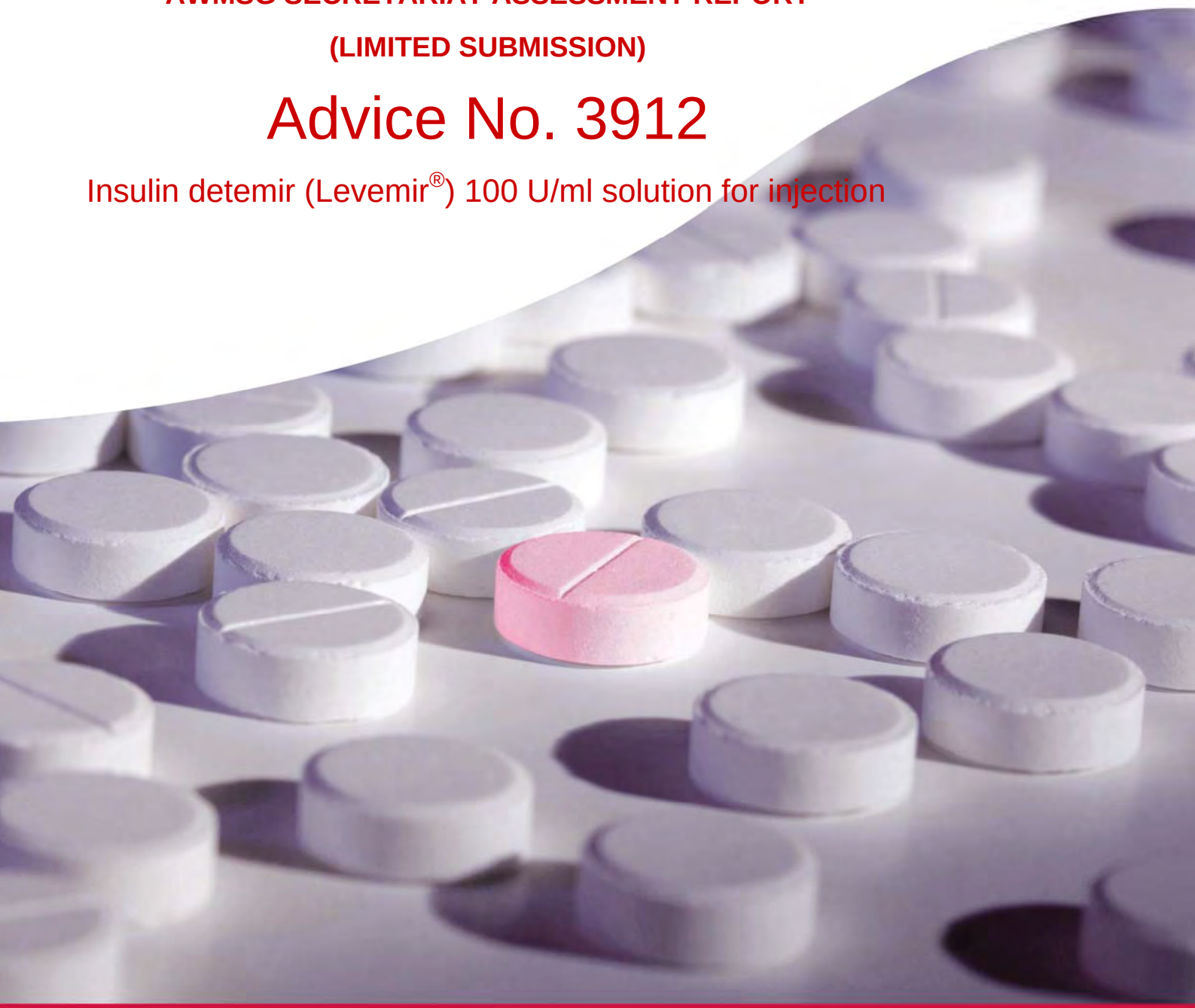
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 3912

Insulin detemir (Levemir®) 100 U/ml solution for injection



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 3912
Insulin detemir (Levemir®) solution for injection in cartridge (Penfill®) or pre-filled pen (FlexPen® and InnoLet®)

This assessment report is based on evidence from a limited submission by Novo Nordisk Ltd on 5 July 2012[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Insulin detemir (Levemir®) for the treatment of diabetes mellitus in children aged 2–5 years. Insulin detemir was previously licensed for the treatment of diabetes mellitus in adults, adolescents and children aged 6–17 years[2].
Marketing authorisation date	24 October 2011[3]
Comparators	The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were insulin glargine and isophane insulin (neutral protamine Hagedorn [NPH]).
Limited submission details	Insulin detemir 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 comparators.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Summary of evidence supplied in submission

The applicant company submitted evidence from a 52-week randomised, multicentre, open-label, parallel group trial in children aged 2–16 years with type 1 diabetes mellitus (T1DM)[1]. Results from a subgroup analysis of children aged 2–5 years were presented in support of the licence extension under consideration; however, no statistical analyses were performed due to the low patient numbers[4]. Patients in the subgroup (n = 82) received basal insulin as either insulin detemir (IDet; n = 42) or NPH (n = 40), in addition to bolus insulin (insulin aspart as NovoRapid®/NovoLog®) with meals. The dose of basal insulin was adjusted according to plasma glucose measurements, with a target fasting/preprandial plasma glucose of 4.0–7.0 mmol/L.

The primary endpoint, level of haemoglobin A1c (HbA1c) after 52 weeks, was 8.1% (8.2% at baseline) for IDet and 8.3% (8.1% at baseline) for NPH. The percentage of children with hypoglycaemic episodes was similar between the IDet and NPH treatment groups (95% versus 98%); however, children treated with IDet had fewer hypoglycaemic episodes (2,072 versus 3,050 episodes in NPH group). No severe hypoglycaemic episodes (characterised by patients becoming semiconscious, unconscious or in a coma with or without convulsions) were reported for IDet whereas six severe episodes (in three children) were reported for patients treated with NPH.

Further, no episodes of severe nocturnal hypoglycaemia were reported for patients treated with IDet verses two episodes in patients treated with NPH. The mean number of episodes of hypoglycaemia per patient-year was lower for IDet than NPH in terms of total (50.6 versus 78.3), severe (0 versus 0.2) and nocturnal (8.0 versus 17.4) episodes. The change in observed mean weight (standard deviation score, standardised by age and gender) was −0.17 with IDet compared to 0.03 with NPH[4].

A slightly lower percentage of subjects reported adverse events (AEs) with IDet than NPH (69.0% versus 77.5%). Five serious adverse events (SAEs) were recorded in the IDet arm compared to seven in the NPH arm; the most common SAEs in both groups were gastroenteritis and dyspepsia. One case of T1DM inadequate control was reported for IDet. No deaths were reported[4].

Children receiving IDet were eligible to enter a 52-week extension phase (2–5 years: n = 37; 6–16 years: n = 109). Insulin antibodies increased in the 2–16 year cohort during the initial 52-week trial, but decreased during the 52-week extension to levels slightly higher than pre-trial. The Committee for Medicinal Products for Human Use (CHMP) concluded that the results indicate that antibody development had no negative effect on glycaemic control, and that IDet dose and persistence of efficacy was preserved over the 104 weeks[5].

2.2 Points to note

- CHMP was of the opinion that glycaemic control (HbA1c level) with IDet when given as part of a basal-bolus therapy in children aged 2–5 years with T1DM is comparable to NPH using a non-inferiority margin of 0.4%[5].
- In the subgroup analysis of children aged 2–5 years, patients that received IDet experienced fewer hypoglycaemic events, fewer severe nocturnal hypoglycaemia episodes, less weight gain and fewer AEs/SAEs than those in the NPH arm. In addition to these factors, CHMP noted that the longer duration of action and the lower within-subject variation in fasting blood glucose of IDet may also offer advantages for the treatment of young children[5].
- No statistical analyses were performed for the 2–5 year subgroup due to the low patient numbers; however, the hypoglycaemic risk differences followed the same trend as the overall cohort (aged 2–16 years, n = 347), in which the mean number of 24-hour episodes of hypoglycaemia per patient-year was lower for IDet than NPH (55.4 versus 72.5; $p < 0.05$[6]). Overall, children in the 2–5 year subgroup maintained better glycaemic control compared to the older children[5].
- The six-week shelf-life of IDet after first use is equal to that of the NPH brand Insulatard®[7], but greater than the four-week open shelf-lives of other NPH brands (Insuman® Basal[8] and Humulin®[9]), as well as insulin glargine (Lantus®)[10].
- The applicant company stated that they were unable to provide clinical data for comparison with insulin glargine because it was not licensed for children aged 2–5 years with diabetes mellitus at the time that AWTTC requested a limited submission[11]. On April 19 2012, CHMP recommended a change in the marketing authorisation for insulin glargine which, if granted by the European Commission, will extend its licence to the treatment of diabetes mellitus in children aged two years and above[12]. However, the All Wales Medicines Strategy Group (AWMSG) considers the use of unlicensed medicines as comparators within its appraisal process where appropriate[13].

3.0 ASSESSMENT OF THE EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

Based on a prevalence of 186.3/100,000, the company estimates that there are 263 children aged 2–5 years with T1DM in Wales in 2012[14]. Using Welsh population forecasts, and an implicit assumption of no increasing incidence, this figure is expected to rise to 279 in 2016. Using market research data, 75% of these children are expected to receive treatment with basal insulin. The budget impact analysis compares IDet (Levemir®) against the most commonly prescribed (Insulatard®) and the least costly (Insuman® Basal) brands of human insulin[1].

The company has based its cost estimates around the mean dose requirements observed in the supporting clinical trial (0.32 U/Kg) and average weight estimates for children in this age group (17 Kg), yielding an average daily dose of 5.5 U[4]. Cost offsets with the use of IDet, based on numerically lower rates of non-severe and severe hypoglycaemic episodes observed with IDet compared with NPH in the supporting clinical trial, have been included (see Section 2.1)[4]. Unit costs for hypoglycaemic events are reportedly based on direct medical costs obtained from published estimates[15,16]. It is assumed that 10% of eligible children would use IDet instead of NPH in 2012, rising to 25% from 2014 onwards.

The company estimates that treatment costs will increase with the use of IDet instead of NPH, but that there will be net cost savings due to a reduction in the number of hypoglycaemic events. Table 1 presents the net budget impact estimates provided by the company, using the most commonly prescribed brand of NPH as the comparator.

Table 1. Company estimates of budget impact for IDet compared with the most commonly prescribed NPH brand (Insulatard®)

	2012	2013	2014	2015	2016
Total number of children to be treated with basal insulin	197	203	203	207	210
Potential number to be treated with IDet	20	56	93	121	143
Costs if all treated with Insulatard®					
Drug cost	£6,038	£6,210	£6,210	£6,338	£6,423
Hypoglycaemia costs	£178,617	£183,684	£183,684	£187,484	£190,018
Costs if above patients switch to IDet					
Drug cost	£6,542	£7,648	£8,583	£9,440	£10,089
Hypoglycaemia costs	£172,006	£164,798	£152,523	£146,766	£141,896
Net budget impact	**−£6,107**	**−£17,447**	**−£28,787**	**−£37,617**	**−£44,456**

Using the least costly NPH (Insuman® Basal) as the comparator, estimated net cost savings are similar at −£5,965 in 2012, rising to −£43,419 in 2016.

3.2 AWTTC critique of the budget impact analysis

- The number of children eligible for treatment is based on the prevalence of T1DM in children aged 0–17 years. Most cases contributing to this prevalence were in children aged ten years and older[14]. The number of children aged 2–5 years eligible for treatment with IDet in Wales appears subject to uncertainty.
- The company has assumed the costs of cartridges only in its analyses, and no differences in costs of injection devices and disposable needles, etc. The company has also assumed no wastage in estimating the annual acquisition costs of the basal insulins. IDet[2] and Insulatard®[7] both have shelf-lives of six weeks once opened, and Insuman® Basal has a shelf life of four weeks once

opened[8]. Based on the assumed daily insulin dose of 5.5 U, the company appears to have underestimated the annual cost of all of the basal insulins. However, the impact of this on net costs presented by the company is minimal.

- The frequency of non-severe hypoglycaemic events were numerically lower with IDet in the supporting clinical trial, but no statistical analyses have been conducted, reportedly due to the small sample size of this patient subgroup, which adds to the uncertainty around these figures[4].
- The published study used to provide costs of non-severe hypoglycaemic episodes was conducted in adults with both type 1 and type 2 diabetes mellitus, which may not reflect the resource use and costs in the target patient group.
- AWTTC requested comparison against both NPH and insulin glargine; however the company has not included comparisons against the latter (see Section 2.2).
- Collectively, the extent to which the company's estimated cost savings would be realised in practice is unclear.

3.3 Comparative unit costs

Table 2 provides example comparative annual acquisition costs for basal insulins, assuming an average daily dose of 5.5 U as per the company submission.

Table 2. Example acquisition costs for basal insulins at a daily dose of 5.5 U

Drug	Annual cost of treatment
IDet (Levemir®) 5 x 3 ml Penfill® cartridge; FlexPen®; InnoLet®	£73–78*
Insulin glargine (Lantus®)§ 5 x 3 ml Penfill® cartridge; SoloSTAR® pen	£108†
NPH (Insulatard®) 5 x 3 ml Penfill® cartridge; InnoLet®	£35–40*
NPH (Insuman® Basal) 5 x 3 ml Penfill® cartridge; SoloSTAR® pen	£46–52†
NPH (Humulin®) 5 x 3 ml Penfill® cartridge; Kwikpen®	£50–57†

NPH: neutral protamine Hagedorn (isophane insulin)

Costs are based on MIMS[17] list prices as of 20 July 2012 for daily dose of 5.5 U and open shelf-lives of six weeks or four weeks† as per Summaries of Product Characteristics (SPCs).*
§ Not licensed for use in children less than six years of age.
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[2,7–10].

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, IDet 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: 12 July 2012
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Novo Nordisk Ltd. Form C: Limited appraisal submission. Insulin detemir (Levemir®). Jul 2012.

2 Novo Nordisk Ltd. Levemir cartridge 100 U/ml - Penfill®, levemir pre-filled pen 100 U/ml - FlexPen® and InnoLet®. Summary of Product Characteristics. Jan 2012. Available at: http://www.medicines.org.uk/EMC/medicine/14584/SPC/Levemir++Cartridge+100+U+ml+-+Penfill%2c++Levemir+Pre-filled+Pen+100+U+ml+-+FlexPen+and+InnoLet/. Accessed Jul 2012.

3 European Medicines Agency. Levemir®. Procedural steps taken and scientific information after the authorisation. 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000528/WC500036660.pdf. Accessed Jul 2012.

4 Thalange N, Bereket A, Larsen J et al. Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus. *Pediatric Diabetes* 2011; 12: 632-41.

5 European Medicines Agency. Assessment report for Levemir®. Procedure No.: EMEA/H/C/000528/II/0051. Sep 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000528/WC500120034.pdf. Accessed Jul 2012.

6 Thalange N, Bereket A, Larsen J et al. A 52-week randomised clinical trial comparing insulin detemir and NPH in children and adolescents (2-16 years) with type 1 diabetes (T1DM). *Diabetic Medicine* 2010; 27 (S1).

7 Novo Nordisk Ltd. Insulatard® 100 IU/ml, Insulatard Penfill® 100 IU/ml, Insulatard InnoLet® 100 IU/ml. Summary of Product Characteristics. May 2011. Available at: http://www.medicines.org.uk/EMC/medicine/3512/SPC/Insulatard+100+IU+ml%2c+Insulatard+Penfill+100+IU+ml%2c+Insulatard+InnoLet+100+IU+ml/. Accessed Jul 2012.

8 Sanofi-Aventis Ltd. Insuman® Basal 100 IU/ml suspension for injection in a cartridge. Summary of Product Characteristics. Jul 2012. Available at: http://www.medicines.org.uk/EMC/medicine/26468/SPC/Insuman+Basal+100+IU+ml+suspension+for+injection+in+a+cartridge/. Accessed Jul 2012.

9 Eli Lilly and Co Ltd. Humulin® vials, cartridges and KwikPens®. Summary of Product Characteristics. Jun 2012. Available at: http://www.medicines.org.uk/EMC/medicine/3425/SPC/Humulin+Vials%2c+Cartridges+and+KwikPens/. Accessed Aug 2012.

10 Sanofi-Aventis Ltd. Lantus®. Summary of Product Characteristics. Jul 2012. Available at: http://www.medicines.org.uk/EMC/medicine/25506/SPC/Lantus+100+units+ml+solution+for+injection+in+a+vial/. Accessed Jul 2012.

11 Novo Nordisk Ltd. Scope acknowledgement letter to AWMSG. Jun 2012.

12 European Medicines Agency. Summary of opinion (post authorisation) Lantus (insulin glargine). Apr 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000284/WC500125685.pdf. Accessed Jul 2012.

13 All Wales Medicines Strategy Group. AWMSG Guidelines for appraising medicines. Jul 2012. Available at: http://www.wales.nhs.uk/sites3/docmetadata.cfm?orgid=371&id=195383. Accessed Aug 2012.

14 Royal College of Paediatrics and Child Health. Growing up with diabetes: children and young people with diabetes in England. 2009. Available at: http://www.diabetes.org.uk/Documents/Reports/CYP_Diabetes_Survey_Report.pdf. Accessed Jul 2012.
15 Brod M, Christensen T, Thomsen TL et al. The impact of non-severe hypoglycemic events on work productivity and diabetes management. *Value in Health* 2011; 14 (5): 665-71.
16 Hammer M, Lammert M, Mejias SM et al. Costs of managing severe hypoglycaemia in three European countries. *Journal of Medical Economics* 2009; 12 (4): 281-90.
17 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Jul 2012. Available at: http://www.mims.co.uk/. Accessed Jul 2012.