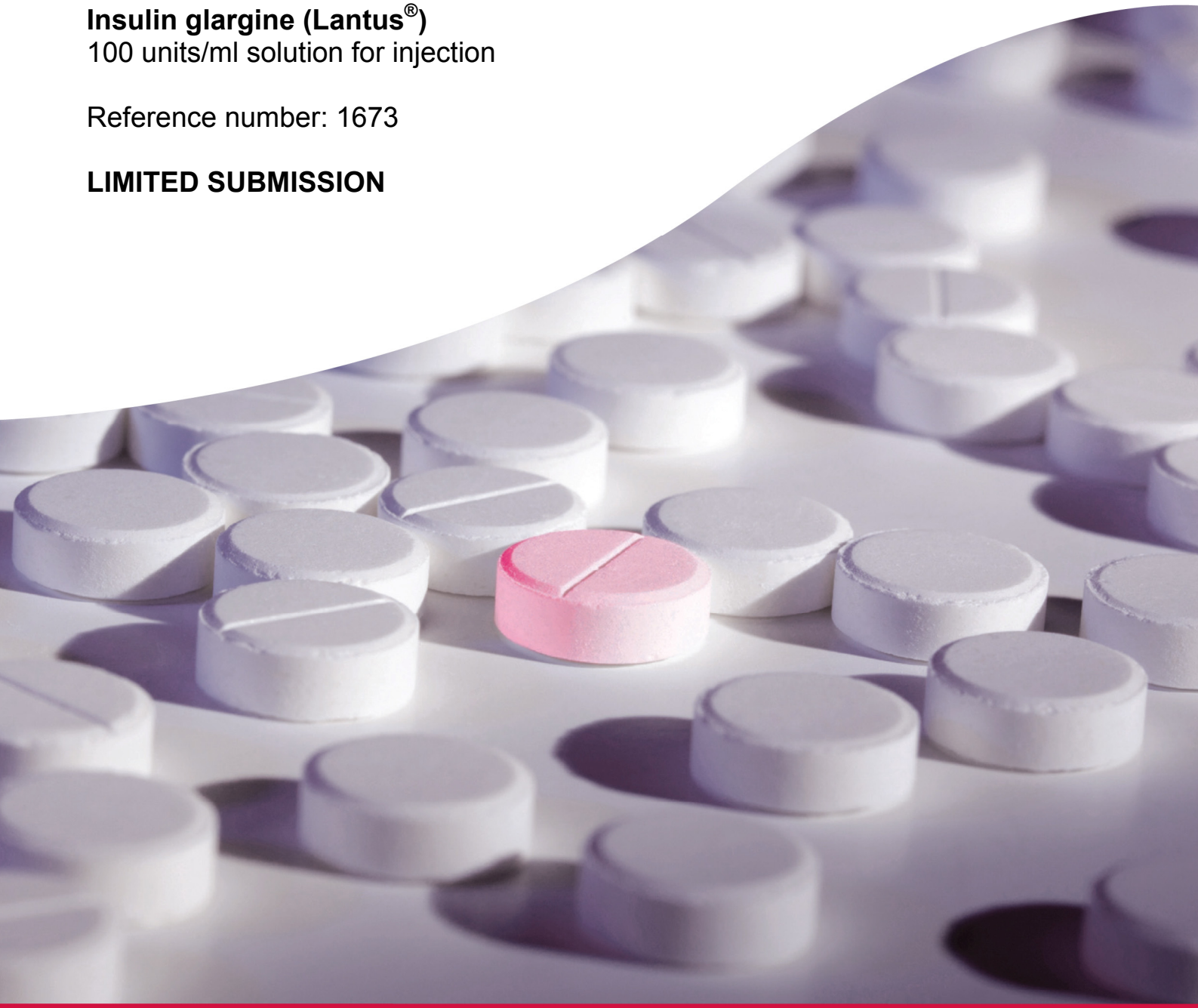
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Insulin glargine (Lantus®)
100 units/ml solution for injection

Reference number: 1673

LIMITED SUBMISSION



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AWMSG Secretariat Assessment Report
Insulin glargine (Lantus®) 100 units/ml solution for injection

This assessment report is based on evidence from a limited submission by Sanofi-Aventis Ltd on 25 September 2012[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Insulin glargine (Lantus®) for the treatment of diabetes mellitus in children aged 2 to less than 6 years. Insulin glargine was previously licensed for the treatment of diabetes mellitus in adults, adolescents and children aged 6–17 years[2–4].
Marketing authorisation date	25 May 2012[5].
Comparators	The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were isophane insulin (neutral protamine Hagedorn [NPH]) and insulin detemir (Levemir®).
Limited submission details	Insulin glargine (Lantus®) for the above indication met the following criteria for eligibility for a limited submission: • A minor licence extension. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact. • Estimated small difference in cost compared to comparator(s).

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Summary of evidence supplied in submission

The applicant company submitted evidence from EFC11202 (PRE-SCHOOL): a 24-week, multinational, multicentre, randomised, open-label, parallel arm, phase III study in children aged one to less than six years with type 1 diabetes mellitus (T1DM)[1,6]. Patients (n = 125) received basal insulin as either insulin glargine once daily (n = 61) or isophane insulin (NPH) once or twice daily (n = 64), titrated to achieve glycaemic targets without hypoglycaemia. In addition, all patients received multiple daily injections of bolus insulin as insulin lispro (Humalog®) or regular human insulin before meals and/or at bedtime. The insulin glargine group did not include any patients below the age of two years[6].

The primary endpoint was the composite endpoint "all hypoglycaemia", which consisted of low fingerstick blood glucose (FSBG) values (< 70 mg/dl [3.9 mmol/l]), low confirmed continuous glucose monitoring system (CGMS) (< 70 mg/dl [3.9 mmol/l]) and symptomatic hypoglycaemia episodes. Event rate was then calculated as the total number of episodes divided by the total duration of treatment period (events per patient-year). The incidence of "all hypoglycaemia" events was 193 per patient-year and 169 per patient-year for the insulin glargine and NPH group respectively (incidence ratio 1.18; 95% confidence interval [CI]: 0.97, 1.44), which did not meet the pre-specified noninferiority margin.

Secondary endpoints included analysis of glycosylated haemoglobin (HbA1c) levels after 24 weeks of treatment. At this time, mean HbA1c levels were 8.07% and 8.34% in the glargine and NPH groups respectively (compared with 8.02% and 8.25% at baseline). This difference was not statistically significant. Only 22–23% of patients in either

treatment group achieved levels within the target range (≤ 7.5%) by the end of the treatment period[6].

The components of the primary endpoint were analysed individually as secondary analyses. Low FSBG values comprised the largest proportion of the "all hypoglycaemia" events, and more FSBG events were recorded overall in the insulin glargine group than the NPH group. The differences between the confirmed low CGM excursions and symptomatic hypoglycaemia were relatively small between the two treatment groups (incidence ratio 1.06; 95% CI:0.81, 1.38)[6].

A lower number of patients completed the study in the NPH group (54/64 [84.4%]) than in the insulin glargine group (57/61 [93.4%]). The number of discontinuations due to treatment-emergent adverse events (AEs) was two and zero in the NPH and insulin glargine arms respectively. Overall, the rate of treatment-emergent AEs was comparable between the two groups (40 [64.5%] in the insulin glargine group versus 43 [68.3%] NPH-treated patients). More patients in the insulin glargine group (8 [12.9%]) reported serious treatment-emergent AEs than the NPH group (2 [3.2%]). However, all of the events in the insulin glargine group were assessed as not related to study treatment by the investigator (equivalent results for the NPH group were not reported)[6].

The submission also includes data from a conference abstract that describes an observational clinical study, which aimed to compare insulin glargine once daily and insulin detemir twice daily in newly diagnosed T1DM patients (aged 5–16 years), with a follow-up of 24 months[1,7]. Mean HbA1c values at 24 months were 7.0% for the insulin glargine group versus 7.2% for insulin detemir while the incidence of severe hypoglycaemia was 7.5 versus 6 per 100 patient years respectively. The study also concluded that there was no difference between the groups in terms of weight gain and diabetic ketoacidosis incidence[7]. No safety results were reported.

2.2 Points to note

- The company submission includes data from study EFC11202, which did not demonstrate noninferiority of insulin glargine in terms of the primary endpoint[6]. The difference in "all hypoglycaemic" events was driven by a higher incidence of low FSBG values for insulin glargine than for NPH; differences in the rate of confirmed CGMs and symptomatic hypoglycaemia were relatively small between the two treatment groups. Low FSBG values, particularly those that did not occur at times of symptomatic hypoglycaemia or low continuous glucose monitoring (CGM) values, have been suggested to be responsible for the difference between the treatment groups with respect to the primary endpoint. There were no notable differences between insulin glargine and NPH with respect to glucose control as measured by HbA1c levels at 26 weeks or the percentage of patients achieving target HbA1c levels. Taking the limitations of the study into account, CHMP concluded that EFC11202 demonstrated insulin glargine to be at least as effective as NPH for the indication under consideration[6].
- Most insulin glargine-treated patients (90%) received basal insulin injections once daily, while 80% of the NPH group received twice daily injections[6]. The applicant company expect that the majority of patients receiving insulin glargine in clinical practice would receive fewer injections per day compared to those on an NPH-based regimen, which is suggested to impact on the patient and carer experience and reduce the need for blood glucose monitoring after each administration[1].
- In line with the scope of this assessment of insulin glargine for the treatment of diabetes mellitus in children aged two to less than six years, the comparators requested by AWTTC were NPH and insulin detemir. With regards to insulin detemir, the only evidence supplied on comparative clinical effectiveness is a conference abstract that describes a comparison of insulin glargine and insulin detemir for the treatment of T1DM in patients aged 5–16 years[1]. Full results from this study are not available, and it is not clear to what extent results in this older

age range can be applied to the younger patients being considered by this appraisal.

- The four-week shelf-life of insulin glargine[2–4] is comparable with that of some NPH brands (Insuman® Basal[8] and Humulin I®[9]) but is less than the six-week shelf-life of Insulatard®[10] and insulin detemir[11].
- In November 2012, AWMSG is considering insulin detemir (Levemir®) for the treatment of diabetes mellitus in children aged 2–5 years[12].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The budget impact analysis presented by the company includes a simple comparison of the maximum annual costs associated with using insulin glargine (Lantus®) and NPH for the treatment of diabetes mellitus in children aged two to less than six years[1].

Using incidence data from the Scottish Diabetes Survey (2010)[13], the company submission estimates that there are 43 children between the ages of two and six years with T1DM each year in Wales. Based on the maximum insulin doses derived from the EFC11202 study, the company estimates the annual cost of treatment with insulin glargine to be £398 per person. The estimated treatment cost with NPH is £492 per person. According to the company's estimations, treatment with insulin glargine would save £94 per person per year. Assuming that all 43 incident cases receive insulin glargine instead of NPH, the total saving would be £4,048 per year. A breakdown of the costs of treatment with insulin glargine and NPH is shown in Table 1.

Table 1. Company-estimated comparative costs associated with the use of insulin glargine (Lantus®) and NPH for the treatment of diabetes mellitus in children aged two to less than six years[1].

	Insulin glargine (Lantus®)	NPH	Difference
Basal component			
Cost of basal insulin	£135.32	£80.13	£55.19
Cost of blood glucose monitoring	£137.92	£225.68	-£87.76
Cost of needles	£47.18	£77.20	-£30.02
Bolus component			
Cost of bolus insulin	£77.28	£108.82	-£31.54
Cost of blood glucose monitoring	£376.13	£376.13	£0.00
Cost of needles	£128.66	£128.66	£0.00
Total	**£397.69**	**£491.83**	**-£94.14**

3.2 AWTTC critique of the budget impact analysis

- AWTTC requested NPH and insulin detemir as comparators for insulin glargine; however, the company provided estimates for NPH only. This may not reflect current use of basal insulins in the relevant population group in Wales, as the company reports that insulin detemir, and to a lesser extent premix, are also valid comparators[1]. Cost neutrality has simply been assumed for insulin glargine and insulin detemir.
- The 43 children estimated to be eligible for treatment with insulin glargine in Wales is based on incident cases reported in Scotland in 2010[13]. The company has subsequently provided prevalence data from the Welsh Paediatric Diabetes Interest (Brecon) Group, which are reported to indicate a prevalence of 256 children in Wales in 2009, and 180 children in 2011 (not verified, and conflicting with alternative sources which indicate an increasing prevalence in the UK[14]), but no attempt has been made to incorporate these into the budget impact estimates.

Therefore, the number of children who will be potentially eligible for treatment with insulin glargine in Wales may be underestimated.

- The company estimates of budget impact included the cost of insulin acquisition, administration and monitoring only[1]. This assumes no difference in hypoglycaemic episodes for insulin glargine and NPH. However, as discussed in Section 2, the EFC11202 study failed to demonstrate non-inferiority of insulin glargine to NPH for the composite endpoint of "all hypoglycaemia"[6].
- Insulin acquisition costs are based on daily doses that do not take into account wastage. According to the relevant Summaries of Product Characteristics (SPCs), the open shelf-life is four weeks for insulin glargine[2–4] and six weeks for Insulatard®[10]. With doses lower than 10.71 units per day (the mean daily dose of insulin glargine in EFC11202 study was 7.29 units), wastage will be higher for insulin glargine compared to Insulatard®. Therefore, acquisition costs for insulin glargine may be underestimated.
- The company assumes that insulin pens/cartridges will be used one at a time. However, in practice insulin pens may be kept at different locations (for example, in a car, or at home or place of day care). Given the shorter shelf-life for insulin glargine, this may lead to a further underestimation of the costs.
- In summary, it is unclear whether the company-estimated savings associated with the licence extension would be realised in practice.

3.3 Table of comparative unit costs

Table 2 provides examples of comparative annual acquisition costs for basal insulins, assuming an average daily dose of 10 units. Due to individual dosing requirements and different durations of activity, the comparison of acquisition costs is for illustration purposes only.

Table 2. Example comparative annual acquisition costs for basal insulins for the treatment of diabetes mellitus in children aged two to less than six years.

Drug	Annual cost of treatment
Insulin glargine (Lantus®) 100 units/ml 5 x 3 ml cartridges, SoloStar® pre-filled pen	£108†
Insulin detemir (Levemir®) 100 units/ml 5 x 3 ml cartridges, FlexPen® pre-filled pen	£102*
Human isophane insulin (Humulin I®) 5 x 3 ml cartridges; KwikPen® pre-filled pen	£50–£57*
Human isophane insulin (Insulatard®) 100 units/ml 5 x 3 ml cartridges	£56*
Human isophane insulin (Insuman® Basal) 100 units/ml 5 x 3 ml cartridges, SoloStar® pre-filled pen	£43–£48†
Costs are based on MIMS list prices as of 9 October 2012[15], for a daily dose of 10 units; the shelf-lives of products are as per SPCs. *† Four-week shelf-life* ** Six-week shelf-life* *This table does not imply therapeutic equivalence of drugs or the stated doses.* *See relevant SPCs for licensed indications, and full dosing and product details[2–4,8–11].*	

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, insulin glargine may be appropriate for use within NHS Wales prescribed under specialist recommendation for the indication under consideration.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 15 October 2012
Date range of evidence search: No date limits were applied to database searches.

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