopathy) after 5 years of treatment

Comparison of insulin glargine with insulin detemir (four studies):

- four studies did not demonstrate any difference in favour of insulin glargine after 24 to 52 weeks of treatment
- one study (Meneghini *et al*.[10]) did not demonstrate the non-inferiority of insulin detemir compared with insulin glargine after 26 weeks of treatment

Comparison of insulin glargine with mixed insulins (aspart and lispro) (seven studies):

- six studies did not demonstrate any difference in favour of insulin glargine after 24 to 44 weeks, and one study (Fritsche *et al*.[11]) reported a difference in favour of insulin glargine after 52 weeks of treatment
- one study (Buse *et al.*[12]) reported a difference to the disadvantage of insulin glargine after 24 weeks of treatment
- one study (Rosenstock *et al.* 2008[17]) did not demonstrate the non-inferiority of insulin lispro compared with insulin glargine after 24 weeks of treatment

Given these results versus intermediate-acting NPH insulin and versus insulin detemir, and the modest effect size on the glycaemic control in case of significant difference in favour of insulin glargine versus mixed insulins (a study on the eight studies presented), the efficacy in terms of the glycaemic control of insulin glargine did not appear different from that of other insulins.

8.1.3 General safety data in terms of hypoglycaemia

In type 1 diabetes
The two studies (the one of 24 weeks vs NPH insulin and the other of 52 weeks of treatment vs insulin detemir) did not demonstrate any difference in favour of insulin glargine.

In type 2 diabetes
During the previous review (opinion of RI, 2009), the Committee had concluded that "the risk of hypoglycaemia increases when the glycaemic control is better, whatever the insulin used". With insulin glargine (LANTUS) compared with NPH insulin, no reduced risk of symptomatic hypoglycaemia, whether severe or not, was demonstrated, reduced risk, but several studies suggested a reduction in the risk of nocturnal hypoglycaemia. The size of this effect is difficult to estimate to the extent that the evaluation of hypoglycaemia was carried out with varying definitions of hypoglycaemia and using several (secondary) evaluation endpoints (symptomatic, severe, diurnal, nocturnal hypoglycaemia). The size of this effect appears at best modest and no impact on quality of life was demonstrated (Cochrane 2008 meta-analysis). "

The data newly presented by the company (three studies) do not alter this conclusion:
- o overall hypoglycaemia: information not provided in the three studies.
- o severe or major hypoglycaemia: one study (Rosenstock *et al.* 2009[5]) reported a difference in favour of insulin glargine after 5 weeks of treatment in terms of percentage of patients who had at least one episode, but not in terms of number of episodes/patient/year), and one meta-analysis of five studies (Home *et al*.[19]) reported a difference in favour of insulin glargine after 24 to 52 weeks of treatment, but it only affects severe nocturnal hypoglycaemia, in only one of the two pooled analyses. One pooled analysis (Lee et al,[6] 2012) did not demonstrate any difference.
- o nocturnal hypoglycaemia: one study (Rosenstock *et al.* 2009[5]) did not demonstrate any difference in favour of insulin glargine after 5 years of treatment. One pooled analysis of five studies (Lee *et al.*[6]) reported a difference in favour of insulin glargine after 24 to 48 weeks of treatment.

Regarding the comparison of the risk of hypoglycaemia between the two long-acting insulin analogues, the four studies submitted do not allow any differentiation to be made between insulin glargine and insuline detemir:
- o overall hypoglycaemia: two studies (Raskin et al.[8] ; Hollander et al.[9]) did not demonstrate any difference in favour of insulin glargine after 26 to 52 weeks, and one study (Meneghini et al.[10]) reported a difference to the disadvantage of insulin glargine after 26 weeks of treatment
- o severe or major hypoglycaemia: three studies (Swinnen et al.[7] ; Raskin et al.;[8] Hollander et al.[9]) after 26 to 52 weeks, and 1 study (Meneghini et al.[10]) reported a difference to the disadvantage of insulin glargine after 26 weeks of treatment
- o nocturnal hypoglycaemia: four studies (Swinnen et al.[7]; Meneghini et al.) ; Raskin et al.;[8] Hollander et al.;[9] Meneghini et al.[10]) did not demonstrate any difference in favour of insulin glargine after 26 to 52 weeks of treatment.

Regarding the comparison of the risk of hypoglycaemia between insulin glargine and mixed insulins (aspart and lispro), the seven new studies presented are not very relevant to the extent that the expected risk of hypoglycaemia on mixed insulins is greater because of the presence of a rapid-acting analogue. Moreover, the results of the studies are not comparable:
- o overall hypoglycaemia: three studies (Fritsche et al.,[11] Strojek et al. 2010,[16] Rosenstock et al. 2008[17]) did not demonstrate any difference in favour of insulin glargine after 24 to 52 weeks of treatment, and four studies (Buse et al.,[12] Ligthelm et al.,[13] Bretzel et al.,[14] Strojek et al. 2009[15]) reported a difference in favour of insulin glargine after 24 to 44 weeks of treatment
- o severe or major hypoglycaemia: six studies (Fritsche et al.,[11] Buse et al.,[12] Ligthelm et al.,[13] Bretzel et al.,[14] Strojek et al. 2009,[15] Rosenstock et al. 2008[17])
- o nocturnal hypoglycaemia: 4 studies (Fritsche et al.,[11] Ligthelm et al.,[13] Bretzel et al.,[14] Rosenstock et al. 2008[17]) did not demonstrate any difference in favour of insulin glargine after 24 to 52 weeks of treatment, two studies (Strojek et al. 2009,[15] Strojek et al. 2010[16]) reported a

difference in favour of insulin glargine after 24 to 26 weeks of treatment, and one study (Buse et al.[12]) reported a difference to the disadvantage of insulin glargine after 24 weeks of treatment

In the ORIGIN trial, which included 12,537 patients, the incidence of overall hypoglycaemia and severe hypoglycaemia was more common in the insulin glargine group than in the standard care group after a median duration of follow-up of 6.2 years.

In all, a new study lasting 5 years and a meta-analysis of five studies lasting 24 to 52 weeks suggest a minimum risk of severe or major hypoglycaemia between insulin glargine and NPH insulin. However, in the new study, if the proportion of patients with hypoglycaemia after 5 years of treatment was less under glargine (clinical relevance of questionable difference), the number of episodes of hypoglycaemia per patient and year has not differed between the two groups. Moreover, in the meta-analysis, the difference was not observed in all patients (according to whether they were treated with glargine in the morning or evening). And the observed difference, in those who received treatment with glargine in the evening, was modest (with an upper limit of the confidence interval equal to 1 and a degree of significance p=0.0498).
The data from a pooled analysis of five studies suggest a lower risk of nocturnal hypoglycaemia between insulin glargine and NPH insulin after 24 to 48 weeks of treatment. However, no reduction in nocturnal hypoglycaemia was demonstrated after 5 years of treatment in a new clinical study.
The risk of overall, severe or major and nocturnal hypoglycaemia seems similar between insulin glargine and insulin detemir.
The reduction in the risk of hypoglycaemia observed in the studies which compared insulin glargine with mixed insulins is only slightly relevant to the extent that this risk is increased by the presence of a rapid-acting insulin.

8.1.4 Safety data concerning the risk of cancer

According to ANSM,[31] "given all the data available, the signal of 2009 was not confirmed " .The Bradford Hill criteria to establish a causal link between insulin glargine and the risk of breast cancer were not fully met. Several studies found an association, with a dose effect. However, these studies, carried out from administrative databases, do not allow all the potential confounding factors to be considered. The studies which did not find any statistically significant association also present methodological limits, in particular a relatively short follow up duration (especially the ISICA study and ORIGIN clinical trial).

[31] Insuline glargine et risque de cancer: conclusion de l'évaluation des nouvelles données de sécurité – Point d'information, ANSM, 28 February 2014.

8.2 Discussion & Conclusion

In type 2 diabetes, there is no proof of efficacy of insulin glargine in terms of morbidity and mortality endpoints (ORIGIN trial). There is no difference in terms of glycaemic control evaluated in terms of HbA1c between insulin glargine and the other insulins (NPH as with detemir). There is no clearly established difference in safety in terms of the occurrence of overall, severe or major (and severe nocturnal) hypoglycaemia between insulin glargine and the other insulins. Moreover, the current recommendations for management no longer systematically favour intensified insulin regimens, which would reduce the risk of hypoglycaemia.

In type 1 diabetes, and as part of a basal-bolus insulin therapy regimen, insulin glargine is prescribed as basal insulin at the rate of one injection a day. Insulin detemir may be used at the rate of one or two injections a day. There is no evidence that this difference in ease of use with insulin glargine has an impact in terms of efficacy or safety or quality of life for the patient.

No causal links between the occurrence of cancer (especially breast cancer) and long-acting insulin analogues (especially insulin glargine) were demonstrated. Longer-term data are necessary to rule out this concern.

In all, LANTUS does not differentiate itself from other insulins prescribed in type 1 diabetes and type 2 diabetes.

09 THERAPEUTIC USE

Scientific data regarding treatment of type 1 and type 2 diabetes were considered.[18,32,33,34,35,36,37]

A- Therapeutic use in 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 match the action profile of the insulin and the physical exercise undertaken.
The aims 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 growth and puberty in children.

Several insulin therapy regimens are possible; the choice depends on the glycaemic targets of each patient, his preferences and his lifestyle:

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

Dose regimens of the basal-bolus type or by pump 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 of insulin levels.

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

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32 HAS (Haute Autorité de Santé). Transparency Committee Opinion on LANTUS. January 2009.

33 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(6): 1364-79.

34 ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes). Nathan DM, Buse JB, Davidson MB, *et al*. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2009; 52(1): 17-30.

35 NICE (National Institute for Health and Clinical Excellence). Type 2 diabetes: newer agents – Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes. This short clinical guideline partially updates NICE clinical guideline 66. The recommendations have been combined with unchanged recommendations from CG66 in NICE clinical guideline 87. May 2009.

36 NICE (National Institute for Health and Clinical Excellence). NICE and diabetes: a summary of relevant guidelines. November 2009.

37 SIGN (Scottish Intercollegiate Guidelines Network). Management of diabetes - A national clinical guideline. Guideline 116. March 2010

Place of LANTUS in the therapeutic strategy of the management of type 1 diabetes:
The 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).

B- Therapeutic use in the management of type 2 diabetes:
Objective of treatment: reduce morbidity and mortality, in particular using the correct glycaemic control. The short-term objective is the improvement of symptoms (thirst, polyuria, asthenia, emaciation and blurred vision) and prevention of acute complications (infections and hyperosmolar hyperglycaemic state). The longer-term objective is the prevention of chronic microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (myocardial infarction, strokes and obliterating arteriopathy of the lower limbs) complications and reduction of mortality.

Glycaemic target: according to HAS (2013) guidelines, it should be individualised depending on patient profile and can therefore evolve over time. Diabetes is progressive and treatment should be regularly re-assessed in all its components: hygiene and dietary measures, therapeutic education and drug treatment. Data from literature does not provide the opportunity of defining a lower limit for the HbA1c target. Once the target is achieved, the treatment will be adjusted on a case by case basis. For most patients with type 2 diabetes, an HbA1c target ≤7% is recommended. The drug treatment should be initiated or re-assessed if the HbA1c is higher than 7%.
Special cases: for patients in whom diabetes has been newly diagnosed, with a life expectancy of more than 15 years and with no history of cardiovascular events, a target ≤6.5% is recommended, subject to it being achieved by the implementation or reinforcement of hygiene and dietary measures then, in case of failure, with oral monotherapy.
There is a certain number of special cases where the glycaemic target is less demanding: age > 75years; history of macrovascular complication; chronic renal failure; proven serious comorbidity; limited life expectancy (<5 years); long-lasting diabetes (>10 years) and where the target of 7% proves difficult to achieve because the increase in drugs causes severe hypoglycaemia.
Implementation of effective hygiene and dietary measures is a necessary prerequisite for glycaemic control medication.

Drug strategy:

According to recent HAS guidelines, as a general rule, the recommended strategy for introducing antidiabetics is as follows:
- metformin monotherapy
- then dual metformin + sulfonylurea therapy if the deviation from the target is <1% HbA1c.
- then, triple therapy via metformin + sulfonylurea + alpha glucosidase inhibitors or DPP-4 inhibitors if the deviation from the target is <1% HbA1c.
- then, if the glycaemic target is not reached, insulin is introduced in combination with metformin + sulfonylurea. Possible alternative to insulin: GLP-1 analogues if BMI ≥30 or if the weight gain with insulin is serious.

Insulin therapy is also possible in the following specific situations:

At the triple therapy stage
Insulin may be combined with metformin + sulfonylurea if the deviation from the target is >1% HbA1c with dual therapy.
Alternative: metformin + sulfonylurea + GLP-1 analogues if the BMI ≥30 or if the weight gain with insulin is serious.
At the dual therapy stage in the event of intolerance or contraindication to sulfonylureas or metformin
Insulin may be combined with metformin (or sulfonylurea) if the deviation from the target is >1% HbA1c with monotherapy, and in the event of failure of the oral dual therapy.
Alternative: metformin (sulfonylurea) + GLP-1 analogues combination if the BMI ≥30 or if the weight gain with insulin or the occurrence of hypoglycaemia are serious.

At the monotherapy stage
Insulin therapy is not recommended except in specific situations (pregnancy). Moreover, introducing insulin therapy is recommended if the glycaemic target is not achieved despite monotherapy via repaglinide, alpha-glucosidase inhibitors or DPP-4 inhibitors and if metformin and sulfonylurea are not tolerated or contraindicated.

Place of insulin therapy
The choice of insulin therapy regimen depends on several parameters, such as:
- patient choice: will the patient accept the treatment? The number of injections?
- the glycaemic targets and the patient's ability to achieve them;
- patient autonomy: can she manage her treatment? If the patient is unable, can her relatives help her or is a nurse required?
- the glycaemic profiles: is there an isolated fasting hyperglycaemia or associated with one or more episodes of post-prandial hyperglycaemia?
- patient lifestyle: are the type of food (meal times and carbohydrate content) and physical activity regular or erratic?

Hence, the choice of insulin therapy is based on the expertise of caregivers to transmit to the patient or the person who will be in charge of giving this treatment. Use of an endocrinologist will be considered to initiate or optimise the insulin regimen in case of difficulty in achieving the set glycaemic targets.

When insulin therapy is implemented, and alongside monotherapy or dual therapy, one should start:
- preferably with intermediate-acting (NPH) insulin at bedtime;
- or with a long-acting analogue if the risk of nocturnal hypoglycaemia is serious.

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

In the event of very uncontrolled diabetes, with repeated blood glucose higher than 3 g/l and/or an HbA1c >10%, an intensified insulin regimen can be initiated directly after consulting an endocrinologist.

Place of LANTUS in the therapeutic strategy of the management of type 2 diabetes:
Current recommendations no longer systematically favour intensified insulin regimens. The glycaemic target should take into account the benefit and potential risks of intensification, especially in the elderly and/or patients with comorbidities, especially cardiovascular and renal comorbidities.
Long-acting analogues, including insulin glargine (LANTUS), can be used:
- when insulin therapy, such as basal insulin (in combination with one or more oral antidiabetics), is implemented. **According to the recent guideline from HAS, starting preferably with an intermediate-acting insulin (NPH) at bedtime is recommended in accordance with the guideline from HAS. Prescribing a long-acting analogue as an alternative to intermediate-acting insulin is to be discussed if the risk of severe nocturnal hypoglycaemia is serious.**
- when an intensified insulin regimen, such as basal insulin in a basal bolus regimen (in combination with a rapid-acting or ultra rapid acting insulin or analogue), is implemented.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee believes that the conclusions of its previous opinion of 25 May 2011 do not need to be changed.

10.1 Actual Benefit

In type 1 diabetes (in adults, adolescents and children aged 6 years and above), and in type 2 diabetes (in adults):

- Type 1 and type 2 diabetes is a chronic disease with potentially serious complications, especially cardiovascular and renal complications.
- LANTUS is intended as symptomatic treatment of hyperglycaemia.
- The efficacy/adverse effects ratio for these medicinal products remains high.
- These proprietary medicinal products are recommended treatments for managing type 1 and type 2 diabetes. This is first-line therapy in the management of type 1 diabetes. In type 2 diabetes, these proprietary medicinal products are first-line therapies; they, like insulin detemir, are an alternative to intermediate-acting insulin (NPH) if the risk of severe nocturnal hypoglycaemia is serious.
- There are treatment alternatives to these proprietary medicinal products:
  - other basal insulins or another insulin therapy regimen in type 1 diabetes.
  - intermediate insulin, insulin detemir and mixed insulins at the intensified insulin regimen stage in type 2 diabetes.

Public health benefit:

The public health burden represented by diabetes (type 1 and type 2 diabetes) is substantial due to its high prevalence, which is continually increasing, and the associated microvascular and macrovascular complications.
Improvement in the therapeutic management of diabetics represents a public health need included in the established priorities.
Given the available data (ORIGIN trial in particular), LANTUS does not have any impact on morbidity and mortality. In the absence of data, the impact on the quality of life that might be expected has not been demonstrated.
The applicability of the results presented to clinical practice is acceptable.
Overall, LANTUS does not have any impact on public health.

Taking account of these points, the Committee considers that the actual benefit of the proprietary medicinal products LANTUS remains substantial in type 1 diabetes (in adults, adolescents and children aged 6 years and above), and in type 2 diabetes.

10.2 Improvement in actual benefit

Given, on the one hand:
- the glycaemic control obtained with LANTUS (insulin glargine) compared with that observed with NPH insulin and insulin detemir (LEVEMIR),
- the absence of a difference between insulin glargine, insulin detemir and NPH insulin in terms of the occurrence of severe hypoglycaemia and between insulin glargine and insulin detemir in terms of overall and nocturnal hypoglycaemia,
- the opinion of experts who do not recognise any benefit in their daily practice of using LANTUS compared with another long acting insulin analogue,

And, on the other hand,

- **current recommendations which no longer favour treatment intensification for type 2 diabetes, which reduces the risk of hypoglycaemia,**

the Transparency Committee cannot confirm the previously recognised benefit of LANTUS (minor IAB in terms of safety) in type 1 and type 2 diabetes.

Thus, the Committee considers that LANTUS (insulin glargine) does not provide an improvement in actual benefit (level V, non-existent) in the management of adult or adolescent patients and children aged 2 and above with type 1 or type 2 diabetes.

10.3 Target population

Definition:
The patients eligible for insulin therapy are:
- all patients with type 1 diabetes (DT1);
- some patients with type 2 diabetes (DT2), primarily those who have failed oral triple therapy (metformin + sulfonylurea + other OAD) and those who have failed oral dual therapy (metformin + sulfonylurea) with a deviation from the glycaemic target ≥1% HbA1c.

Reminder of the previous estimate (opinion of 21 January 2009):
"In conclusion, the target population of LANTUS for 2007 is estimated to be 796,000 people (230,000 of whom have DT1 and 566,000 DT2) with a plausibility interval ranging from 588,000 people (358,000 of whom have DT2) to 910,000 people (679,000 of whom have DT2). "

Updated estimate (see Appendix IV):
The methodology used in the previous opinion has been retained. The target population is made up of the total number of diabetic patients already treated with insulin (DT1 and DT2 patients) and DT2 patients treated with OADs alone, uncontrolled and eligible for insulin therapy.
The assumptions used are identical to those which had been established during the previous opinion:
- 70% of DT2 patients treated with OADs alone, uncontrolled with HbA1c ≥8%, are eligible for insulin therapy (sensitivity analysis: lower limit 0%; upper limit 95%);
- 10% of DT2 patients treated with OADs alone, uncontrolled, with 7% ≤HbA1c<8%, are eligible for insulin therapy (sensitivity analysis: lower limit 0%; upper limit 25%)

By updating some epidemiological data (French population,[38] percentage of diabetic patients treated,[39] percentages of DT1 and DT2 patients treated[39], percentages of DT2 patients treated with OADs alone and controlled, treated with OADs alone and uncontrolled, and already treated with insulin[40]), the number of diabetic patients treated in France can be estimated to be 2,886,196, of whom 141,424 DT1 patients treated with insulin and 2,741,700 DT2 patients treated. Among the DT2 patients, 1,724,202 are treated with OADs alone and controlled, 537,700 are treated with OADs alone, but uncontrolled, and 479,798 are already treated with insulin. Among the DT2 patients treated with OADs alone and uncontrolled, 157,707 with an HbA1c ≥8% are eligible for insulin therapy and 31,240 with an HbA1c ≥7% and <8% are eligible for insulin therapy.

[38] INSEE (Institut National de la Statistique et des Études Économiques [National Institute of Statistics and Economic Studies]). French population in 2011 (Metropolitan France, on 1st January 2012)
[39] National Health Insurance. EGB database (Echantillon Généraliste des Bénéficiaires de l'Assurance Maladie [General Sample of Beneficiaries]) 2011.
[40] Cegedim Strategic Data. LPD database (Longitudinal Patient Databases) 2011.

Conclusion:
Overall, the target population of LANTUS can be estimated to be around 810,000 diabetic patients (DT1 and DT2), i.e. the sum of 620,000 diabetic patients already treated with insulin (140,000 patients of whom have DT1 and 480,000 patients of whom have DT2) and 190,000 DT2 patients treated with OADs alone, uncontrolled and eligible for insulin therapy, with a plausibility interval between 620,000 patients (lower limit) and 915,000 patients (upper limit).

Comments:
This estimate corresponds to the target population of diabetic patients (DT1 and DT2) eligible for insulin therapy.
It should be noted that on the basis of the same epidemiological data, the target population was estimated by the company to be around 1,150,000 patients. This estimate is based:
- on the one hand, on the assumption that 100% of DT2 patients treated with OADs alone and uncontrolled (all patients with HbA1c ≥7%) are eligible for insulin therapy (*versus* 70% of DT2 patients treated with OADs alone, uncontrolled with HbA1c ≥8%, and 10% of DT2 patients treated with OADs alone, uncontrolled with 7%≤ HbA1c<8%), i.e. 340,000 additional DT2 patients;
- on the other hand, on a likely overestimation of the number of DT2 patients treated with OADs alone and uncontrolled (all patients with HbA1c ≥7%). The figure of 530,000 patients used in the calculations corresponds in fact to the upper limit of the estimate of this subpopulation, between 370,000 and 530,000 patients.

10.4 Transparency Committee recommendations

The Committee recommends maintaining inclusion of LANTUS on the list of medicines refundable by National Health Insurance in type 1 diabetes (in adults, adolescents and children aged 6 and above) and in type 2 diabetes (in adults) at the dosages in the Marketing Authorisation.

◗ Proposed reimbursement rate: 65%

◗ Packaging
The packaging for LANTUS is appropriate for the prescribing conditions as regards the indication, dosage and treatment duration.

◗ Other requests
The Committee will re-assess LANTUS in the light of scientific developments and the data on recombinant analogues of human long-acting insulin, particularly in terms of the risk of cancer.

011 APPENDICES

Appendix I

Review of the literature – Clinical efficacy and safety data

Appendix II

Amendments to the SPC – Table showing the main changes between January 2008 and May 2012

Appendix III

Data from pharmacoepidemiology reports

Appendix IV

Re-assessment of the target population – Detailed calculations

In type 1 diabetes:

- Comparison of insulin glargine with NPH insulin:

Study	Study design	Numbers	Study population (inclusion criteria)	Treatment regimens	Efficacy (HbA1c reduction)	General safety (hypoglycaemia)
Chase et al.[3]	Open-label, randomised, controlled study Non-inferiority 24 weeks	n=175 glargine: 85 NPH: 87 (detemir: 3)	- DT1 for ≥1 year - aged 9 to 17 years old - treated with insulin administered with ≥2 injections/d or with a pump	• **Insulin glargine** 1 x/d before breakfast versus • **NPH insulin** 2 x/d before breakfast and in the evening before dinner or at bedtime • Prandial insulin lispro and correction bolus as add-on	glargine versus NPH Non-inferiority demonstrated (margin ≤0.4%)	Severe hypoglycaemia: NS Nocturnal hypoglycaemia: NS

- Comparison of insulin glargine with insulin detemir:

Study	Study design	Numbers	Study population (inclusion criteria)	Treatment regimens	Efficacy (HbA1c reduction)	General safety (hypoglycaemia)
Heller et al.[4]	Open-label, randomised, controlled study Non-inferiority 52 weeks	n = 447 detemir: 300 glargine: 147	- DT1 for ≥1 year - aged ≥18 - HbA1c ≤11 % - treated with a basal-bolus regimen for ≥3 months	• **Insulin detemir** 1 x/d in the evening versus • **Insulin glargine** 1 x/d in the evening • Insulin aspart as add-on at main meals	detemir versus glargine Non-inferiority demonstrated (margin ≤0.4%)	Overall hypoglycaemia: NS Major hypoglycaemia: NS (Overall and major) nocturnal hypoglycaemia: NS

In type 2 diabetes:

- Comparison of insulin glargine with NPH insulin:

Study	Study design	Numbers	Study population (inclusion criteria)	Treatment regimens	Efficacy (HbA1c reduction)	General safety (hypoglycaemia)
Rosenstock et al. 2009[5]	Randomised, controlled, open-label study 5 years	n=1,024 glargine: 515 NPH: 509	- DT2 for ≥1 year - aged 30 to 70 years old - HbA1c of 6 to 12% - treated with OADs, or insulin alone, or both for ≥1 year	• **Insulin glargine** 1 x/d generally at bedtime versus • **NPH insulin** 2 x/d generally in the morning and at bedtime • OAD and/or prandial insulin taken	glargine versus NPH -0.55% versus -0.76% difference: +0.21% 95% CI: [0.06%; 0.35%] p=0.0053 **Significant difference to the disadvantage of glargine** (secondary endpoint)	Severe hypoglycaemia: glargine versus NPH 7.6% versus 11.1% of patients p=0.0439 **Significant difference in favour of glargine** 0.04 versus 0.06 episodes/patient/year **NS** Nocturnal hypoglycaemia: NS
Lee et al.[6]	Pooled analysis of data from five randomised, controlled studies 24 to 28 weeks	n=2695 glargine: 1441 NPH: 1254	- DT2 - aged ≤80 - BMI ≤40 kg/m² - HbA1c of 7.5 to 12% - treated with OADs in two studies - treated with glimepiride in three studies	• **Insulin glargine** 1 x/d at bedtime or before breakfast versus • **NPH insulin** 1 x/d at bedtime or before breakfast • OADs taken	glargine versus NPH Difference not significant	Severe nocturnal hypoglycaemia: glargine versus NPH 0.8% versus 2.2% of patients 0.03 versus 0.08 episodes/patient/year p<0.05 **Significant difference in favour of glargine** Symptomatic nocturnal hypoglycaemia : glargine versus NPH 20% versus 34% of patients 1.32 versus 2.86 episodes/patient/year p<0.05 **Significant difference in favour of glargine** **Symptomatic and severe (not nocturnal) hypoglycaemia: NS**
Home et al.[19]	Meta-analysis of patient data from five randomised, controlled studies 24 to 52 weeks (median exposure 25 weeks)	*Group 1:* n=2711 glargine: 1335 NPH: 1376 *Group 2:* n=470 glargine: 237 NPH: 233	*Group 1:* - DT2 - treated with OADs *Group 2:* - DT2 - not treated with OADs	• **Insulin glargine** 1 x/d in the evening (Group 1) 1 x/d in the morning (Group 2) versus • **NPH insulin** 1 x/d in the evening	Not applicable (safety study)	*Group 1:* Severe nocturnal hypoglycaemia: glargine versus NPH OR=0.52; 95% CI: [0.27; 1.00] p=0.0498 **Significant difference in favour of glargine** Severe hypoglycaemia (other): NS *Group 2:* Severe nocturnal hypoglycaemia: NS Severe hypoglycaemia (other): NS

In type 2 diabetes:

- Comparison of insulin glargine with insulin detemir:

Study	Study design	Numbers	Study population (inclusion criteria)	Treatment regimens	Efficacy (HbA1c reduction)	General safety (hypoglycaemia)
Swinnen et al.[7]	Open-label, randomised, controlled study Non-inferiority 24 weeks	n=964 glargine: 478 detemir: 486	- DT2 - HbA1c of 7 to 10.5% - insulin-naive - treated with OADs (including metformin ≥1g/d) for ≥3 months	• **Insulin glargine** 1 x/d in the evening versus • **Insulin detemir** 2 x/d at breakfast and at dinner	glargine versus detemir Difference not significant (secondary endpoint)	Severe hypoglycaemia: NS Nocturnal hypoglycaemia: NS
Raskin et al.[8]	Open-label, randomised, controlled study Non-inferiority 26 weeks	n=385 detemir: 254 glargine: 131	- DT2 - aged ≥18 - BMI ≤40 kg/m² - HbA1c of 7 to 11% - treated with OADs, or insulin alone, or both	• **Insulin detemir** 1x/d in the evening versus • **Insulin glargine** 1 x/d in the evening • Insulin aspart as add-on at main meals	detemir versus glargine Non-inferiority demonstrated (margin ≤0.4%)	Overall hypoglycaemia: NS Major hypoglycaemia: NS Nocturnal hypoglycaemia: NS
Hollander et al.[9]	Open-label, randomised, controlled study Non-inferiority 52 weeks	n=323 detemir: 216 glargine: 107	- DT2 for ≥1 year - aged ≥18 - BMI ≤40.0 - HbA1c of 7 to 11% - treated with OADs, or insulin, or both for ≥4 months	• **Insulin detemir** 1x/d in the evening or 2 x/d versus • **Insulin glargine** 1 x/d in the evening • Insulin aspart as add-on at main meals	detemir versus glargine Non-inferiority demonstrated (margin ≤0.4%)	Overall hypoglycaemia: NS Major hypoglycaemia: NS Nocturnal hypoglycaemia: NS
Meneghini et al.[10]	Open-label, randomised, controlled study Non-inferiority 26 weeks	n=457 detemir: 228 glargine: 229	- DT2 for ≥6 months - aged ≥18 - BMI ≤35 kg/m² - HbA1c of 7 to 9% - insulin-naive - treated with metformin or metformin + other OAD	• **Insulin detemir** 1x/d in the evening + metformin versus • **Insulin glargine** 1x/d in the evening + metformin	detemir versus glargine -0.48% versus -0.74% adjusted difference: +0.30% 95% CI: [0.14%; 0.46%] **Non-inferiority not demonstrated** (upper limit of 95% CI >0.4%) **of detemir vs glargine**	Overall hypoglycaemia: detemir versus glargine RR=0.73; 95% CI: [0.54; 0.98] p=0.034 **Significant difference to the disadvantage of glargine** Severe hypoglycaemia: detemir versus glargine 0 versus 2 episodes in one patient under glargine Nocturnal hypoglycaemia: NS

In type 2 diabetes:

- Comparison of insulin glargine with mixed insulins (aspart and lispro):

Study	Study design	Numbers	Study population (inclusion criteria)	Treatment regimens	Efficacy (HbA1c reduction)	General safety (hypoglycaemia)
Fritsche et al.[11]	Open-label, randomised, controlled study 52 weeks	n=310 glargine: 153 premix: 157	- DT2 for ≥5 years - HbA1c of 7.5 to 11% - treated with mixed insulin ± metformin for ≥3 months	• **Insulin glargine** 1 x/d in the evening + insulin glulisine before meals versus • **Mixed insulin** (aspart or lispro) 2x/d before breakfast and at the evening meal	glargine versus premix -1.31% versus -0.80% adjusted difference: -0.48% 95% CI: [-0.71%; -0.24%] p=0.0001 **Significant difference in favour of glargine**	Overall hypoglycaemia: NS Severe hypoglycaemia: NS Nocturnal hypoglycaemia: NS
Buse et al.[12]	Open-label, randomised, controlled study 24 weeks	n=2091 glargine: 1046 premix: 1045	- DT2 - aged 30 to 80 years old - BMI ≤45kg/m² - HbA1c >7% - treated with ≥2 OADs for 3 months	• **Insulin glargine** 1 x/d in the evening + OAD versus • **Mixed insulin** (lispro) 2 x/d	glargine versus premix -1.7% versus -1.8% difference: +0.1% p=0.005 **Significant difference to the disadvantage of glargine**	Overall hypoglycaemia: glargine versus premix 51.8% versus 57.1% of patients p=0.016 23.1 versus 28.0 episodes/patient/year p=0.007 **Significant difference in favour of glargine** Severe hypoglycaemia: NS Nocturnal hypoglycaemia: glargine versus premix 11.4 versus 8.9 episodes/patient/year p=0.009 **Significant difference to the disadvantage of glargine, but no difference (NS) in proportion of patients with nocturnal hypoglycaemia.**
Ligthelm et al.[13]	Open-label, randomised, controlled study 24 weeks	n=280 premix: 137 glargine: 143	- DT2 for ≥1 year - BMI ≤45kg/m² - HbA1c ≥8% - treated with basal insulin (glargine or NPH) in combination with metformin (≥1g/d) ± other OADs for ≥3 months	• **Insulin glargine** 1 x/d + metformin + secretagogues versus • **Mixed insulin** (aspart) 2 x/d + metformin	Difference not significant	Overall hypoglycaemia: premix versus glargine RR=1.47; 95% CI: [1.01; 2.12] p<0.05 **Significant difference in favour of glargine** Major hypoglycaemia: NS Nocturnal hypoglycaemia: NS

Study	Study design	Numbers	Study population (inclusion criteria)	Treatment regimens	Efficacy (HbA1c reduction)	General safety (hypoglycaemia)
Bretzel et al.[14]	Open-label, randomised, controlled study Non-inferiority 44 weeks	n=412 glargine: 204 premix: 208	- DT2 for ≥1 year - aged 18 to 75 years old - BMI ≤35 kg/m² - HbA1c of 7.5 to 10% - treated with OADs for ≥6 months	• **Insulin glargine** 1 x/d versus • **Mixed insulin** (lispro) 3 x/d before main meals	premix versus glargine Non-inferiority demonstrated (margin <0.4%)	Overall hypoglycaemia: glargine versus premix 66% versus 89% of patients 5.21 versus 24.00 episodes/patient/year p<0.0001 **Significant difference in favour of glargine** Severe hypoglycaemia: NS Nocturnal hypoglycaemia: NS
Strojek et al. 2009[15]	Open-label, randomised, controlled study Non-inferiority 26 weeks	n=480 premix: 239 glargine: 241	- DT2 - aged ≥18 - BMI ≤40 kg/m² - HbA1c of 7 to 11% - insulin-naive	• **Mixed insulin** (aspart) 1 x/d before dinner + metformin + glimepiride versus • **Insulin glargine** 1 x/d at bedtime + metformin + glimepiride	premix versus glargine Non-inferiority demonstrated (margin <0.4%)	Overall hypoglycaemia: premix versus glargine RR=1.41; 95% CI: [1.03; 1.93] p=0.034 **Significant difference in favour of glargine** Major hypoglycaemia: NS Nocturnal hypoglycaemia: premix versus glargine RR=2.41; 95% CI: [1.34; 4.34] p=0.003 **Significant difference in favour of glargine**
Strojek et al. 2010[16]	Open-label, randomised, controlled study Non-inferiority 24 weeks	n=471 premix: 235 glargine: 236	- DT2 for ≥1 year - aged ≥18 - BMI 25 to 45 kg/m² - HbA1c of 7.5 to 10% - insulin-naive - treated with ≥2 OADs	• **Mixed insulin** (lispro) 1 then 2 x/d versus • **Insulin glargine** 1 x/d at bedtime + metformin + glimepiride	premix versus glargine Non-inferiority demonstrated (margin <0.4%)	Overall hypoglycaemia: NS Nocturnal hypoglycaemia: glargine versus premix 38.2% versus 50.2% of patients p=0.01 4.1 versus 6.1 episodes/patient/year p<0.001 **Significant difference in favour of glargine** **Severe hypoglycaemia:** glargine versus premix 2 versus 9 patients p=0.04 Significant difference in favour of glargine, but no difference (NS) in number of episodes/patient/year.
Rosenstock et al. 2008[17]	Open-label, randomised, controlled study Non-inferiority 24 weeks	n=374 glargine: 187 premix: 187	- DT2 - aged 30 to 75 years old - BMI ≤40 kg/m² - HbA1c of 7 to 12% - treated with glargine for ≥3 months (≥30 U/d) + 1, 2 or 3 OADs	• **Insulin glargine** 1 x/d at bedtime + insulin lispro at main meals versus • **Mixed insulin** (lispro) 3 x/d at mealtimes	premix versus glargine -1.87% versus -2.09% adjusted difference: +0.22% 95% CI: [0.07%; 0.38%] (upper limit of 95% CI >0.3%) **Non-inferiority not demonstrated for premix versus glargine (margin <0.3%)**	Overall hypoglycaemia: NS Severe hypoglycaemia: NS Nocturnal hypoglycaemia: NS

Appendix II: Amendments to the SPC – Side-by-side table showing the main changes between January 2008 and May 2012

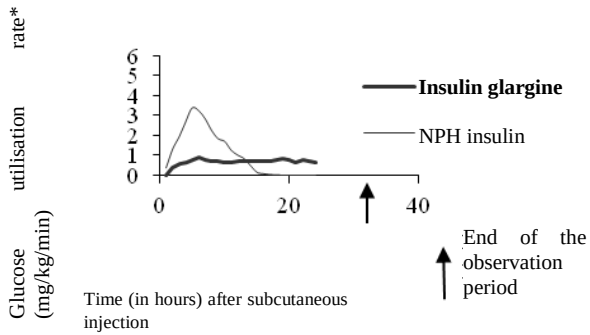
SPC in force on 1st January 2008	SPC in force since 25 May 2012
4. CLINICAL PARTICULARS **4.1 Therapeutic indications** Diabetes mellitus in adults, adolescents and children aged 6 years and above who require insulin treatment.	**4. CLINICAL PARTICULARS** **4.1 Therapeutic indications** Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.
4.2 Posology and method of administration The potency of this medicinal product is stated in units. These units are exclusive to Lantus and are not the same as IU or the units used to express the potency of other insulin analogues. See section 5.1 (Pharmacodynamic properties). Lantus contains insulin glargine, an insulin analogue, and has a prolonged duration of action. It should be administered once daily at any time but at the same time each day. The dose and timing of Lantus should be individually adjusted. In patients with type 2 diabetes mellitus, Lantus can also be given together with oral antidiabetic medicinal products.	**4.2 Posology and method of administration** Dosage Lantus contains insulin glargine, an insulin analogue, and has a prolonged duration of action. LANTUS should be administered once daily at any time but at the same time each day. The Lantus dose regimen (dose and timing) should be individually adjusted. In patients with type 2 diabetes mellitus, Lantus can also be given together with orally active antidiabetic medicinal products. The potency of this medicinal product is stated in units. These units are exclusive to Lantus and are not the same as IU or the units used to express the potency of other insulin analogues (see section 5.1).
	Special populations *Elderly population (≥65 years old)* In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements. *Renal impairment* In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism. *Hepatic impairment* In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism. *Paediatric population* Safety and efficacy of LANTUS have been established in adolescents and children aged 2 years and older (see section 5.1). LANTUS has not been studied in children below the age of 2 years.
Children In children, efficacy and safety have been demonstrated only when LANTUS is administered in the evening. Since experience is limited, the efficacy and safety of LANTUS have not been demonstrated in children under 6 years of age.	
Transition from other insulins to Lantus [unchanged]	Transition from other insulins to Lantus [unchanged]
Administration Lantus is administered subcutaneously. Lantus should not be administered intravenously. The prolonged duration of action of Lantus is dependent on its injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia. There are no clinically relevant differences in serum insulin or glucose levels after abdominal, deltoid or thigh administration of Lantus. Injection sites must be rotated within	Method of administration Lantus is administered subcutaneously. Lantus should not be administered intravenously. The prolonged duration of action of Lantus is dependent on its injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.

a given injection area from one injection to the next. Lantus must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation. For further details on handling, see section 6.6. As experience is limited, the efficacy and safety of Lantus could not be assessed in the following patient groups: patients with hepatic failure or patients with moderate to severe renal failure (see section 4.4).	There are no clinically relevant differences in serum insulin or glucose levels after abdominal, deltoid or thigh administration of Lantus. Injection sites must be rotated within a given injection area from one injection to the next. Lantus must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation. For further details on handling, see section 6.6.
4.4 Special warnings and precautions for use Lantus is not the insulin of choice for the treatment of diabetic ketoacidosis. Instead, regular insulin administered intravenously is recommended in such cases. The safety and efficacy of LANTUS have been established in adolescents and children aged 6 years and above. As the experience is limited, the efficacy and safety of Lantus could not be assessed in children aged 6 years and above or in patients with hepatic failure or patients with moderate to severe renal failure (see section 4.2). In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism. In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements. In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism. In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered. Substitution by another type or brand of insulin should be done under strict medical supervision and may result in the need for a change in dose.	**4.4 Special warnings and precautions for use** Lantus is not the insulin of choice for the treatment of diabetic ketoacidosis. Instead, regular insulin administered intravenously is recommended in such cases.
Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia (see section 4.8). Hypoglycaemia [unchanged] Intercurrent diseases [unchanged]	In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered. Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose. Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia (see section 4.8). Hypoglycaemia [unchanged] Intercurrent diseases [unchanged] Medication errors Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of insulin glargine. Insulin label must always be checked before each injection to avoid medication errors between insulin

	glargine and other insulins. Combination of Lantus with pioglitazone Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Lantus is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.
4.6 Fertility, pregnancy and lactation **Pregnancy** No clinical data on the use of this medicinal product in pregnant women from controlled clinical studies are available. Use of insulin glargine in a limited number of pregnancies during post marketing surveillance apparently did not indicate any specific harmful; effects on pregnancy or for the foetus/new-born. There are, to date, no other relevant epidemiological data. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, delivery and post-natal development (see section 5.3). The clinical data available are not sufficient to exclude a risk. The use of Lantus may be considered during pregnancy, if clinically needed. It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential. **Breast-feeding** Breast-feeding women may require adjustments in insulin dose and diet.	**4.6 Fertility, pregnancy and lactation** **Pregnancy** For insulin glargine no clinical data on the use of this medicinal product in pregnant women from controlled clinical studies are available. A moderate amount of data on pregnant women exposed to marketed insulin glargine (between 300 and 1000 pregnancies) indicate no specific adverse effects of insulin glargine on pregnancy and no specific malformative nor foetal/neonatal toxicity of insulin glargine. Animal data do not indicate reproductive toxicity. The prescription of Lantus may be considered during pregnancy, if clinically needed. It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential. **Breast-feeding** It is unknown whether insulin glargine is excreted in human milk. No metabolic effects of ingested insulin glargine on the breast-fed newborn/infant are anticipated since insulin glargine, as a peptide, is digested into aminoacids in the human gastrointestinal tract. Breast-feeding women may require adjustments in insulin dose and diet. **Fertility** Animal studies do not indicate direct harmful effects with respect to fertility.
4.8 Undesirable effects [unchanged except for last paragraph] Paediatric population In general, the safety profile for patients ≤18 years of age is similar to the safety profile for patients >18 years of age. The adverse reaction reports received from post marketing surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in patients ≤18 years of age than in patients >18 years of age. Clinical study safety data are not available for children under 6 years of age.	**4.8 Undesirable effects** [unchanged except for last paragraph] Paediatric population In general, the safety profile for children and adolescents (≤18 years of age) is identical to the safety profile for adults. The adverse effect reports received from post-marketing surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in children and adolescents (≤ 18 years of age) than in adults. Clinical study safety data are not available for children under 2 years. **5. PHARMACOLOGICAL PROPERTIES**

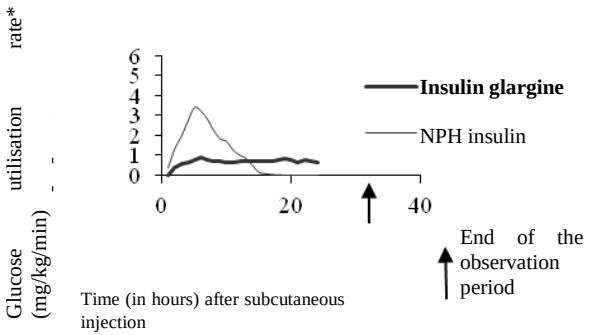
5. PHARMACOLOGICAL PROPERTIES **5.1 Pharmacodynamic properties** Pharmacotherapeutic group: Antidiabetic agents, insulins and its analogues, long-acting. ATC code: A10AE04 Insulin glargine is a human insulin analogue with a low solubility at neutral pH. It is completely soluble at the acidic pH of the Lantus injection solution (pH 4). After injection into the subcutaneous tissue, the acidic solution is neutralised leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action. Insulin receptor binding: The affinity of insulin glargine for the insulin receptor is similar to the one of human insulin. It is therefore estimated that it has the same effect via the insulin receptor. The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis. In clinical pharmacology studies, intravenous insulin glargine and human insulin have been shown to be equipotent when given at the same doses. As with all insulins, the time course of action of insulin glargine may be affected by physical activity and other variables. In euglycaemic clamp studies in healthy subjects and in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than with human NPH insulin, its effect profile was smooth and peakless, and the duration of its effect was prolonged. The following graph shows the results from a study in patients:	**5.1 Pharmacodynamic properties** Therapeutic category: drugs used in diabetes, insulins and analogues for injection, long-acting. ATC code: A10A E04 Mechanism of action Insulin glargine is a human insulin analogue with a low solubility at neutral pH. It is completely soluble at the acidic pH of the Lantus injection solution (pH 4). After injection into the subcutaneous tissue, the acidic solution is neutralised leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action. Insulin glargine is metabolised into 2 active metabolites M1 and M2 (see section 5.2). Insulin receptor binding: In vitro studies indicate that the affinity of insulin glargine and its metabolites M1 and M2 for the human insulin receptor is similar to the one of human insulin. IGF-1 receptor binding: The affinity of insulin glargine for the human IGF-1 receptor is approximately 5 to 8-fold greater than that of human insulin (but approximately 70 to 80-fold lower than the one of IGF-1), whereas M1 and M2 bind the IGF-1 receptor with slightly lower affinity compared to human insulin. The total therapeutic insulin concentration (insulin glargine and its metabolites) found in type 1 diabetic patients was markedly lower than what would be required for a half maximal occupation of the IGF-1 receptor and the activation of the mitogenic proliferative pathway initiated by the IGF-1 receptor. Physiological concentrations of endogenous IGF-1 may activate the mitogenic-proliferative pathway; however, the therapeutic concentrations found in insulin therapy, including in Lantus therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway. The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis. In clinical pharmacology studies, intravenous insulin glargine and human insulin have been shown to be equipotent when given at the same doses. As with all insulins, the time course of action of insulin glargine may be affected by physical activity and other variables. In euglycaemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than with human NPH insulin, its effect profile was smooth and peakless, and the duration of its effect was prolonged. The following graph shows the results from a study in patients:

Action profile in those with type 1 diabetes



The longer duration of action of insulin glargine is directly related to its slower rate of absorption and supports once daily administration. The time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual.
In a clinical study, symptoms of hypoglycaemia or counter-regulatory hormone responses were similar after intravenous insulin glargine and human insulin both in healthy volunteers and patients with type 1 diabetes.

Action profile in those with type 1 diabetes



The longer duration of action of subcutaneous insulin glargine is directly related to its slower rate of absorption and supports once daily administration. The time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual.
In a clinical study, symptoms of hypoglycaemia or counter-regulatory hormone responses were similar after intravenous insulin glargine and human insulin both in healthy volunteers and patients with type 1 diabetes.
Effects of insulin glargine (once daily) on diabetic retinopathy were evaluated in an open-label 5 year NPH-controlled study (administered twice daily) in 1024 type 2 diabetic patients in which progression of retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale was investigated by fundus photography. No significant difference was seen in the progression of diabetic retinopathy when insulin glargine was compared to NPH insulin.

Paediatric population
In a randomised, controlled clinical study, children and adolescents (age range 6 to 15 years) with type 1 diabetes (n=349) were treated for 28 weeks with a basal-bolus regimen where rapid-acting human insulin was used before each meal. Insulin glargine was administered once daily at bedtime and NPH human insulin was administered once or twice daily. The effects on glycohaemoglobin and the incidence of symptomatic hypoglycaemia were similar in both treatment groups, however fasting blood glucose decreased more from baseline with insulin glargine than with NPH insulin. There was less severe hypoglycaemia with insulin glargine as well. One hundred and forty three of the patients treated with insulin glargine in this study continued treatment with insulin glargine in an uncontrolled extension of the study with a mean duration of follow-up of 2 years. No new safety signals were seen during this extended treatment with insulin glargine.
A crossover study comparing insulin glargine plus lispro insulin with NPH insulin plus rapid-acting human insulin (each treatment administered for 16 weeks in random order) in 26 adolescent type 1 diabetic patients aged 12 to 18 years was also performed. As in the

5.2 Pharmacokinetic properties [unchanged except for last paragraph]	paediatric study described above, fasting blood glucose reduction with baseline was greater from insulin glargine than with NPH insulin. HbA1c changes from baseline were similar between treatment groups, however blood glucose values recorded overnight were significantly higher in the insulin glargine/lispro group than in the NPH insulin/rapid-acting human insulin group, with a mean nadir of 5.4 mM vs 4.1 mM. Consequently, the incidences of nocturnal hypoglycaemia were 32% in the insulin glargine/lispro group vs 52% in the NPH insulin/rapid acting human insulin group. A 24-week parallel group study was conducted in 125 children with type 1 diabetes aged 2 to 6 years, comparing insulin glargine given once daily in the morning with NPH insulin given once or twice daily as basal insulin. Both groups received boluses of insulin before meals. The primary aim of demonstrating the non-inferiority of insulin glargine to NPH in all hypoglycaemia was not met, and there was a trend to an increase of hypoglycaemic events with insulin glargine [hypoglycaemia rate ratio with insulin glargine/NPH = 1.18 (95% CI: 0.97-1.44)]. Glycohaemoglobin and blood glucose variabilities were comparable in both treatment groups. No new safety signals were observed in this study. **5.2 Pharmacokinetic properties** [unchanged except for last paragraph] *Paediatric population* Pharmacokinetics in children aged 2 to less than 6 years with type 1 diabetes were assessed in one clinical study (see section 5.1). The plasma “trough” levels of insulin glargine and its main M1 and M2 metabolites at equilibrium were measured in children treated with insulin glargine. They revealed a profile similar to that of adults, and provided no evidence for accumulation of insulin glargine or its metabolites with chronic dosing.

Appendix III: Data from pharmacoepidemiology reports

1. Context and Proposed studies

After the publication in Diabetologia of four retrospective studies, databases, three of which suggested a possible link between taking insulin analogues (especially insulin glargine) and the risk of cancer, the CHMP (EMA), in its opinion of 18 February 2010, stipulated that the benefit/risk balance remained positive, renewed the Marketing Authorisation of Lantus for 5 years and combined this opinion with the implementation of a European RMP which included the following:

- Amendments to the protocol of the ORIGIN trial (on cardiovascular events) to integrate cancer cases (results expected in Q4 2012).
- Completion of three epidemiological studies (protocols approved by EMA)
    1. "Breast, prostate and colorectal cancer and antidiabetics" cohort study from prescription databases in Sweden, Norway, Denmark, Finland and Scotland (final results initially planned for Q2 2011 and announced at the end of Q1 2012).
    2. "Cancer and insulins" cohort study from Californian Kaiser Permanente database on around 160,000 patients monitored for 9 years (final results initially planned in Q3 2011, recently announced in Q1 2012)
    3. ISICA "breast cancer and insulin" case-control study on 750 patients with breast cancer and 3000 controls (final results initially planned in Q2 2012, announced in Q4 2012).

The results below are for the three epidemiological studies cited above, and a study carried out by the CNAM-TS at the request of the ANSM from the SNIIRAM database and an additional study provided by the company, carried out by the University of North Carolina from the American database MedAssurant.

2. Main results

- **Northern European cohort study, performed using databases (Sweden, Norway, Denmark, Finland and Scotland)**

This study was performed using databases of prescriptions, cancers and the mortality of five European countries (Sweden, Norway, Denmark, Finland and Scotland)
For Sweden, Norway, Finland and Denmark, additional information on confounding factors (BMI, use of tobacco, alcohol consumption) was also collected.
The main objective of this study was to evaluate the risk of cancer (breast, prostate and colorectal cancer) in adult DT1 and DT2 patients treated with insulin glargine compared with patients treated with human insulins, and in all patients on insulin.
The secondary objective was to evaluate the risk of lung and, pancreatic cancer and the risk of all forms of cancer (except skin cancer) in these same patients.
The population of patients exposed was the same as the diabetic patients for whom insulin glargine was prescribed and the non exposed patients were those for whom insulin was prescribed, who did not have insulin glargine, but who did previously have treatment with other types of insulin.
The expected size of the sample was greater than 10,000 patients so as to detect, with a sufficient power, a relative risk (RR) higher than or equal to ≥ 1.2 for all types of cancer.
The statistical analysis primarily consisted of a meta-analysis of 5 countries, completed by a pooled analysis (all patients together)
The prescription data were extracted from national databases over the following periods:

- Denmark: May 2004 – December 2009
- Finland: July 2003 – December 2007
- Norway: January 2004 – December 2008
- Scotland: August 2002 – December 2007
- Sweden: July 2005 – December 2009

Initially, 269,246 users of insulin were extracted from national databases, 40.6% of whom were considered type 2 diabetics, 22.8% type I diabetics and for 21.1%, the type of diabetes was

unknown. Men represented 56% of the subjects included in the study. The most represented age brackets were 55-64 (22.5% of the population), 65-74 (19.7%), 45-54 (16.5%) and subjects aged 75 years and above (15.6%).
Among this population, a subpopulation of "presumed new users of insulin" (without insulin prescription within the first 6 months of the study) of 116,925 people was defined.
It should be noted that metformin was prescribed concomitantly with insulin for 47.5% of the subjects in the general population and 61% of the "new users".

Breast cancer
For breast cancer, the meta-analyses demonstrate:
- in the total study population: no statistically significant increased risk in women using glargine compared with all female users of insulins (RR=1.15 [0.97; 1.34]) and compared with all female users of human insulins (RR=1.14 [0.96; 1.36]);
- in the subpopulation of new female users of insulin: a statistically significant increased risk in new female users of glargine compared with all other insulins (RR=1.45 [1.10; 1.90]).
The dose-response analyses showed that this increase appeared early, in the first year that glargine was used.

General population: Glargine vs other insulins

Chart I.1.5.4
Breast cancer risk in women with type 1 or type 2 diabetes who have used glargine compared to all other insulins
Country-specific hazard ratios** and summary hazard ratios** (95% CIs)

Country	All users of insulin	All users of human insulin	New users of insulin
Denmark	0.95 (0.61, 1.47)	0.95 (0.69, 1.48)	1.75 (0.91. 3.38)
Finland	1.08 (0.81, 1.43)	1.07 (0.85, 1.43)	1.22 (0.77, 1.94)
Norway	1.33 (0.77, 2.30)	1.35 (0.78, 2.33)	2.09 (0.92, 4.72)
Scotland	1.32 (1.00, 1.73)	1.30 (0.98, 1.73)	1.42 (0.90, 2.24)
Meta-analysis*	1.15 (0.97, 1.34)	1.14 (0.96, 1.36)	1.45 (1.10, 1.90)
Sweden	1.03 (0.77, 1.38)		
Meta-analysis	1.13 (0.98, 1.31)		

* All Fixed Effects Meta-analysis
** All hazard ratios adjusted for metformin and stratified by age.
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Chart I.1.5.3
Breast cancer risk in women with type 1 or type 2 diabetes among new users of insulin
Country-specific hazard ratios** and summary hazard ratios** (95% CIs)

				Compared to non long-acting insulins	Compared to non long-acting insulins	Compared to non long-acting insulins	Compared to non long-acting insulins
Country	Glargine vs all other insulins	Trend in risk with duration glargine use	Glargine vs other long-acting insulins	Glargine only	Non-glargine long-acting insulins and non-long-acting insulins	Glargine plus non long-acting insulins	Non-glargine long-acting insulins plus glargine plus non long-acting insulins
Denmark	1.75 (0.91, 3.38)	β=-0.73 (-1.78, 0.33)	2.30 (1.11, 4.76)	1.48 (0.37, 6.01)	0.36 (0.09, 1.48)	1.77 (0.81, 3.97)	1.46 (0.20, 10.59)
Finland	1.22 (0.77, 1.94)	β=-0.26 (-0.84, 0.31)	0.70 (0.37, 1.35)	0.86 (0.37, 1.98)	2.75 (0.66, 11.52)	1.42 (0.81, 2.48)	1.51 (0.20, 11.64)
Norway	2.09 (0.92, 4.72)	β=0.48 (-0.35, 1.30)	1.01 (0.52, 1.97)	____	1.91 (0.58, 6.33)	2.06 (0.86, 4.95)	6.87 (0.91, 52.15)
Scotland	1.42 (0.90, 2.24)	β=0.24 (-0.22, 0.70)	1.02 (0.60, 1.71)	1.88 (1.08, 3.26)	1.55 (0.48, 5.03)	1.03 (0.51, 2.07)	1.36 (0.18, 10.09)
Meta-analysis*	1.45 (1.10, 1.90)	β=0.04 (-0.28, 0.35)	1.09 (0.80, 1.49)	1.50 (0.97, 2.30)	1.33 (0.70, 2.52)	1.42 (1.00, 2.01)	2.05 (0.75, 5.63)
Sweden				0.76 (0.39, 1.50)			
Meta-analysis				1.22 (0.84, 1.76)			

* All Fixed-Effects Meta-analysis
** All hazard ratios adjusted for metformin and stratified by age.

Other cancers

For colorectal cancer, there was no increased risk associated with the use of insulin glargine. For prostate cancer, the results of the meta-analysis cannot be considered because of the screening differences between the countries studied.

For the other cancer localisations (all localisations, lung and pancreatic), the meta-analyses do not show any increased risk associated with the use of glargine.

- **"Insulin glargine and risk of cancer among diabetic patients" cohort study - Kaiser Permanente (USA)**

This retrospective cohort study was conducted in the state of Carolina (North and South), representing around 6.6 million insured parties. The cohort was made up of adults, carriers of DT1 or DT2, who had at least two prescriptions of insulin glargine or an NPH insulin within 6 months between 01/05/2001 and 31/12/2008 and who had been included in the database at least 12 months before the first prescription. Patients with a history of cancer were excluded. Cancer cases were identified by "linkage" with the cancer registries. Potential confounding factors were identified: other drugs used for diabetes (metformin in particular), age, sex, HbA1c, BMI, comorbidities, level of education and alcohol consumption.

The cohort included 115,514 people. At the end of the follow-up, 27,418 patients were exposed to glargine and 100,757 to NPH insulin (12,661 have been exposed to two types of insulin).

Among the new users of insulin, 269 breast cancers, 253 prostate cancers and 205 colorectal cancers were identified. A total of 1856 new users of insulin (glargine or NPH) were diagnosed with cancer (all localisations combined).

The median duration of treatment was 1.2 years for glargine and 1.4 years for NPH insulin.

Among all patients, there was no association between insulin glargine and breast cancer (HR=1.0 [0.9; 1.3]), prostate cancer (HR=0.7 [0.6; 0.9]), or colorectal cancer (HR=1.0 [0.8; 1.2]).
Moreover, there is no association between insulin glargine and the risk of "all localisation" cancer (HR = 0.9 [0.9; 1.0]).
In contrast, there is an association between insulin glargine and breast cancer in new users of insulin (HR=1.3 [1.0; 1.8]), especially in those who initiated insulin glargine over 2 years ago (HR=1.6 [1.0; 2.8]) taking into account the time elapsed between the prescriptions and HR=2.2 [1.2; 4.2] taking into account the duration of prescription).

This study, which was performed by Peter Boyle of the CIRC [International Agency for Research on Cancer (IARC)], only focuses on four or five countries in northern Europe (according to analyses carried out). Not all the potential confounding factors were taken into account even though some of the analyses take account of the BMI and alcohol and tobacco consumption of subjects in four countries.
However, the preliminary results of this study do not demonstrate an increased risk of all cancers, but are in line with an increased risk of breast cancer in the new users of glargine, an increased risk primarily underpinned by the results of the study in Scotland.

- **ISICA study**

The ISICA study is an international case-control study (France, UK, Canada), implemented at the request of the EMA, whose main objective was to evaluate the association between different types of insulin therapy (glargine, human insulin, aspart and lispro) and the risk of breast cancer in diabetic women. The secondary objectives were to study the influence of a series of risk factors on the risk of breast cancer, the impact of different methods (dose, duration, etc.), the influence of metformin on the risk of breast cancer, the relative risk in users vs non-users of insulin, the study of more specific subgroups (DT2, developmental stages of cancer, most-menopausal women...).

Case selection was made from the results of biopsies performed in "major" cancer centres (>100 cases/year), between 1 January 2008 and 30 June 2009, restricting it to women treated for diabetes (with OADs and/or insulin). Women were then contacted for their consent and information, which was collected once contact with an attending physician and pharmacist had been made.

The controls were identified from the patient base of general practitioners (PGRx network) with matching according to age, region, type of diabetes and also (by amendment) type of treatment (general practitioner or diabetologist) and date of recruitment (6 months maximum). The methods of collecting information were the same for the controls as for the cases.

Exposure was subdivided by types of insulin, then by type of exposure within the previous 5 years (window of 8 years by amendment): definite or probable (3 consecutive months with or without objective confirmation) or absent. A more detailed analysis of the exposure was planned: basal or bolus use, shelf life, accumulated dose.

This study was calibrated to detect an OR of 1.4 or more for glargine and K sein with a 95% CI and power of 80%.

Overall, 92 oncology centres treating more than 100 cases of breast cancer/year (38 in France, 39 in GB and 15 in Canada) and 580 general practitioners (392 in France, 91 in GB, 97 in Canada) participated in this study and 775 cases and 3050 controls (2/3 of whom live in France) were included, with 10.6% with carcinoma in situ and 94% of patients with type 2 diabetes.
Concerning the cases, initially 39,558 records of patients with breast cancer were identified: 3131 patients (7.9%) presented with diabetes, 2735 were still alive at the time of recruitment and, ultimately, 775, for whom at least one control could be identified were selected).

Concerning the controls, the general practitioners recruited 4398 diabetic patients, potential controls, 3050 of whom were able to be successfully matched (controls averaged 3.9 for 1 case).

The participants were slightly younger, showed somewhat different tumour stage distribution and were more often suffering from invasive cancer than the non-participants of the study.
The distribution of the following factors (BMI, duration of diabetes, insulin use, glycaemic control, frequency of complications, type of treatment) was similar between cases and controls. In contrast, but this was expected, exposure to exogenous oestrogens and family history of cancer were more common in cases.
The mean use of glargine was 3.2 years.

The main results (adjusted OR) are as follows:

- **Type of insulin and breast cancer:**
  - OR Glargine = 1.04 [0.76; 1.44]
  - OR Lispro = 1.23 [0.79; 1.92]
  - OR Aspart = 0.95 [0.64; 1.40]
  - OR Human insulin = 0.81 [0.55; 1.20]
  - OR Other insulins = 0.75 [0.45; 1.23]

- **Glargine vs other insulin**
  - OR Glargine vs lispro = 0.85 [0.48; 1.50]
  - OR Glargine vs aspart = 1.10 [0.64; 1.89]
  - OR Glargine vs human insulin = 1.29 [0.78; 2.13]

The risk factors of breast cancer demonstrated were the following: duration of diabetes, menopause, intake of HRT.
The factors associated with the risk of breast cancer had a distribution as expected: the risk score compared between the 1st quartile and the following quartiles showed an OR which rose from 1.07 to 2.74.
Finally, regardless of insulin used there is no significant difference in the occurrence of breast cancer.

This study did not show any increased risk of breast cancer among the users of glargine compared with non-users or compared with users of human insulin. However, the short duration of follow-up only allows evaluation of the role the different types of insulin have in promoting, not initiating, cancer.
Moreover, a comparison was made between the duration of exposure to glargine and the absence of use of glargine in users of insulin, who were therefore exposed to a different type of insulin. The "comparator" is therefore an insulin "mix"; a "long-acting +/- bolus human insulin" comparator type could have been more relevant. Finally, concerning the possible protector role of metformin in this study, the adjustment is made to an OAD treatment and not to metformin specifically, which is regrettable.

- **CNAMTS study**

The CNAMTS study is a retrospective cohort of patients who started treatment with long- or intermediate-acting insulin in 2007, 2008 or 2009, and compared subjects exposed to insulin glargine, insulin detemir and long- or intermediate-acting human insulin, together, in each case, with subjects treated by other insulins.
The primary endpoints for the study were the occurrence of a cancer of all localisations and breast cancer. The secondary endpoints were the occurrence of prostate, colorectal, liver, kidney, bladder, lung and ENT cancer.
Subjects were included if they were affiliated with a general health insurance scheme (excluding SLM [local mutual groups]) and if, during the calendar year preceding the initiation, they were not

dispensed any insulin (regardless of type) and had at least three prescriptions for OADs filled. They had to be 40 to 79 years old at baseline.
Entry into the study was the first date on which the exposure condition was met for one of the three types of long- or intermediate acting insulin (exposure condition = at least two prescriptions filled for the same type of insulin during a 6-month period).
People with cancer treated before entering the study or within the next 12 months (medical, surgical and obstetric hospitalisations, HAH, follow-up and convalescence care or chronic conditions since 2005) and subjects with a follow-up duration of less than 12 months were excluded.
A patient was considered to be exposed from the 12th calendar month following the first filled prescription and the subject was considered to be exposed up to the end of follow-up.
An adjustment was made for the following confounding factors: age and sex, OAD treatments (metformin, rosiglitazone, pioglitazone, sulfonylureas, and other OADs) during follow-up, duration of diabetes at the time of inclusion from the start date of the chronic diabetes (subpopulation).

Risk of breast cancer according to the cumulative dose during follow-up: adjusted HR estimated from three multivariate Cox models with age as timescale.

		Model 1		Model 2		Model 3	
		HR	95% CI	HR	95% CI	HR	95% CI
Insulin glargine	[0 - 14 000 UI[	0.91	[0.59-1.40]	0.90	[0.58-1.39]	0.88	[0.54-1.45]
	[14 000 - 27 000 UI[	0.91	[0.59-1.42]	0.91	[0.58-1.42]	1.02	[0.62-1.67]
	27,000 and over	1.33	[0.85-2.09]	1.31	[0.84-2.05]	1.49	[0.91-2.45]
Insulin detemir	[0 - 14 000 UI[	1.28	[0.78-2.07]	1.20	[0.74-1.95]	1.13	[0.66-1.96]
	[14 000 - 27 000 UI[	0.99	[0.52-1.89]	0.95	[0.50-1.81]	1.02	[0.51-2.03]
	27,000 and over	1.18	[0.60-2.32]	1.12	[0.57-2.21]	1.04	[0.48-2.26]
HI (Human Insulin	[0 - 14 000 UI[	1.05	[0.52-2.15]	1.11	[0.54-2.27]	1.21	[0.56-2.60]
	[14 000 - 27 000 UI[	1.27	[0.56-2.87]	1.41	[0.62-3.21]	1.51	[0.61-3.72]
	27,000 and over	0.27	[0.04-1.91]	0.30	[0.04-2.18]	0.00	

Source SNIIRAM-PMSI, January 2006 - December 2010

The CNAMTS study did not show an increased risk of cancer of "all localisations combined" linked to insulin glargine use.
For breast cancer, even though the data presented did not show a statistically significant increased risk (study power), the fact that the RRs increase in accordance with the cumulative dose (dose effect) is a cause for caution.

Also, these first results are reassuring regarding the risk of all localisation cancers but do not permit ruling out an increased risk of breast cancer in glargine users.

New results with an additional year of follow-up:

A new analysis was performed with an additional year of follow-up: The preliminary study results study showed a dose effect between insulin glargine and breast cancer; the main analysis was thus conducted on this localisation.
The adjustments made in breast cancer related to whether a screening mammogram was done, exposure to other classes of antidiabetics during follow-up and the social disadvantage of the municipality of residence.
For colorectal cancer, an adjustment was made for sex, whether a colonoscopy was done, exposure to other classes of antidiabetics during follow-up and the social disadvantage of the municipality of residence.
For both localisations, an additional adjustment was made for the duration of diabetes in a second model.

Initially, 90,111 individuals with a General Scheme, 40 to 79 years old, newly treated with long-or intermediate-acting insulin and with at least three filled OAD prescriptions in the previous year were taken from the CNAMTS database (SNIIRAM).
In this population, the following were excluded: 11,299 individuals who had cancer before inclusion, 2610 individuals who had cancer in the 12 months following inclusion, 5677 individuals for whom the duration of follow-up was less than 12 months and 4279 patients residing in overseas departments (due to the lack of a social disadvantage index for these departments).
In all, the population selected for the cohort is comprised of 66,246 individuals.

The primary results are the HRs comparing the cancer risk between the third and first tercile of exposure (model in only those exposed to the insulin studied). For each localisation, three types of models are presented: cumulative dose, mean daily dose and cumulative duration.

For each localisation, both models give similar results. A statistically significant increased risk is found in 40-79 year-olds for breast cancer with insulin glargine (HR=1.86 [1.29; 2.68] for model 1 and HR=2.10 [1.42; 3.12] for model 2) and with insulin detemir (HR=1.95 [1.05; 2.05] for model 1 and HR=1.50 [1.03; 2.19] for model 2), for cumulative doses >=37,000 IU vs. <18,000 for glargine and >=34,000 IU vs. < 15,000 for detemir. Equally statistically significant results were found with the mean dose for both types of insulin. No statistically significant result was found with cumulative duration.

For the analysis of the more restrictive population of 40-64 years, a statistically significant increased risk was found with the cumulative dose for glargine and insulin detemir, with no statistically significant results for the mean dose and cumulative duration for glargine and the mean dose in model 1 and the cumulative duration for detemir (for the mean dose in model 2, the HR was 2.73 [1.04; 7.15] for detemir).

For colorectal cancer, an increased risk is found for glargine only in the analysis relating to mean dose (HR=1.39 [1.03; 1.88] for model 1 and HR=1.55 [1.12; 2.14] for model 2 in 40-79 year-olds) and for detemir in the analysis relating to cumulative dose (HR=2.62 [1.55; 4.45] for model 1 and HR=2.84 [1.62; 4.99] for model 2 in 40-79 year-olds) and the mean dose (HR=2.06 [1.21; 3.48] for model 1 and HR=2.39 [1.36; 4.20] for model 2 in 40-79 year-olds).

On the other hand, no increased risk was found with human insulin, regardless of the type of cancer considered, the type of analysis conducted or the population considered.

In all, these new results show:
- a significant association between cumulative dose of insulin glargine and breast cancer;
- a significant association between cumulative dose of insulin detemir and breast cancer;
- an association between high mean dose of insulin glargine and colorectal cancer (while neither the duration of exposure or the cumulative dose of glargine are associated with an increased risk of colorectal cancer);
- an association for insulin detemir with an increased risk of colorectal cancer in terms of cumulative dose and mean daily dose.
- no association between human insulin and cancer (breast or colorectal).

In this study, the results of analyses by duration and by cumulative dose do not agree. Remember, no adjustment was made for BMI, HbA1c and insulin resistance.

- **Study conducted from MedAssurant**

This study included 43,306 patients who were new users of insulin glargine and 9147 users of NPH insulin; with a mean duration of treatment of 1.2 years for glargine and 1.1 years for NPH insulin. This study for which we only have very patchy results, in which the median duration of follow-up is very short (less than one year) and the number of events low (122 cases of breast cancer whatever the insulin considered), indicates a non-adjusted HR of the same order of magnitude as presented in the other studies, between use of glargine and breast cancer, but not statistically

significant (HR=1.517 [0.976; 2.358]) and an adjusted HR of 1.05 [0.830; 2.050] (propensity score including the following factors: age, sex, year of entry into cohort, comorbidities, associated medical treatments, participation in screening tests, use of healthcare services).

3. Reminder of the position of the FDA (January 2011) and EMA (July 2009 and May 2013)

The FDA assessed the first four published epidemiological studies on 26 June 2009 in the journal for the European Association for the Study of Diabetes (EASD), Diabetologia, and gave its official position in January 2011 (this opinion does not therefore focus on the studies subsequently carried out).
The FDA concluded at that time that the available clinical data did not allow a aonclusion to be made on whether there was an increased risk of cancer with the long-acting insulin analogue Lantus. The FDA said in a progress report that this work had not allowed them to draw conclusions about an increased risk of cancer with this treatment "because of methodological limitations." The American agency also performed a post-hoc analysis using data from a trial comparing LANTUS* with NPH (Novo Nordisk) insulin for 5 years, with the same conclusion.
It also underlined that these studies were not specifically designed to evaluate an increased risk of cancer.

The EMA made a ruling in July 2009, after the publication of the epidemiological studies in the journal Diabetologia, then again on 31 May 2013, after expert assessment of the results of further studies it requested from the company.
In July 2009, the EMA concluded that because of the methodological limits of the studies published in Diabetologia, a link between LANTUS* and an increased risk of cancer could neither be confirmed or excluded. Moreover, the European agency stressed that the published data were not consistent. The agency added that its Comité des médicaments à usage humain (CMUH) [Committee for Medicinal Products for Human Use (CHMP)] would look at the studies and question many of their characteristics (relative short duration and possibility of other factors being involved).
The CHMP therefore asked Sanofi to carry out further studies and to also carry out a review of the literature.

In May 2013, the EMA indicated that the Committee for Medicinal Products for Human Use concluded that there was no increased risk of cancer in diabetic patients treated with long-acting insulin LANTUS* (glargine). "From the assessment of population studies, the CHMPconcluded that, overall, the data did not demonstrate an increased risk of cancer with insulin glargine, noting that there is no known mechanism by which insulin glargine would cause cancer and that a cancer risk has not been found in studies carried out by the company".

4. ORIGIN trial

In this open-label, randomised clinical trial, cancer incidence was a secondary endpoint.
The median duration of follow-up was 6.2 years.
All-cause cancer incidence (breast, lung, colon, prostate, melanoma, other) did not differ between the two groups (insulin glargine versus standard care: HR=1.00 [0.88; 1.13]; p=0.97). The mortality rate linked to all cancers did not differ between the two groups (insulin glargine versus standard care: HR=0.94 [0.77; 1.15]; p=0.52). Cancer incidence, localisation by localisation, did not differ between the two groups (insulin glargine versus standard care: HR between 0.88 and 1.21; p between 0.27 and 0.95), particularly with regards to breast cancer (insulin glargine versus standard care: HR=1.01 [0.60; 1.71]; p=0.95).
This trial does not demonstrate any association between glargine and cancer. However, some bias can be highlighted: significant use of metformin in the two arms (initially around 27% and 46.5% in the glargine arm versus 59.7% in the standard arm at the end of the trial) and a post-hoc comparison excluding subjects on metformin and leading to a loss of the benefit of randomisation.

5. Discussion

All the studies conducted have methodological limitations, variable depending on the studies (particularly the relatively short duration of follow-up, not taking account of all risk factors, particularly obesity, use of tobacco, etc.).
However, a signal is given in several studies on the possible link between insulin glargine and breast cancer.
Reconsidering the Bradford Hill criteria, the association found between glargine and breast cancer (HR between 1.4 and 2.3 based on the studies and populations/subpopulations recorded) is not very strong. The results are not all consistent from one study to another. The ISICA case-control study, taking into account the main confounding factors does not demonstrate any association between glargine and breast cancer (but the duration of follow-up in this study, as in the ORIGIN clinical trial, is relatively short), while the studies based on data, including those from the CNAMTS in particular, demonstrate a statistically significant association (but these studies do not allow all confounding factors to be taken into account).
The criterion on the temporal relationship and a dose-response relationship is found, in particular, in the study carried out by the CNAMTS.
The issue of biological plausibility seems to be able to be taken into account since there was a possible mechanism: insulin and its analogues can function as growth factors and therefore have a theoretical potential for promoting tumour proliferation.

6. Conclusion

Overall, given the data available to date, the Bradford Hill criteria to establish a causal link between insulin glargine and the risk of breast cancer were not fully met. Several studies found an association, with a dose effect. However, these studies, carried out from administrative databases, do not allow all the potential confounding factors to be considered. The studies which did not find any statistically significant association also present methodological limits, especially a relatively short follow up duration (in particular the ISICA study and ORIGIN clinical trial).

Publications found results consistent with there being no increased risk of "all localisation" cancer and, in contrast, an increased risk of breast cancer among users of glargine.

Main publications since 2009: All cancers

Study	Comparator	Adjusted HR or RR	Adjustment variables
USA ECT sanofi database analysis (Home-Lagarenne, 2009]	Human insulin, analogue, or OAD	0.90 [0.60; 1.36]	Non-adjusted RR
USA randomised trial (Rosenstock *et al*, 2009]	NPH insulin	0.90 [0.64; 1.26] 0.63 [0.36; 1.09] SAE	Non-adjusted RR
Germany (Hemkens *et al*, 2009]	Human insulin (monotherapy)	0.86 [0.79; 0.94]	Age, sex
	Human insulin (monotherapy)	**1.14 [1.05; 1.24]**	Age, sex, mean dose
United Kingdom (Currie *et al*, 2009]	Human insulin	0.81 [0.59; 1.11]	Age, sex, smoking, history of cancer
Sweden (Jonasson *et al*, 2009]	Other insulins	1.06 [0.90; 1.25]	Age, sex, BMI, smoking, age at onset of diabetes, cardiovascular disease
Sweden (Ljung *et al,* 2011]	Other insulins	1.10 [0.90; 1.35]	Age, sex, BMI, smoking, age at onset of diabetes, cardiovascular disease
Netherlands - Pharmo (Ruiter *et al*, 2012]	Human insulin	0.75 [0.71; 0.80]	age, sex, concomitant medication, no. of hospital visits, no. of days of OAD treatment, no. of OADs, mean dose
France – EGB (Blin et al, 2012]	Human insulin	0.59 [0.28; 1.25] exclusively for new users 0.58 [0.34; 1.01] predominantly among all users	Use of insulin, biguanide and sulfonylurea
Scotland (Colhoun *et* al, 2009]	Other insulins	1.02 [0.77; 1.36]	Age, sex, history of cancer, type of diabetes, calendar year
	Other insulin (monotherapy)	**1.55 [1.01; 2.37]**	Age, sex, history of cancer, type of diabetes, calendar year
	Other insulin (monotherapy)	1.73 [0.98; 3.05]	Age, sex, history of cancer, type of diabetes, year, BMI, smoking
Taiwan (Chang et al, 2011]	Human insulin	0.86 [0.73; 1.02]	Age, sex, date treatment initiated, dose and shelf life, complications of diabetes, hospitalisation etc.

Main publications: Breast cancer

Study	Comparator	Adjusted HR	Adjustment variables
United Kingdom - GPRD (Suissa *et al*, 2011]	Human insulin	**Total cohort:** 1.0 [0.7; 1.4] **Subgroup already treated with insulin before inclusion:** 1.0 [0.7; 1.5] throughout **2.7 [1.1; 6.5] if treatment >5 years**	age, oophorectomy, other cancer, HRT, smoking, diabetes duration, duration of insulin treatment before inclusion
Netherlands - Pharmo (Ruiter *et al*, 2011]	Human insulin	**1.58 [1.22; 2.05]**	age, sex, concomitant medication, no. of hospital visits, no. of days of OAD treatment, no. of OADs, mean dose
France – EGB (Blin et al, 2012]	Human insulin	0.59 [0.28; 1.25] exclusively for new users 0.58 [0.34; 1.01] predominantly among all users	Use of insulin, biguanide and sulfonylurea
USA - Medicare (Morden *et al*, 2011]	Human insulin	**Glargine alone: NS Combination: 1.75 [1.10; 2.78] [according to abstract]**	Patient characteristics, dose, metformin use
Taiwan (Chang et al, 2011]	Human insulin	0.53 [0.21; 1.31]	Age, sex, date treatment initiated, dose and shelf life, complications of diabetes, hospitalisation etc.

Appendix IV: Update of the target population – Detailed calculations

Population	Quantity	Estimate	Reference
French population	65,298,552	-	INSEE 2011 French National Institute for Statistics and Economic Research]
- including diabetics treated	2,886,196	4.42% of the French population	EGB 2011
DT1 treated	141,424	4.9% of diabetics treated	EGB 2011
- including DT1 treated with insulin	**141,424**	100% of DT1 treated	LPD [Longitudinal Patient Data] Cegedim 2011
DT2 treated	2,741,700	95.0% of diabetics treated	EGB 2011
- including DT2 treated with OADs alone, controlled	1,724,202	62.9% of DT2 treated	LPD Cegedim 2011
- including DT2 treated with OADs alone, uncontrolled	537,700	19.6% of DT2 treated	LPD Cegedim 2011
- including DT2 treated with insulin	**479,798**	17.5% of DT2 treated	LPD Cegedim 2011
DT2 treated with OADs alone, uncontrolled with HbA1c ≥8%	225,296	41.9% of DT2 treated with OADs alone, uncontrolled	CEMKA 2007
- including DT2 with HbA1c ≥8% eligible for insulin	**157,707**	Baseline value: 70% of DT2 treated with OADs alone, uncontrolled with HbA1c ≥8%	HAS 2007
	214,031	Maximum expected value: 95% of DT2 treated with OADs alone, uncontrolled with HbA1c ≥8%	
DT2 treated with OADs alone, uncontrolled with HbA1c ≥7% and <8%	312,404	58.1% of DT2 treated with OADs alone, uncontrolled	CEMKA 2007
- including DT2 with HbA1c ≥7% and <8% eligible for insulin	**31,240**	Baseline value: 10% of DT2 treated with OADs alone, uncontrolled with HbA1c ≥7% and <8%	HAS 2007
	78,101	Maximum expected value: 25% of DT2 treated with OADs alone, uncontrolled with HbA1c ≥7% and <8%	
TOTAL Diabetics (DT1+DT2) eligible for insulin	**810,170**	-	-
- lower limit	621,222	-	-
- upper limit	913,354	-	-

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