Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for insulin detemir (rys)

Proprietary Product Name: Levemir

Sponsor: Novo Nordisk Pharmaceuticals

March 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ADA	American Diabetes Association
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AUC_{0-24}	Area under the serum concentration–time curve from time 0 to 24 hours
$AUC_{GIR,0-24}$	Area under the glucose infusion rate curve from time 0 to 24 hours
B/T%	Percentage of bound antibodies versus total antibody level
CCDS	Core Company Data Sheet
CI	Confidence interval
C_{max}	Maximum concentration
CTR	Clinical trial report
DAE	Adverse event leading to discontinuation
DBP	Diastolic blood pressure
EMA	European Medicines Agency
FAS	Full analysis set
$FAS_{Pregnant}$	FAS for pregnant subjects
FFA	Free fatty acid
FPG	Fasting plasma glucose
GIR	Glucose infusion rate
GIR_{max}	Maximum glucose infusion rate
GPRD	General Practice Research Database
GW	Gestation week
h	Hour

Abbreviation	Meaning
HbA1c	Glycosylated haemoglobin
HDL-C	High density lipoprotein cholesterol
HI	Human insulin
HOMA	Homeostasis model assessment
HOMA-B	HOMA index of beta-cell function
HOMA-IR	HOMA index of insulin resistance
IDF	International Diabetes Federation
IV/WRS	Interactive Voice/Web Response System
LDL-C	Low density lipoprotein cholesterol
LOCF	Last observation carried forwards
LS Mean	Least-square mean
MAA	Marketing Authorisation Application
MESI	Medical event of special interest
NN	Novo Nordisk Pharmaceuticals
NPH	Neutral Protamine Hagedorn
OAD	Oral antidiabetic drug
PD	Pharmacodynamic(s)
PG	Plasma glucose
PK	Pharmacokinetic(s)
$PP_{Pregnant}$	Per-protocol data set for pregnant subjects
RCT	Randomised controlled clinical trial
RPM	Repeated-measurement
SAE	Serious adverse event
SAS	Safety analysis set
SBP	Systolic blood pressure
SMPG	Self-measured plasma glucose

Abbreviation	Meaning
SOC	System organ class
t½	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TG	Triglycerides
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
t_{GIRmax}	Time to maximal glucose infusion
t_{max}	Time to maximal serum concentration
U	Unit(s)
UNL	Upper normal limit
VLDL-C	Very low density lipoprotein cholesterol

I. Introduction to product submission

Submission details

Type of submission:	Major variation (change in patient group/pregnancy category).
Decision:	Approved
Date of decision:	16 October 2013
Active ingredient:	Insulin detemir (rys)
Product name(s):	Levemir (Penfill / Flexpen / Innolet)
Sponsor's name and address:	Novo Nordisk Pharmaceuticals Level 3 / 21 Solent Circuit Baulkham Hills NSW 2153
Dose form:	Solution for injection
Strength:	100 units/mL
Container(s):	cartridge
Pack size:	5 times 3 mL multidose cartridge
Approved therapeutic use:	*Treatment of diabetes mellitus*
Route of administration:	Subcutaneous injection
Dosage:	For patients with type I diabetes mellitus, Levemir must be used in combination with rapid- or short-acting insulin. When Levemir is used as part of a basal-bolus insulin regimen Levemir should be administered once or twice daily depending on patients' needs. Dosage of Levemir should be adjusted individually
ARTG number (s):	172213 (Levemir Penfill), 172234 (Levemir Flexpen), 172235 (Levemir Innolet)

Product background

Type I diabetes mellitus (T1DM) is a metabolic disorder characterised by pancreatic insufficiency of insulin production, resulting in hyperglycaemia and end-organ complications such as accelerated atherosclerosis, neuropathy, nephropathy, and retinopathy.

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterised by insulin resistance and relative insulin deficiency leading to hyperglycaemia.

T2DM is one of the most common chronic diseases in Australia. Its prevalence is rising. In Australia, the proportion of people with T2DM has increased from 1.1% in 1995 to 3.3% in 2007-08 (National Health Survey data) (Australian Bureau of Statistics, 2011[1]). In the same time period, 88% or 721,000 people had T2DM and 10% or 82,000 people had T1DM (2% were unclear on which type of diabetes they had) (Australian Bureau of Statistics, 2011).

This is a submission to update the currently approved Australian Product Information (PI) document for the above medicine with respect to the following aspects:

- **Change 1**: include clinical trials information on co-administration with liraglutide (Victoza).
- **Change 2**: include longer term (24 months) safety data (antibody formation & glycaemic control) for the use of Levemir in adolescents and children (2-16 years) with T1DM.
- **Change 3**: Allow use in pregnancy, that is, change in Pregnancy category from current B3[2] to Pregnancy category A[3].
- **Change 4:** Align with the Core Company Data Sheet, version 12.0 (CCDS), as well as various editorial changes.

These data have been reviewed overseas and are currently reflected in the approved prescribing information documents in the EU (EMA) and the USA (FDA).

The proposed changes 1, 2 and 4 above were negotiated with the sponsor.

Proposed Change 3 which was to allow use in pregnancy consequent with a change in Pregnancy category from current B3 to proposed category, was referred to the Advisory Committee for Prescription Medicines (ACPM)for their advice.

The currently approved indication for Levemir is:

Treatment of diabetes mellitus

This submission does not involve any change to the currently approved indication, population, drug formulation or dosage form.

Regulatory status

The product received initial ARTG Registration on 9 September 2011.

Applications for have been submitted or approved in several jurisdictions The sponsor has provided four tables to indicate the overseas registration status in regard to the four changes proposed for the Australian market (listed in Table 1).

[1] Australian Bureau of Statistics, 2011. *Diabetes in Australia: A Snapshot, 2007-08*. Cat. no. 4820.0. Canberra: ABS

[2] **Category B3**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans

[3] **Category A**: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Table 1: International regulatory status

Country	Use of Levemir with liraglutide	Paediatric safety data for Type 1 diabetes	Use of Levemir in pregnancy	Alignment with the sponsor's CCDS
European Union (EU)	**Approval:** 24-10-2011 Levemir as an add-on to Victoza. **Indications:** Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.	**Approval Date** 14-10-2011 **Indications**: Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.	**Approval Date:** 19-12-2011 **Indications:** Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.	**Approval Date:** 19-12-2011 **Indications:** Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.
United States of America	**Approval Date**: 27-14-2012 Levemir in combination with GLP-1. **Indications and usage:** Levemir is indicated to improved glycaemic control in adults and children with diabetes mellitus.	**Approval Date:** 18-05-2012 **Indications and usage:** Levemir is indicated to improved glycaemic control in adults and children with diabetes mellitus.	**Approval Date**: 29-03-2012 **Indications and usage:** Levemir is indicated to improved glycaemic control in adults and children with diabetes mellitus.	**Approval Date**: 18-04-2012 **Indications and usage**: Levemir is indicated to improved glycaemic control in adults and children with diabetes mellitus.
Canada	N/A	N/A	N/A	N/A
Switzerland	N/A	**Approval Date:** 28-04-2011 **Indications**: Diabetes mellitus in adults, adolescents and children age 2 years if insulin treatment is necessary.	N/A	**Approval Date**: 18/04/2012 **Indications:** Diabetes mellitus in adults, adolescents and children age 2 years if insulin treatment is necessary.

Product Information

The approved PI current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

With regard to nonclinical matters, the sponsor proposes the following modifications to the PI statement on *Metabolism*:

> "The metabolism of insulin detemir is similar to that of human insulin."
>
> To be amended to :
>
> "Degradation of insulin detemir is similar to that of human insulin; all metabolites formed are inactive."

The current submission did not contain non-clinical data. The sponsor cited two nonclinical studies submitted in the original application for the registration of insulin detemir as the evidence base for the modified statement. These studies compared the *in vitro* metabolism of 14C-insulin detemir and human insulin (HI) in liver cytosol (from rat, dog, pig and human) and in kidney S9 mix (rat and human) [Study NN201126] and related to the identification of major urinary metabolites of insulin detemir in rats (with the structure of one of the three metabolites elucidated) [Study NN01234]. Neither study contained any data on the pharmacological activity of the metabolites formed. However, Study NN201126 did identify that cleavage of the disulfide bonds between the A-chain and the B-chain was the first step of metabolism. This is recognised to be associated with loss of pharmacological activity for HI, although some single chain analogues of HI that largely retain activity are reported in the literature[4].

Nonclinical summary and conclusions

Given the absence of specific data for insulin detemir, the proposed PI statement on metabolism should be revised as follows:

> "*Metabolism*
>
> Degradation of insulin detemir is similar to that of human insulin; all metabolites formed are <u>likely to be</u> inactive."

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

The rationales provided by the Sponsor for each change are:

Change 1:

In T2DM "basal insulin, co-administered with liraglutide, would provide additional glucose-lowering potency, while the presence of liraglutide may substantially reduce weight gain associated with insulin, reduce required insulin dose and maintain low risk of hypoglycaemia. Insulin detemir, a basal insulin analogue shown to provide lower risk of hypoglycaemia and less weight gain compared to Neutral Protamine Hagedorn (NPH) insulin (intermediate-acting insulin), is a promising candidate to be tested for efficacy and safety in combination with a once-daily human GLP-1 analogue, such as liraglutide."

[4] Le Flem G., Pecher J., Le Flem-Bonhomme V., Rochette J., Pujol J.P. and Bogdanowicz P. 2009. Human insulin A-chain peptide analog(s) with *in vitro* biological activity. *Cell Biochem. Funct.* **27:**370–377.

Change 2:

"In connection with the approval of the paediatric indication of insulin detemir by EMA, a new long-term safety trial (NN304-1689) was discussed and agreed with EMA as part of a post-approval commitment". The purpose of the application is to update the PI with long-term safety data from this trial.

Change 3:

"The use of insulin analogues is increasing in T1DM as well as in T2DM. Their use expands into special populations, such as children, elderly patients and patients with kidney failure. Use of insulin analogues implies that an increasing number of women conceive during insulin analogue treatment. Switching their treatment may carry a risk of deteriorated glycaemic control with an inherent risk of adverse influence on the pregnancy outcome. Pregnant women with diabetes need optimal glycaemic control with as few hypoglycaemic episodes as possible to reduce their risk of diabetes complications and to reduce the risk of adverse pregnancy outcome as described above. Hence, there is a medical need for optimising diabetic control in this population."

Change 4:

The Sponsor proposes to align the PI more closely with the CCDS. The Sponsor also has made some editorial changes to align the PI with the format described in Appendix 8 of the Australian Regulatory Guidelines for Prescription Medicines.

Scope of the clinical dossier

The submission contained the following clinical information:

- Change 1 contained three studies: Study NN2211-3673 (Pharmacokinetic (PK)/Pharmacodynamic (PD)), Study NN2211-1842 (efficacy and safety) and Study NN2211-1842-extension (long-term safety)
- Change 2 contained one study: Study NN304-1690 (long-term open label safety in children)
- Change 3 contained one study: Study NN304-1687 (efficacy and safety in pregnancy)

Paediatric data

The submission included paediatric safety data.

Good clinical practice

The studies submitted in the application were stated to have been conducted according to GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

Study NN2211-3673 was an open label, three treatment phase, single sequence, PK and PD (euglycaemic clamp at 100 mg/dL) study of detemir, liraglutide and the combination of liraglutide and detemir. The study was conducted at a single centre in the US from April 2009 to September 2009. The study included male or female subjects ≥ 18 years of age; insulin naïve and diagnosed with T2DM; treated with stable doses of oral anti-diabetics (one of which had to be metformin); BMI of ≤ 45 kg/m^2, screening HbA1c of 7 to 10% on

monotherapy and 7 to 9.5% on dual therapy; FPG ≤ 250 mg/dL at Visit 2; and FPG ≥ 140 and ≤ 240 mg/dL at Visit 5 (Study Day 1).

The study treatments were: insulin detemir 0.5 U/kg on Day 1, followed by 24 hour eugycaemic clamp; liraglutide titrated to 1.8 mg/day from Day 2 to Day 22, with 24 hour euglycaemic clamp on Day 22; liraglutide 1.8 mg daily from Day 22 to Day 36, and insulin detemir 0.5 U/kg on Day 36, with 24 hour euglycaemic clamp. All subjects were treated with metformin as a background medication.

There were 33 subjects: 23 (69.7%) male, 10 (30.3%) female, and the age range was 33 to 68 years. Twenty subjects were treated with metformin alone and 13 with metformin and another oral anti-diabetics. There was no effect of liraglutide on exposure to detemir: the mean ratio (90% CI) detemir + liraglutide / detemir was 1.03 (0.97 to 1.09) for AUC_{0-24} and 1.05 (0.98 to 1.13) for C_{max}. There was no effect of detemir on exposure to liraglutide: the mean ratio (90% CI) detemir + liraglutide / liraglutide was 0.97 (0.87 to 1.09) for AUC_{0-24} and 1.03 (0.93 to 1.13) for C_{max}.

Evaluator's overall conclusions on pharmacokinetics

There was no evidence of a PK interaction between insulin detemir and liraglutide.

Pharmacodynamics

Studies providing pharmacodynamic data

In Study NN2211-3673 from the euglycaemic clamp studies, the AUC for glucose infusion rate (AUC_{GIR}) was greater for detemir and liraglutide in combination than for detemir alone, and for liraglutide alone compared with detemir alone, but there was no significant difference between detemir and liraglutide in combination and liraglutide alone.

The mean $AUC_{GIR(0-24)}$ (SD) was 1057.6 (803.18) mg/kg for detemir alone, 1981.6 (1167.60) mg/kg for liraglutide alone and 2947.0 (1460.57) mg/kg for detemir and liraglutide in combination. The mean (95% CI) ratio for $AUC_{GIR(0-24)}$ was 2.98 (1.84 to 4.81) for detemir + liraglutide / detemir, 1.32 (0.82 to 2.14) for detemir + liraglutide / liraglutide and 2.25 (1.39 to 3.64) for liraglutide / detemir. Average C-peptide plasma concentrations over 24 hours were lower for detemir alone compared with detemir and liraglutide in combination, and higher for liraglutide alone.

Glucagon concentrations were lower with detemir and liraglutide in combination than with detemir alone, but there was no significant difference compared with liraglutide alone.

Evaluator's overall conclusions on pharmacodynamics

Insulin detemir and liraglutide have a synergistic effect in decreasing plasma glucose. Insulin detemir when added to liraglutide decreases overall insulin secretion.

Dosage selection for the pivotal studies

Dosage selection was based on the approved dosing recommendations.

Efficacy

Change 1:

Pivotal efficacy study (Study NN2211-1842)

Study NN2211-1842 was a multicentre, randomised, open label, two arm, parallel group trial with an additional open-label; non-randomised arm carrying subjects who achieved target glycaemic control after the run-in period. The study was conducted at 202 centres in nine countries from March 2009 to April 2010.

Other efficacy studies

Study NN2211-1842-extension included 140 subjects from the detemir group and 122 from the control. Of these, there were 130 subjects in the detemir group and 92 in the control that completed the 52 weeks of treatment.

Evaluator's conclusions on clinical efficacy for Change 1

Insulin detemir in combination with liraglutide and metformin resulted in an incremental decrease in mean HbA1c of 0.51% over 26 weeks. This is a clinically significant improvement in diabetes control. The improvement was maintained over a 52 week period. There was weight loss in the group treated with detemir, liraglutide and metformin in combination, but less than in those treated with liraglutide and metformin alone.

Change 2:

Study NN304-1690

Study NN304-1690 was an open label, multicentre, single arm, 52-week extension of Study NN304-1689 investigating insulin detemir administered once or twice daily to children and adolescents diagnosed with T1DM. The Study was conducted at 29 sites in eleven countries from February 2008 to September 2009. The study included subjects who had completed 52 weeks of treatment in Study NN304-1689 previously evaluated by the TGA.

Evaluator's conclusions on clinical efficacy for Change 2

The data presented for Change 2 were primarily intended as safety data. The efficacy data are difficult to interpret in the absence of a control group. There appears to be a loss of efficacy over the second year of treatment but this most likely reflects the natural history of T1DM in a paediatric clinical trial population.

Change 3:

Study NN304-1687

Study NN304-1687 was a multicentre, open label, randomised, parallel group efficacy and safety study to compare detemir with NPH insulin, in combination with insulin aspart (rys) (IAsp)as bolus insulin, in the treatment of pregnant women with T1DM. The study was conducted at 79 sites in 17 countries from May 2007 to August 2010.

Evaluator's conclusions on clinical efficacy for Change 3

Insulin detemir has similar efficacy to NPH in the management of diabetes during pregnancy.

Safety

Studies providing evaluable safety data

Evaluable safety data were available from all the clinical studies. These were:

- Change 1: Study NN2211-3673 (PK/PD), Study NN2211-1842 (efficacy and safety), and Study NN2211-1842-extension (long-term safety).
- Change 2: Study NN304-1690 (long-term open label safety in children)
- Change 3: Study NN304-1687 (efficacy and safety in pregnancy)

Patient exposure

Change 1:

In Study NN2211-3673 there were 32 subjects exposed to a single dose of detemir 0.5 U/kg in combination with liraglutide 1.8 mg during a PK/PD study.

In Study NN2211-1842 there were 162 subjects exposed to detemir in combination with liraglutide and metformin for up to 26 weeks. The median duration of exposure was 182.5 days. In the extension study, Study NN2211-1842-extension, 140 subjects from the detemir group and that had completed 26 weeks treatment were included. Of these, 130 subjects completed the 52 weeks of treatment. The total patient year exposures to detemir in this study was 144.5 years.

Change 2:

In Study NN304-1690 there were 146 subjects exposed to detemir for up to one year. There were 37 subjects aged two to five years, 59 aged six to 12 years and 50 aged 13 to 16 years. There were 105 subjects exposed to detemir for a total duration of 104 weeks in the original and extension studies. At the end of the study the median (range) daily dose of detemir was 0.61 (0.09 to 1.63) U/kg.

Change 3:

In Study NN304-1687 there were 152 subjects exposed to detemir during pregnancy, corresponding to 119.4 subject year exposures. The mean duration of exposure during pregnancy was 6.5 months.

Deaths and other serious adverse events

Change 1:

In Study NN2211-3673 there were no deaths or serious adverse events (SAEs).

In Study NN2211-1842, there were no deaths reported during the main period of the trial (to Week 26) but there were two deaths in the control groups (treated with liraglutide and metformin): bronchogenic cancer, gall bladder cancer. There were 21 SAEs reported in 17 (10.4%) subjects in the detemir group and 16 in eleven (6.9%) in the control. There was no clear pattern to the SAEs to Week 26. Chronic pancreatitis was reported in one subject in the control group. In the extension study there were four subjects in the detemir group with neoplasia, but none in the control.

Change 2:

In Study NN304-1690, there were no deaths reported during the study. There were 17 SAEs reported in 116 (79.5%) subjects in the combined population including four in three (8.1%) subjects in the two to five year age group, nine in six (10.2%) in the six to 12 year and four in three (6.0%) in the 13 to 16 year. The overall rate of SAEs was 5.9/100

exposure years, in the two to five year group 5.5/100 exposure years, in the six to 12 year group 7.7/100 patient years exposure and in the 13 to 16 year group 4.1/100 patient years exposure. There were three subjects with ketoacidosis and two with hypoglycaemia.

Change 3:

In Study NN304-1687 there were no maternal deaths. There were three perinatal deaths: two in the detemir group (stillbirth, intrauterine death) and one in the NPH (Dandy-Walker malformation/pulmonary hypoplasia). In addition there were two early pregnancy losses: one in the detemir group (intrauterine death) and one in the NPH (spontaneous abortion). There were 94 SAEs reported in 61 (40.1%) maternal subjects in the detemir group (corresponding to an event rate of 114.1/100 exposure years) and 76 in 49 (31.0%) in the NPH (corresponding to an event rate of 88.1/100 exposure years). There was a higher rate of spontaneous abortion in the detemir group: eight (5.3%) subjects compared with four (2.5%) in the NPH; and also of pre-eclampsia: eight (5.3%) subjects compared with one (0.6%) in the NPH.

In the neonatal population, there were 51 SAEs reported in 36 (23.7%) subjects in the detemir group and 53 in 32 (20.3%) in the NPH. The pattern of SAEs in neonates was similar for the two treatment groups. The rates and patterns of congenital malformations for both populations were consistent with the known patterns of malformations in infants of diabetic mothers.

Evaluator's overall conclusions on clinical safety

Change 1:

The rate of treatment-emergent adverse events (TEAEs) with detemir in combination with liraglutide and metformin was similar to that for liraglutide and metformin. There were no deaths in the detemir treated patients. More subjects were reported with neoplasia in the detemir group in the extension study but there was no apparent pattern to this. The rates of adverse event leading to discontinuation (DAE) were similar for detemir and control. To Week 52, elevated lipase was reported at a greater rate in the detemir group than in the control: 26 (16.0%) subjects in the detemir group compared with 16 (10.1%) in the control. Levels of antibodies to detemir increased through the study to 4.30 % B/T at Week 53. Minor hypoglycaemic events were more common with detemir than control: 21 (12.9%) subjects in the detemir group and four (2.5%) in the control.

Change 2:

The rate of TEAEs with detemir was not influenced by age and the profile was predominantly that expected for the paediatric age group alone. Treatment related TEAEs were as expected for insulins. The rate of SAEs was not affected by age group. The rate of hypoglycaemic events was similar for the three age groups.

Change 3:

The rates and patterns of TEAEs were similar for detemir and NPH for both mothers and infants. Treatment related TEAEs were similar for detemir and NPH. There were no maternal deaths. There were three perinatal deaths: two in the detemir group (stillbirth, intrauterine death) and one in the NPH (Dandy-Walker malformation/pulmonary hypoplasia). In addition there were two early pregnancy losses: one in the detemir group (intrauterine death) and one in the NPH (spontaneous abortion). There was a higher rate of spontaneous abortion in the detemir group: eight (5.3%) subjects compared with four (2.5%) in the NPH; and also of pre-eclampsia: eight (5.3%) subjects compared with one (0.6%) in the NPH. The rates of SAEs for infants were similar for detemir and NPH. The rates and patterns of congenital malformations for both populations were consistent with the known patterns of malformations in infants of diabetic mothers. DAE occurred at a

higher rate in the detemir group: 13 (8.6%) subjects compared with six (3.8%) in the NPH. The rates of hypoglycaemia were similar for detemir and NPH.

Pregnancy outcome was slightly better in the NPH group. There were 128 (90.14%) live children at follow up in the detemir group and 135 (93.10%) in the NPH. This was not statistically significant (Chi^2 Fisher's exact test performed by the evaluator, p = 0.40).

First round benefit-risk assessment

First round assessment of benefits

Change 1:

Insulin detemir in combination with liraglutide and metformin resulted in an incremental decrease in mean HbA1c of 0.51% over 26 weeks. This is a clinically significant improvement in diabetes control. The improvement was maintained over a 52 week period. There was weight loss in the group treated with detemir, liraglutide and metformin in combination, but less than in those treated with liraglutide and metformin alone. The evaluator considers that the usual sequence of treatment would be liraglutide and metformin, with detemir added if patients were not adequately controlled on that combination.

Change 2:

The data presented for Change 2 were primarily intended as safety data. The efficacy data are difficult to interpret in the absence of a control group. There appears to be a loss of efficacy over the second year of treatment but this most likely reflects the natural history of T1DM in a paediatric clinical trial population.

Change 3:

Insulin detemir has similar efficacy to NPH in the management of diabetes during pregnancy.

First round assessment of risks

Change 1:

The rate of TEAEs with detemir in combination with liraglutide and metformin was similar to that for liraglutide and metformin. There were no deaths in the detemir treated patients. More subjects were reported with neoplasia in the detemir group in the extension study but there was no apparent pattern to this. The rates of DAE were similar for detemir and control. To Week 52, elevated lipase was reported at a greater rate in the detemir group than in the control: 26 (16.0%) subjects in the detemir group compared with 16 (10.1%) in the control. Levels of antibodies to detemir increased through the study to 4.30 % B/T at Week 53. Minor hypoglycaemic events were more common with detemir than control: 21 (12.9%) subjects in the detemir group and four (2.5%) in the control.

Change 2:

The rate of TEAEs with detemir was not influenced by age and the profile was predominantly that expected for the paediatric age group alone. Treatment related TEAEs were as expected for insulins. The rate of SAEs was not affected by age group. The rate of hypoglycaemic events was similar for the three age groups.

Change 3:

The rates and patterns of TEAEs were similar for detemir and NPH for both mothers and infants. Treatment related TEAEs were similar for detemir and NPH. There were no

maternal deaths. There were three perinatal deaths: two in the detemir group (stillbirth, intrauterine death) and one in the NPH (Dandy-Walker malformation/pulmonary hypoplasia). In addition there were two early pregnancy losses: one in the detemir group (intrauterine death) and one in the NPH (spontaneous abortion). There was a higher rate of spontaneous abortion in the detemir group: eight (5.3%) subjects compared with four (2.5%) in the NPH; and also of pre-eclampsia: eight (5.3%) subjects compared with one (0.6%) in the NPH. The rates of SAEs for infants were similar for detemir and NPH. The rates and patterns of congenital malformations for both populations were consistent with the known patterns of malformations in infants of diabetic mothers. DAE occurred at a higher rate in the detemir group: 13 (8.6%) subjects compared with six (3.8%) in the NPH. The rates of hypoglycaemia overall and nocturnal hypoglycaemia were similar for detemir and NPH.

Pregnancy outcome was slightly better in the NPH group. There were 128 (90.14%) live children at follow up in the detemir group and 135 (93.10%) in the NPH. This was not statistically significant (Chi^2 Fisher's exact test performed by the evaluator, $p = 0.40$).

First round assessment of benefit-risk balance

Change 1:

The benefit-risk balance of insulin detemir, given the proposed usage, is favourable.

Change 2:

The benefit-risk balance of insulin detemir, given the proposed usage, is favourable.

Change 3:

The benefit-risk balance of insulin detemir, given the proposed usage, is favourable.

Change 4:

No data were presented for this proposed change as it relates to alignment of the PI with the CCDS.

First round recommendation regarding authorisation

The evaluator recommends that the proposed changes to the conditions of registration for Levemir Flexpen, Levermir Penfill and Levemir Innolet should be approved. The proposed changes are:

Change 1: Update of the PI to include information on the use of Levemir (insulin detemir [rys]) as add-on therapy to Victoza (liraglutide [rys]).

Change 2: Update of the PI to include safety data from long-term trials in use of Levemir in adolescents and children (from two years old) with T1DM.

Change 3: Update of the PI to allow use of Levemir in pregnancy.

Change 4: Update of the PI to more closely align with the CCDS.

List of questions

There are no questions.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

EU-RMP Edition 15 (dated 04/06/2012, DLP 31/10/2010) with Safety Risk Management Plan Australian Implementation Version 1 (dated 11/09/2012).

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 2):

Table 2 Important identified and potential risks and missing information

Summary of risks	MedDRA terms or special populations
Identified risks	Hypoglycaemia Immunogenicity – injection site reactions Immunogenicity – systemic allergic reactions Lipodystrophy Oedema
Important potential risks	Cardiovascular and cerebrovascular events Immunogenicity – antibody formation Microvascular complications of the eye (late-stage) Potential anti-insulin antibody development in relation to NN729 process (allergic reactions and lack of efficacy) Potential risk of malignant neoplasms following combination treatment with insulin detemir + liraglutide + metformin
Important missing information	Elderly patients with renal, hepatic or cardiac impairment and children < 2 years. Unexpected safety issued arising from exposure to insulin detemir of pregnant women and long-term safety of children exposed *in utero*.

OPR reviewer comment:

Notwithstanding the evaluation of the non-clinical and clinical aspects of the SS this is considered acceptable.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information (as stated above). Furthermore, additional activities are planned for some of the risks. These activities are summarised in Table 3.

Table 3: Activities additional to routine planned by the sponsor regarding certain safety concerns.

Additional activity	Assigned safety concern	Actions/outcome proposed	Planned submission of final data
Prospective cohort study into the prescribing of metformin + liraglutide in combination with insulin as add-on and the risk of neoplasms in the GPRD (NN2211-3880) Protocol not available Protocol addendum available	Potential risk of malignant neoplasms following treatment with combination of insulin detemir + liraglutide + metformin	*No protocol available*	31/12/2012 (final report)
Diabetes Pregnancy Registry An international non-interventional cohort study to evaluate the safety of treatment with Levemir® (insulin detemir) in pregnant women with diabetes mellitus (NN304-4016) Protocol available	Unexpected safety issues arising from exposure to insulin detemir of pregnant women and the long-term safety of children exposed *in utero*	Primary objective: To compare the proportion of pregnancies in pregnant women treated with Levemir® to pregnant women treated with other basal insulin regimens which results in none of the following events: Major congenital anomalies Perinatal death Neonatal death Spontaneous abortion Secondary objectives: Multiple (see protocol)	Q4, 2019 (LPLV)
A summary analysis based on descriptive statistics will be provided at the end of the LEADER trial. (EX2211-3748)	Potential risk of malignant neoplasms following treatment with combination of insulin detemir + liraglutide + metformin		LEADER trial LPLV 19/01/2016
Meta analysis of selected clinical trials	Cardiovascular and cerebrovascular events		Aligned with the post-approval PSURs

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The sponsor mainly plans routine pharmacovigilance activities. Some additional pharmacovigilance activities are planned in the EU-RMP. It is noted the overall RMP for Australia in the Australian Specific Annex omits all additional pharmacovigilance activities. This is not acceptable. At a minimum, the sponsor needs to conduct all additional pharmacovigilance activities proposed for the EU, considering that the submitted EU-RMP is used to establish safety, in particular for the pregnant patient population. These are:

- Prospective cohort study into the prescribing of metformin + liraglutide in combination with insulin as add-on and the risk of neoplasms in the General Practice Research Database (GPRD) (NN2211-3880);
- An international non-interventional cohort study to evaluate the safety of treatment with Levemir (insulin detemir) in pregnant women with diabetes mellitus (NN304-4016);
- A summary analysis based on descriptive statistics will be provided at the end of the LEADER trial (EX2211-3748); and
- Meta-analysis of selected clinical trials.

It is noted that the proposed pregnancy registry will not collect data from Australian women.

The following refers to the assumption that the sponsor will conduct the abovementioned additional pharmacovigilance activities and makes the results available to the TGA:

The sponsor's proposed pharmacovigilance activities and milestones are considered acceptable. The study protocol submitted is considered acceptable in regard to the assigned safety concern for RMP purposes.

It is noted that the final report for the Prospective cohort study into the prescribing of metformin + liraglutide in combination with insulin as add-on and the risk of neoplasms in the GPRD (NN2211-3880) was due at the end of 2012. The sponsor is advised to submit the final report.

Risk minimisation activities

The sponsor states that no additional risk minimisation activities are necessary.

OPR reviewer comment: The sponsor's conclusion is acceptable.

Potential for medication errors

For the purposes of this RMP evaluation different types of medication errors, as suggested by Ferner & Aronson (2006[5]), have been considered.

OPR reviewer comment: The sponsor's actions regarding name confusion, labelling and presentation are considered acceptable.

Potential for overdose

There is a risk for overdose with any insulin product, which could potentially lead to life-threatening hypoglycaemia. In the proposed PI, hypoglycaemia and its management have been discussed to a satisfactory standard.

[5] Ferner RE & Aronson JK. 2006. Clarification of terminology in medication errors: definitions and classification. *Drug Saf* 29:1011-1022

Potential for paediatric off-label use

The sponsor recognises that this product is indicated for patients that are two years of age or older. This is reflected in the proposed PI.

Risk minimisation plan

Planned actions

No additional risk minimisation activities are proposed for Levemir.

OPR reviewer comment: The sponsor proposes pregnancy category A be assigned to Levemir. In regard to the use of Levemir in pregnancy, the sponsor has presented the following in their RMP:

> 'In an open-label randomised controlled clinical trial (RCT) pregnant women with T1DM (n=310) were treated in a basal-bolus treatment regimen with Levemir (n=152) or NPH insulin (n=158) as basal insulin, both in combination with NovoRapid. Primary objective of this study was to assess the effect of Levemir on blood glucose regulation in pregnant women with diabetes.
>
> The overall rates of maternal adverse events were similar for Levemir and NPH insulin treatment groups; however, a numerically higher frequency of SAEs in the mothers (61 (40%) versus 49 (31%)) and in the newborn children (36 (24%) versus 32 (20%)) was seen for Levemir compared to NPH insulin. The number of live born children of women becoming pregnant after randomisation were 50 (83%) for Levemir and 55 (89%) for NPH. The frequency of congenital malformations was 4 (5%) for Levemir and 11 (7%) for NPH with three (4%) major malformations for Levemir and three (2%) for NPH.
>
> Post-marketing data from an additional 250 outcomes from pregnant women exposed to Levemir indicate no adverse effects of insulin detemir on pregnancy and no malformative or feto/neonatal toxicity of insulin detemir.'

The abovementioned information should be considered to assign a pregnancy category for Levemir. A total number of 402 pregnant women have been taking Levemir. It is noted that the data presented contains no assessment of a potential statistically significant difference of the adverse events of Levemir versus adverse events of NPH insulin in pregnant women.

In regard to the proposed routine risk minimisation activities, the Delegate may wish to consider revising the draft PI document.

In regard to the proposed routine risk minimisation activities, the draft consumer medicine information (CMI) document is considered satisfactory.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP (Safety RMP (in EU-RMP format) Edition 15 (dated 04/06/2012, DLP 31/10/2010) with Safety RMP Australian Implementation Version 1 (dated 11/09/2012)) is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft PI and consumer medicine information documents should NOT be revised until the Delegates Overview has been received:

Further safety considerations

1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for further information and/or the Nonclinical and

Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

Unless the sponsor can provide compelling justification against any of the following recommendations, the following should be considered:

Recommendations in regard to pharmacovigilance activities

2. The sponsor needs to conduct all additional pharmacovigilance activities proposed for the EU, considering that the submitted EU-RMP is used to establish safety, in particular for the pregnant patient population. These are:
   - Prospective cohort study into the prescribing of metformin + liraglutide in combination with insulin as add-on and the risk of neoplasms in the GPRD (NN2211-3880);
   - An international non-interventional cohort study to evaluate the safety of treatment with Levemir (insulin detemir) in pregnant women with diabetes mellitus (NN304-4016);
   - A summary analysis based on descriptive statistics will be provided at the end of the LEADER trial (EX2211-3748); and
   - Meta-analysis of selected clinical trials.
3. It is noted that the final report for the prospective cohort study into the prescribing of metformin + liraglutide in combination with insulin as add-on and the risk of neoplasms in the GPRD (NN2211-3880) was due at the end of 2012. The sponsor is advised to submit the final report.

Recommendations in regard to risk minimisation activities

4. In regard to the proposed routine risk minimisation activities, the Delegate may wish to consider revising the draft PI document.

Second round review

Table 4 seeks to reconcile issues identified in the RMP evaluation report with consideration of the following documents:

1. RMP (in EU-RMP format) Version 15 (dated 04/06/2012, DLP 31/10/2010) with Australian Specific Annex Version 1.0 (dated 11/09/2012)
2. Sponsor's response to TGA request for further information (dated 27/03/2013).
3. OMA Clinical Evaluation Report (CER) (first round dated 05/02/2012; no second round report).
4. OSE Non-clinical Evaluation Report (NCER) (dated 05/04/2013).

It is considered that the sponsor's response to the TGA request for further information has adequately addressed most of the issues identified in the RMP evaluation report. The outstanding issues are listed below.

Table 4: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these include a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	*'No clinical issues have been raised via the Section 31 Request for Information. No Module 4 data were submitted with this application and a nonclinical evaluation report is not expected to be issued. NN acknowledges that safety questions may be raised in the clinical evaluation report and these will be addressed in the Australian Specific Annex to the EU-RMP as necessary and the EU-RMP if appropriate.'*	This is considered acceptable. A short non-clinical evaluation report was prepared by OSE and has been considered for this RMP Round 2 advice document.
2. The sponsor needs to conduct all additional pharmacovigilance activities proposed for the European Union, considering that the submitted EU-RMP is used to establish safety, in particular for the pregnant patient population. These are: – Prospective cohort study into the prescribing of metformin + liraglutide in combination with insulin as add-on and the risk of neoplasms in the GPRD (NN2211-3880); – An international non-interventional cohort study to evaluate the safety of treatment with Levemir (insulin detemir) in pregnant women with diabetes mellitus (NN304-4016);	*As clarified with the RMP evaluator via email correspondence on 13-Mar-2013 (enclosed as Appendix 1), NN commits to providing TGA with the data from the abovementioned pharmacovigilance activities, which will be conducted by NN A/S as described in the EU-RMP.* *The meta-analysis of selected clinical trials of cardiovascular and cerebrovascular events (point 4 above) has been completed. The EU-RMP (v.1.0, dated 04 June 2012) submitted to TGA with this application incorrectly states that the activity is outstanding. The report is enclosed with this response (enclosed as Appendix 2). The next edition of the EU-RMP will be updated to remove this activity from the outstanding actions.* *Events of cardiovascular disorders will continue to be monitored through routine pharmacovigilance.* *Furthermore, when agreement is*	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
– A summary analysis based on descriptive statistics will be provided at the end of the LEADER trial (EX2211-3748); and – Meta-analysis of selected clinical trials.	*reached with the Delegate on safety issues raised, NN accepts to undertake to update the Australian Specific Annex to the EU-RMP as necessary, and to provide this and, as available, an updated EU-RMP to the TGA.*	
3. It is noted that the final report for the Prospective cohort study into the prescribing of metformin + liraglutide in combination with insulin as add-on and the risk of neoplasms in the GPRD (NN2211-3880) was due at the end of 2012. The sponsor is advised to submit the final report.	*As clarified with the RMP evaluator via email correspondence on 13-Mar-2013 (See Appendix 1), the study report for NN2211-3880 is planned for completion by 31-Dec-2015. NN commits to submitting the final report to TGA when available.*	The final report date had been misread by the evaluator. The sponsor's response is considered acceptable
4. In regard to the proposed routine risk minimisation activities, the Delegate may wish to consider revising the draft PI document.	*'NN accepts the evaluator's recommendation and will update the PI accordingly after receipt of the Delegate's Overview.'*	This is considered acceptable.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The submission included toxicology data to support modification of a current text in the PI about metabolites of insulin detemir. A revised statement has been recommended by the toxicology evaluators to that initially proposed by the sponsor.

The Toxicology evaluators have not provided any recommendation in regard to the proposed change in the Pregnancy category from B3 to A as the change is based on clinical data.

Clinical

The clinical evaluator supports approval of change from B3 to Pregnancy category A.

The change is based on Study NN304-1687. This was an open label, randomised trial to compare efficacy of insulin detemir against NPH insulin with respect to glycaemic control in the treatment of pregnant women with T1DM. Women (≥ 18 years of age) with T1DM on treatment with (any) insulin for at least 12 months who were pregnant (gestational age eight - 12 weeks) or were planning to become pregnant were eligible to enter this trial.

A total of 470 women were randomised to two parallel treatment groups (233 & 237 subjects in detemir and NPH groups respectively). Pregnancy status at the time of randomisation was a stratification factor. Non-pregnant subjects who did not reach HbA1c ≤ 8.0% after nine months were withdrawn. Women who did not conceive within 12 months of randomisation or whose HbA1c was > 8.0% at the time of confirmation of pregnancy were also withdrawn.

The Full Analysis Set ($FAS_{Pregnant}$) consisted of 152 women in detemir group (79 pregnant at randomisation; 73 pregnant post randomisation) and 158 women in NPH group (83 pregnant at randomisation; 75 pregnant post randomisation). The $PP_{Pregnant}$ analysis set comprised of 127 & 137 women in detemir & NPH groups respectively.

The subjects received the respective randomised treatment (insulin detemir 100 U/mL or NPH insulin (100 U/mL) by subcutaneous route. Both groups also received bolus (short acting) IAsp (100 U/mL). The study drugs were administered from entry into the trial until termination or 6 weeks post-delivery. The insulin doses were titrated.

The primary efficacy outcome was change in HbA1c at gestational week 36 (GW36) with non-inferiority limit no greater than 0.4% for the upper border of 95%CI for the treatment difference in change in HBA1c from baseline to GW36.

The non-inferiority was demonstrated satisfactorily using both FAS and PP analysis sets as shown below:

Table 5: Linear regression analysis of HbA_{1c} (%) at GW 36, LOCF, $FAS_{Pregnant}$

Detemir Mean (SE)	NPH Mean (SE)	Estimated Mean Difference Detemir-NPH (SE)	95% CI	Non-inferiority Criterion (Met?)	P-value (Superiority?)
6.27(0.053)	6.33(0.052)	-0.06(0.074)	[-0.21; 0.08]	0.4 (Yes)	0.400 (No)

Note: The estimates are based on a model where HbA_{1c} at Visit P4 (GW 36) is the dependent variable, treatment, country and pregnancy status at randomisation are fixed factors, and HbA_{1c} at randomisation (V2 or P1 depending on the pregnancy status at randomisation) and the HbA_{1c} at randomisation by pregnancy status at randomisation interaction are covariates. Number of subject (N) contributing to the analysis: N(Detemir)=138 and N(NPH)=145
Abbreviations: SE: Standard Error, CI: Confidence Interval

Table 6: Linear regression analysis of HbA_{1c} (%) at GW 36, $PP_{Pregnant}$

Detemir Mean (SE)	NPH Mean (SE)	Estimated Mean Difference Detemir-NPH (SE)	95% CI	Non-inferiority Criterion (Met?)	P-value (Superiority?)
6.22(0.069)	6.37(0.067)	-0.15(0.096)	[-0.34; 0.04]	0.4 (Yes)	0.122 (No)

Note: The estimates are based on a model where HbA_{1c} at Visit P4 (GW 36) is the dependent variable, treatment, country and pregnancy status at randomisation are fixed factors, and HbA_{1c} at randomisation (V2 or P1 depending on the pregnancy status at randomisation) and the HbA_{1c} at randomisation by pregnancy status at randomisation interaction are covariates. Number of subject (N) contributing to the analysis: N(Detemir)=127 and N(NPH)=135
Abbreviations: SE: Standard Error, CI: Confidence Interval

The results were consistent across the two strata with respect to pregnancy status at baseline:

Table 7: Exploratory Linear Regression Analysis of HbA_{1c} (%) with Treatment by pregnancy status at randomisation interaction, LOCF, $FAS_{Pregnant}$

Pregnancy Status at Randomisation	Detemir Mean (SE)	NPH Mean (SE)	Estimated Mean Difference Detemir-NPH (SE)	95% CI
AT	6.39(0.072)	6.44(0.070)	-0.05(0.098)	[-0.25; 0.14]
AFTER	6.11(0.080)	6.19(0.082)	-0.07(0.112)	[-0.29; 0.15]

Note: The estimates are based on a model where HbA_{1c} at Visit P4 (GW 36) is the dependent variable, treatment, country, pregnancy status at randomisation, and the interaction between treatment and pregnancy status at randomisation are fixed factors, and HbA_{1c} at randomisation (V2 or P1 depending on the pregnancy status at randomisation) and the HbA_{1c} at randomisation by pregnancy status at randomisation interaction are covariates. Number of subject (N) contributing to the analysis: N(Detemir)=138 and N(NPH)=145 p-value for test of no interaction= 0.892
Abbreviations: SE: Standard Error, CI: Confidence Interval

Pregnancy outcomes

There were 152 pregnancies and 128 live births in detemir group.

There were 160 pregnancies and 136 live births in NPH group.

There were no maternal deaths. There were no neonatal deaths.

A composite pregnancy outcome (live births with birth weight < 10th or > 90th percentile; preterm delivery including abortion; major malformations; early foetal death; perinatal mortality; neonatal mortality) was defined.

Based on known pregnancy outcomes at follow up in this study (142 & 145 subjects in detemir and NPH groups respectively), 62.7% (89/142) pregnancy outcomes in detemir group compared to 66.2% (96/145) outcomes in NPH group had at least one component of the composite endpoint (odds ratio 0.86; 95%CI 0.53, 1.40) as shown below:

Table 8: Pregnancy outcomes[6]

	IDet		NPH		Odds ratio [95% CI]	*p* Value
	n	%	*n*	%		
Number of subjects	152	–	158	–	–	–
Number of pregnancies	152	–	160	–	–	–
Pregnancy outcome at follow-up	142		145		–	–
Live births‡	128	90.1	136*	93.8	0.61 [0.25;1.50]	$p=0.284$
Early fetal death‡	11	7.7	9	6.2	–	–
Spontaneous abortion	10	7.0	8	5.5	–	–
Ectopic pregnancy	1	0.7	1	0.7	–	–
Induced abortion‡	1	0.7	0	0.0	–	–
Perinatal death‡	2	1.4	1	0.7	–	–
Neonatal death‡	0	0.0	0	0.0	–	–
Composite outcome: at least one issue present‡	89	62.7	96	66.2	0.86 [0.53;1.40]	$p=0.551$
Preterm delivery (<37 weeks)¶	26	20.3	36	26.5	0.71 [0.40;1.26]	$p=0.238$
Small‡ for GA (<10th percentile)¶	3	2.3	1	0.7	–	–
Large‡ for GA (>90th percentile)¶	59	46.1	73	53.7	0.74 [0.46;1.21]	$p=0.228$
Macrosomia (>4000 g)¶	24	18.8	35	25.7	0.67 [0.37;1.20]	$p=0.180$
Neonatal hypoglycemia <24 hours post-delivery¶	15	11.7	24	17.6	0.65 [0.32;1.30]	$p=0.223$
	IDet		NPH		Treatment difference [95% CI]	*p* Value
	Mean	SD	Mean	SD		
Birth weight (g)§	3504	645	3571	601	−41.8 [−191.0;107.1]	$p=0.581$
GA at delivery (weeks)§	38.2	1.9	37.8	1.5	0.49 [0.11;0.88]	$p=0.012$

*There is 1 less live child at follow-up compared with live births as 1 liveborn child died shortly after birth (classified as a perinatal death); †Refers to body weight; ‡Percentage of pregnancy outcomes at follow-up; ¶Percentage of live births; §Analyses based on live births.
GA, gestational age; g, grams; IDet, insulin detemir; NPH, neutral protamine Hagedorn.

Other notable findings reported in this publication were higher occurrence of spontaneous abortion in detemir group (7.0%) compared to NPH group (5.5%). Treatment with detemir insulin compared to NPH appeared to be advantageous with respect to preterm delivery (20.3% versus 26.5%), large for gestational age baby (46.1% versus 53.7%),

[6] Hod *et al* (2013) in the *Journal of Maternal-Fetal & Neonatal Medicine*, published online [DOI: 10.3109/14767058.2013.799650] (accessed online 12 August 2013)]:

macrosomia (18.8% versus 25.7%) and neonatal hypoglycaemia within 24 hours of birth (11.7% versus 17.6%). Overall, the reported occurrence of major malformations was 3.5% (5/142) versus 0.7% (1/145) in detemir and NPH groups respectively as shown below:

Table 9: Summary of congenital malformations

Group	Expert 1 classification				Expert 2 (blinded *post hoc*) classification			
Randomized treatment	IDet ($n=142$)		NPH ($n=145$)		IDet ($n=142$)		NPH ($n=145$)	
	n	%	*n*	%	*n*	%	*n*	%
Children with congenital malformations	8	5.6	8*	5.5	5	3.5	4*	2.8
Minor	3	2.1	7	4.8	0	0.0	1	0.7
Major	5	3.5	1	0.7	5	3.5	3	2.1
Treatment during organogenesis†	IDet ($n=84$)		NPH ($n=154$)		IDet ($n=84$)		NPH ($n=154$)	
	n	%	*n*	%	*n*	%	*n*	%
Children with congenital malformations	4	4.8	11	7.1	2	2.4	6	3.9
Minor	1	1.2	8	5.2	0	0.0	0	0.0
Major	3	3.6	3	1.9	2	2.4	6	3.9

*There was one additional malformation (preferred term: pelvic kidney; treatment during organogenesis: NPH; randomized treatment: NPH; classification: major), that was diagnosed after the mother was withdrawn from the trial (detail in Table 2). As this table is based only on those women who gave birth during the trial, this malformation is not included.

†Those subjects treated with a basal insulin other than IDet or NPH ($n=35$) or who were unclassifiable ($n=14$; i.e. used more than one basal insulin or had missing information about their basal insulin) were not included in the treatment during organogenesis calculations. The woman treated with insulin glargine during organogenesis (detail in Table 2) is not included.

IDet, insulin detemir; NPH, neutral protamine Hagedorn.

A total of 73 women in detemir group and 75 women in NPH group became pregnant post-randomisation and were thus comparably exposed to the study drugs for the whole period of interest for organogenesis (three to 12 GWs). The reported malformations were as follows:

Table 10: Congenital malformation by pregnancy status at randomisation

Group	MedDRA preferred term	Basal insulin at organogenesis	Expert 1 classification	Expert 2 (blinded *post hoc*) classification
Pregnant at randomization				
	Hip dysplasia	IDet	Major (reclassified to minor due to FU information)	Not a congenital malformation (developmental disorder that disappears)
	Cleft lip	NPH	Major	Major
IDet ($n=79$)	Meningomyelocele	NPH	Major	Major
	Atrial septal defect Hemangioma congenital	NPH	Both minor	Both major
	Hemangioma congenital (diagnosed after the EOT)	NPH	Minor	Not a congenital malformation
	Dandy–Walker syndrome Pulmonary hypoplasia	NPH	Both major	Both major
	Polydactyly	Insulin glargine	Minor	Minor
NPH ($n=83$)	Cardiac hypertrophy Patent ductus arteriosus	NPH	Both minor	Not congenital malformations (FU: patent ductus arteriosus was minor and did not require surgery)
	Atrial septal defect	NPH	Minor	Not a congenital malformation (FU: atrial septal defect spontaneously closed)
Pregnant after randomization				
	Congenital hydronephrosis Pelviureteric obstruction Pyelocaliectasis	IDet	All major	All major
IDet ($n=73$)	Hydronephrosis	IDet	Major	Major
	Heart disease congenital	IDet	Minor	Not a congenital malformation. Transient minor anomaly
NPH ($n=75$)	Heart disease congenital	NPH	Minor	Not a congenital malformation. Transient minor anomaly
	Congenital laryngeal stridor	NPH	Minor	Not a congenital malformation
	Atrial septal defect	NPH	Minor	Major
	Ventricular septal defect	NPH	Minor	Major
	Pelvic kidney* (diagnosed after mother was withdrawn while pregnant due to A1C >8% [>64 mmol/mol] at confirmation of pregnancy	NPH	Major	Major

*This malformation from a woman withdrawn from the study is not included in the trial database or further calculations.
Follow-up was from birth until 6 weeks after birth.
A1C, glycated hemoglobin; EOT, end of trial; FU, follow-up; IDet, insulin detemir; MedDRA, Medical Dictionary for Regulatory Activities; NPH, neutral protamine Hagedorn.

Additional notable findings included reported occurrence of pre-eclampsia of 10.5% in detemir group compared to 7.0% in NPH group.

Post-marketing experience

The post-market data supplied by the sponsor comprise 528 pregnancies with outcomes as shown below:

Table 11: Pregnancy outcomes based on post-marketing surveillance

	Report Source		
Pregnancy Outcome[1]	**Spontaneous**	**Solicited**	**Total**
Live birth without congenital anomalies	199	56	**255**
Live birth with congenital anomalies	14	-	**14**
Termination (no information reported on foetal defects)	3	7	**10**
Termination with foetal defects	4	1	**5**
Termination without foetal defects	-	0	**0**
Spontaneous abortion	16	9	**25**
Ectopic pregnancy	1	-	**1**
Stillbirth without foetal defects	2	2	**4**
Stillbirth (no information reported on foetal defects)	1	1	**2**
Unknown or still pregnant	187	25	**212**
Total	**427[2]**	**101**	**528**

1) Terminology for pregnancy outcomes as coded in the Global Safety database.
2) Two were twin pregnancies (Case No. 300556 and 283388) with 2 outcomes each; one 'Live birth without congenital anomalies' and three 'Live birth with congenital anomalies'.

Risk management plan

Risk Management Plan (EU-RMP format) Version 15 (dated 04/06/2012; DLP 31/10/2010) with Australian Specific Annex Version 1.0 (dated 11/09/2012) is intended for inclusion as a condition of approval for the proposed variations.

Delegate considerations

The Trial NN304-1687 was an open label, randomised trial intended to investigate the use of insulin detemir for glycaemic control in pregnancy (women with T1DM) compared to NPH insulin. The results support non-inferior efficacy and comparable safety.

The trial also collected data with respect to pregnancy outcomes in association with insulin detemir use. Overall, the results were comparable between insulin detemir and NPH. The notable differences include pre-eclampsia (10.5% versus 7.0% for detemir and NPH respectively) and congenital malformations (major 3.5% versus 0.7%; minor 2.1% versus 4.8% for detemir and NPH respectively).

At present, two bolus insulin analogues (IAsp from the same sponsor based on a randomised study and insulin lispro from another sponsor based on observational data) are assigned Pregnancy category A. HIs (rcb) are uncategorised. No basal insulin currently has Pregnancy category A.

As noted earlier the data submitted in Australia have been reviewed overseas and are included in the EMA and FDA approved prescribing information for insulin detemir. The EU does not use discreet pregnancy categories whereas FDA category B applies to this product in the US.

The category A in the Pregnancy categories adopted in Australia is not necessarily equivalent to the B category in the FDA Pregnancy categories. As well, the Australian categories are not hierarchical and there appears to be no insistence on randomised trial data recognising the fact that a hypothesis driven, adequately powered randomised trial to establish nil effect in pregnancy outcomes may not be practical. A consideration of all available experience may be more appropriate.

The data from this randomised study makes available very valuable prescribing information for the treating doctors in the management of diabetes mellitus during pregnancy using insulin detemir. In addition, it provides valuable data with respect to pregnancy outcomes.

However, the B3 category is considered still applicable. The current B3 category allows use of insulin detemir when clinically needed and data from this trial will be useful in making that judgement and detailed inclusion is supported in the PI.

It is considered that the large dataset needed to recommend Pregnancy category A is not yet available (73 women in insulin detemir group who became pregnant post-randomisation and were thus exposed through the whole risk period of three-12 GWs relevant for organogenesis and provided unconfounded comparison; limited post market data).

It should also be noted that a cohort study has been agreed between the sponsor and the EMA, which will include 2500 subjects, to be conducted in seven European countries to further assess pregnancy outcomes associated with insulin detemir use.

Proposed action

Pending ACPM advice, the current Pregnancy Category B3 is considered to continue to be applicable.

Request for advice

The Committee is requested to provide advice on the following issues:

- Advice on suitability of change from the current Pregnancy category B3 to Pregnancy category A for this long-acting (basal) insulin analogue, in particular whether sufficiently large data is considered to be available supporting this change.
- The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on this submission.

Response from Sponsor

Executive Summary

Novo Nordisk (NN) seeks approval of a labelling extension to the Australian Levemir (insulin detemir (rys)) (detemir PI to revise the pregnancy category from B3 to A and to give specific guidance on use of detemir during pregnancy. This request is based on an extensive body of robust evidence:

- Data used to evaluate detemir in pregnancy (Clinical Trial 1687) was of the highest standard that is an RCT, which is consistently referred to as the gold-standard of clinical trials.
- NN is the only company to carry out large scale RCTs with insulin in pregnancy in T1DM.
- A sample size of 310 exposed pregnant women with T1DM (detemir N=152; NPH N=158) participating in Trial 1687 is substantial, particularly in view of the vulnerable nature of this sub-population.
- Trial 1687 was of a similar sample size and design as that accepted by TGA to substantiate pregnancy category A for NovoRapid (IAsp), Clinical Trial ANA-1474. Indeed, compared with Trial ANA-1474 a considerably higher number of pregnancies were exposed to study treatment during organogenesis in Trial 1687.

- In total, 789 reports of pregnant women exposed to detemir are available from cumulative postmarketing data (1 November 2003 – 15 August 2013) no safety signals related to maternal or fetal exposure during pregnancy have been identified.
- The use of detemir in pregnancy in Australian clinical practice has been endorsed by a leading local expert.
- The clinical evaluator supports the proposed pregnancy category, finding no issue with the size of the dataset, and did not contest the clinical or safety outcomes which substantiate pregnancy category A, concluding that the benefit-risk balance of detemir use in pregnancy is favourable and endorsing approval. The OPR evaluator accepted this evaluation.
- NN contends that the data package submitted, the positive clinical evaluation report and the commitment made to conduct pharmacovigilance activities to complement routine on-going safety monitoring, provide sufficient justification for detemir to be approved for use in pregnancy in Australia with pregnancy category A.

Changes to the Indications and/or Dosage and Administration Information from the Original Application

No changes to the Indications are proposed from the version of the PI submitted originally. In response to recommendations from the OPR evaluator, the Dosage and Administration text has been updated to: replace the tradename "Victoza" with the active substance name "liraglutide"; include a statement that, in T1DM, detemir needs to be used in combination with a rapid or short acting insulin; include a statement that, in paediatric patients, glucose monitoring should be intensified and insulin dosage adjusted individually; include a statement that, in pregnant patients, glucose monitoring should be intensified and insulin dosage adjusted individually; include a statement that, in patients with hypoalbuminaemia, glucose monitoring should be intensified and insulin dosage adjusted individually.

NN's comments to the Delegate's evaluations and proposed actions

Comments from the Delegate's Request for ACPM Advice are discussed below:

1. *The Delegate states that "it is considered that the large dataset needed to recommend Pregnancy category A is not yet available (73 women in insulin detemir group who became pregnant post-randomisation and were thus exposed through the whole risk period of three to12 GWs relevant for organogenesis and provided unconfounded comparison; limited post market data)."*

    a. Data from all sources should be considered collectively to characterise the safety of a medicinal product in pregnancy and to inform pregnancy labelling.

    NN agrees with the Delegate that "a consideration of all available experience may be more appropriate" to characterise the safety of a medicinal product in pregnancy and to inform pregnancy labelling. This approach was adopted by TGA in the assessment of NN's application for approval of use of IAsp in pregnancy in 2006, where consideration was given to all available experience, including Trial ANA-1474, a limited number of exposures available from post-marketing data and the widespread prescribing of IAsp in clinical practice, particularly in the treatment of T1DM. The body of evidence available for detemir is more extensive compared with that accepted for IAsp, in terms of both exposures during organogenesis in Trial 1687 and post-marketing data (discussed further below).

    b. Data are available for a large number of exposures and outcomes from Trial 1687

NN contends that in the present overall context the sample size of 310 exposed pregnant subjects with T1DM in Trial 1687 is large. 470 subjects were randomised, of these 310 (detemir N=152; NPH N=158) were pregnant and were exposed to study treatment up to 12 months before pregnancy (48%) or during pregnancy at eight to 12 weeks (52%). This sample size was predefined, discussed with regulators, and the trial was designed on that basis. Given the vulnerable nature of this sub-population and the scarcity of randomised data, it is NN's contention that this is not a "limited number". Trial ANA-1474 was of a similar sample size, with a total 322 pregnant women with T1DM exposed to trial treatment (IAsp N=157; soluble HI N=165).

The Delegate questions the number of women in Trial 1687 who became pregnant post-randomisation and were thus exposed throughout the "period of interest" that is, organogenesis. A considerable proportion of subjects were exposed to trial treatment during the entire gestational period, including the first trimester where major organogenesis occurs (detemir N=73; NPH N=75). In contrast, the cohorts of subjects exposed to trial treatments in Trial ANA-1474 were considerably fewer (IAsp N=44; HI N=55).

c. Data on a significant number of outcomes is available from post-marketing surveillance

Ongoing post-marketing monitoring of detemir use in pregnancy has demonstrated a favourable risk-benefit profile. This evaluation of safety is based on worldwide exposure from 1 November 2003 (product international birth date) to 15 August 2013, representing approximately 11,053,050 patient years of exposure (PYE). No safety concerns associated with detemir were raised during the latest Periodic Safety Update Report (PSUR) review period, 1 November 2011 – 31 October 2012. Moreover, no safety concerns were identified during an interim review covering the period 1 November 2012 – 15 August 2013, during which 218 additional reports of detemir exposure during pregnancy were received, comprising 376 adverse events (AEs) (350 non-serious and 26 serious events). No cases of 'live birth with congenital anomalies' or 'termination with fetal defects' were received.

In total, 789 reports of exposed pregnant women, comprising 1329 AEs, are available from cumulative worldwide data, excluding case reports from clinical trials. 678 of the 789 case reports were non-serious cases. The vast majority of the 789 cases were for the reported events 'pregnancy' (560 events) and 'exposure during pregnancy' (185 events). Where trimester of exposure was reported, 133 pregnancies were exposed during the entire gestational period and 134 pregnancies were exposed during the first trimester.

The post-market data available for detemir is considerable compared with the limited experience available for IAsp at the time of application for the equivalent variation, that is, use in pregnancy, in 2006. Based on worldwide spontaneous case reports received over a six year period from Oct 1999 to Jan 2006, 26 cases of AEs in women exposed to IAsp during pregnancy were received. The estimated worldwide exposure for IAsp during this period was approximately 5.5 million PYE.

d. NN have established a comprehensive pharmacovigilance programme

Collection of data with relation to intended and unintended exposure during pregnancy forms part of NN's routine pharmacovigilance monitoring for all NN products. These data are submitted to regulatory authorities, including TGA, via PSURs and individual case reports. NN has committed to submitting PSURs for detemir to TGA for an extended period (2008 - 2018).

A further pharmacovigilance initiative is planned to expand the safety database and to increase systematic follow-up on exposures in pregnancy. As outlined in the EU RMP, NN plans to perform an international prospective cohort study, NN304-4016, across seven countries including more than 2500 subjects (protocol discussed and approved by EMA), as a post-variation commitment with EMA. NN Australia's commitment to provide TGA with data from this pharmacovigilance activity is acceptable to the OPR Evaluator

e. There is increasing use in pregnant women of insulin analogues, including detemir, in clinical practice

Factors considered in clinical practice are related to the established safety and efficacy profile of detemir in non-pregnant populations and benefits such as reduced risk of nocturnal hypoglycaemia[7], and to continued treatment where the woman is achieving optimal glycaemic control on their current regimen[8]. There are an increasing number of women with T1DM, who are planning or entering pregnancy while treated with a long-acting insulin analogue. This trend is illustrated by pre-trial insulin treatment seen in Trial ANA-1474, where approximately 48% of subjects were treated with insulin analogues. In comparison, Trial 1687 showed a marked increase in pre-trial treatment with approximately 90% and 47% of subjects using a bolus and basal insulin analogue, respectively[9]. Insulin treatment in pregnancy is also growing in women with T2DM and gestational diabetes mellitus (GDM) due to increasing numbers of women developing T2DM related to rising rates of obesity and an increase in the number of women with GDM, possibly related to improved detection and later age at pregnancy. Moreover, an 'absolute increase' in the number of women with T1DM has been observed over the last 20 years[10].

2. *The Delegate observes that at present, only two insulin analogues (IAsp and insulin lispro) are assigned pregnancy category A, and that no basal insulin currently has pregnancy category A status. Additionally the Delegate comments that "there appears to be no insistence on randomised trial data recognising the fact that a hypothesis driven, adequately powered randomised trial to establish nil effect in pregnancy outcomes may not be practical."*

a. NN's clinical development program to assess efficacy and safety of detemir in pregnancy, derived from high level evidence, is consistent with that previously approved by TGA for IAsp

Two rapid-acting insulin analogues, IAsp and insulin lispro, have been assigned pregnancy category A by TGA, in contrast to HI, which in the absence of high level evidence to characterise safety in pregnancy has historically been considered the treatment of choice[11]. The Delegate also noted that the datasets accepted by TGA

[7] Callesen NF, Damm J, Mathiesen JM, Ringholm L, Damm P, Mathiesen ER. 2013. Treatment with the long-acting insulin analogues detemir or glargine during pregnancy in women with type 1 diabetes: comparison of glycaemic control and pregnancy outcome. *J Matern Fetal Neonatal Med*. 26(6):588-92. doi: 10.3109/14767058.2012.743523.

[8] Lambert K, Holt RI. 2013. The use of insulin analogues in pregnancy. *Diabetes Obes Metab*. doi: 10.1111/dom.12098

[9] Mathiesen ER, Hod M, Ivanisevic M, Duran Garcia S, Brøndsted L, Jovanovic L, Damm P, McCance DR; 2012. Detemir in Pregnancy Study Group. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care.*;35(10):2012-7.

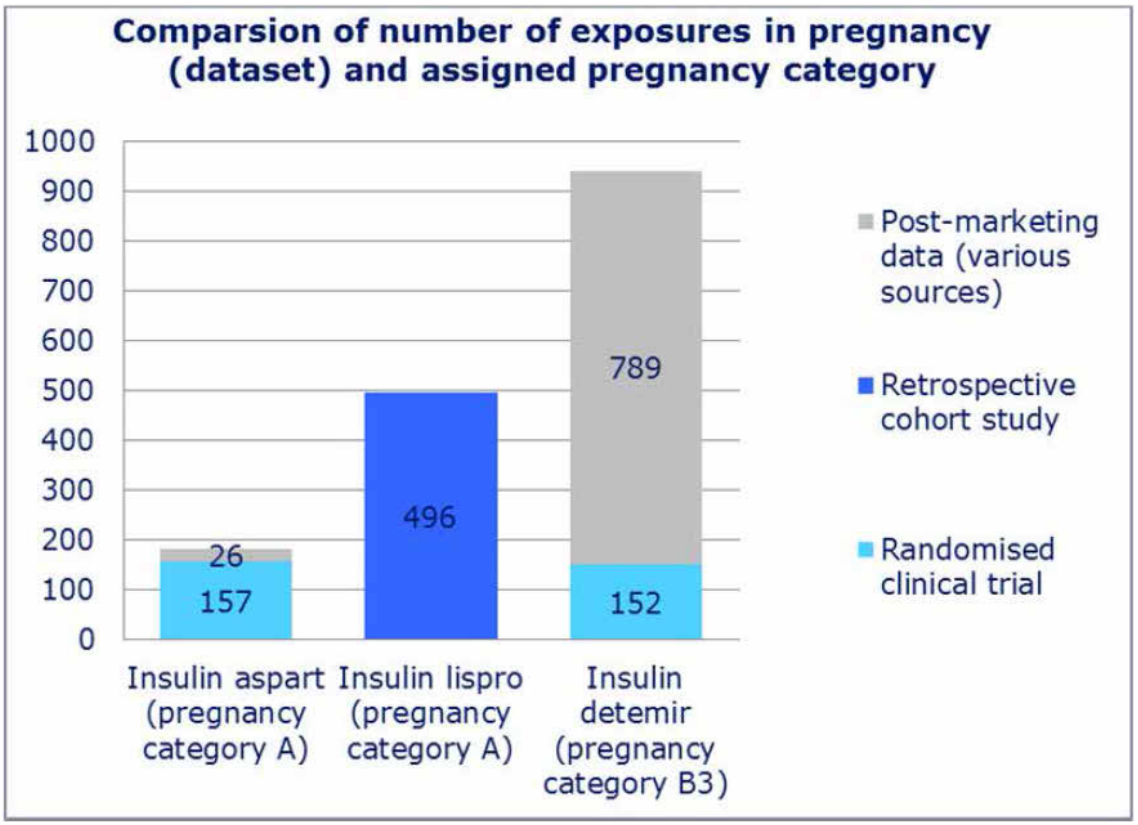
[10] McElduff A, Moses RG. 2012. Insulin therapy in pregnancy. *Endocrinol Metab Clin North Am* ;41(1):161-73. doi: 10.1016/j.ecl.2011.12.002.

[11] McElduff, A. 2012. Insulin Detemir in Pregnancy: A Small but Significant Step Forward? doi:10.2337/dc12-0971 *Diabetes Care* vol. 35 no. 10 1968-1969

to characterise "large number of pregnant women and women of childbearing age" for IAsp and insulin lispro were derived using different clinical methodologies.

IAsp was assigned pregnancy category A on the basis of an RCT (NHMRC level 'II' evidence6) which included pregnancy outcomes of 322 women with T1DM (IAsp N=157; HI N=165). Insulin lispro was assigned pregnancy category A on the basis of an uncontrolled retrospective cohort study of a lower evidence ranking (NHMRC level 'III-2' evidence[12]), which included pregnancy outcomes of 496 women with T1DM or T2DM. An overview of current pregnancy categories and supportive dataset is given in Figure 1.

Figure 1: Comparison of number of exposures in pregnancy (dataset) and assigned pregnancy category



b. Scientifically rigorous data should guide risk–benefit assessment

Typically, clinical development programs preclude pregnant women due to ethical considerations and implications for the safety of the fetus/neonate. Industry may also moderate investment in conducting RCTs in this population due to factors such as design and recruitment challenges, risk of adverse outcome and potential litigation, and cost[13]. Despite these challenges, NN conducted the first RCT of a long-acting insulin analogue in pregnant women with T1DM. The randomised nature of the dataset as well as robust design underlines the value of these data in informing risk-benefit assessment for prescribers, which is accepted by the Delegate, who remarked that Trial 1687 "makes available very valuable prescribing information. In addition, it provides valuable data with respect to pregnancy outcomes."

[12] National Health and Medical Research Council. 1998. A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra: Commonwealth of Australia. P 56. ISBM 1-86496-048-5. Retrieved 28 March 2010.
[13] Webster LM, Shennan AH. 2013. The challenges of licencing drugs for use in pregnancy. Expert Opin Pharmacother. 14(13):1707-10. Doi:10.1517/14656566.2013.813019.

3. *The Delegate notes that "FDA category B applies to this product in the US. The category A in the Pregnancy categories adopted in Australia is not necessarily equivalent to the B category in the FDA Pregnancy categories." Further to this the Delegate states that "the B3 category is considered still applicable."*

    a. Outcomes from pre-clinical animal studies demonstrate that detemir does not warrant the current pregnancy category, B3

    On the basis of data from Trial 1687, the FDA reclassified detemir from pregnancy category C to B, which is the same class as IAsp, insulin lispro and HI. FDA pregnancy category B takes into consideration adverse outcomes observed in pre-clinical studies, specifically in that "animal reproduction studies have failed to demonstrate a risk to the fetus".[14]. Nonclinical data submitted to TGA in the original detemir registration application demonstrated that detemir and NPH, when given at several fold normal human exposure, had similar effects regarding embryotoxicity and teratogenicity. The adverse outcomes observed were secondary to maternal hypoglycaemia and were NOT due to the direct actions of the insulins. Based on these data, NN believes that detemir does not warrant the current Australian pregnancy category B3, which specifies that "studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans".[15].

4. *With reference to Trial 1687, the Delegate comments that "The results support non-inferior efficacy and comparable safety.'*

    a. Efficacy and Safety of detemir use in pregnancy has been substantiated in Trial 1687, a large scale, Phase III, multinational clinical trial conducted at 79 trial sites in 17 countries, including Australia, demonstrated important clinical benefits, including glycaemic control which has implications for reducing fetal congenital abnormalities in pregnancies complicated by diabetes.

    Treatment with detemir was non-inferior to NPH, as demonstrated by HbA1c at 36 GWs. Statistically significantly lower fasting plasma glucose (FPG) at 24 and 36 GWs was seen with detemir compared with NPH. Importantly, this was not associated with increased rates of hypoglycaemia. The TGA clinical evaluator and Delegate accept that non-inferior efficacy and comparable safety were demonstrated for detemir. The clinical evaluator concludes that the benefit-risk balance of detemir for use in pregnancy is favourable and endorses approval.

5. *The Delegate observes that "Overall, the results were comparable between insulin detemir and NPH. The notable differences include pre-eclampsia (10.5% versus 7.0% for detemir and NPH respectively) and congenital malformations (major 3.5% versus 0.7%; minor 2.1% versus 4.8% for detemir and NPH respectively)."*

    a. The incidence of pre-eclampsia seen in Trial 1687 was within expected rates for pregnancy complicated by diabetes.

    A numerical difference was observed between the treatment groups in the incidence of pre-eclampsia in Trial 1687 (detemir N=16 (10.5%); NPH N=11 (7.0%)). The difference between the treatment groups was NOT statistically significant and the incidence was within expected rates for pregnancy complicated by diabetes. Eight events of pre-eclampsia in the detemir group and one in the NPH group were SAEs. For all pre-eclampsia SAEs, the seriousness criterion was

[14] Code of Federal Regulations. 2013. 21CFR201.57, available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=201.57

[15] Definitions of the Australian categories for prescribing medicines in pregnancy, available at: http://www.tga.gov.au/hp/medicines-pregnancy.htm

hospitalisation. In eight cases caesarean sections were performed and one woman had a vaginal induced delivery. In all nine SAE cases the women had live-born healthy infants. All events were considered unlikely related to trial treatment. No plausible causality can be established due to the multiple underlying possible causes involved in the development of pre-eclampsia. In addition, detemir and NPH share the same mechanism of action, they are both used as treatment for improvement of glycaemic control, and the efficacy results demonstrated that detemir was non-inferior to NPH with respect to HbA1c. The OPR Evaluator acknowledges that the events of pre-eclampsia seen in Trial 1687 "seem unrelated to the use of Levemir". Furthermore, no questions were raised by the clinical evaluator on this matter. At the OPR evaluator's request, NN agreed to include a precautionary statement regarding the incidence of pre-eclampsia in the detemir PI.

In conclusion, the incidences of pre-eclampsia observed in the detemir and NPH treatment groups were within expected rates for pregnancy complicated by diabetes. NN considers that the numerical but nonstatistically significant difference in incidence of pre-eclampsia does not indicate an increased risk of pre-eclampsia associated with the use of detemir during pregnancy compared to NPH.

b. *The frequencies of malformations seen in the detemir and the NPH groups in Trial 1687 were similar, and were consistent with the known patterns of malformations in infants of diabetic mothers.*

Congenital malformations were classified and evaluated by randomised treatment and by treatment received during organogenesis, in order to assess treatment causality. Most subjects were treated with detemir or NPH during organogenesis. A number of subjects were treated with insulin glargine or 'other' insulin during organogenesis. By randomised treatment in the primary analysis, among subjects who gave birth or terminated their pregnancy during the trial, a total of 16 children were recorded as having one or more malformations (detemir: 5.6% (N=8); NPH: 5.5% (N=8)). Of these, 10 children had minor malformations (detemir: 2.1% (N=3); NPH: 4.8% (N=7)) and six children had major malformations (detemir: 3.5% (N=5); NPH: 0.7% (N=1)). The overall frequency of malformations by treatment during organogenesis, was 4.8% (N=4) and 7.1% (N=11) for subjects treated with detemir and NPH, respectively. The frequency of minor malformations was 1.2% (N=1) and 5.2% (N=8) for subjects treated with detemir and NPH, respectively. The frequency of major malformations was 3.6% (N=3) and 1.9% (N=3) for subjects treated with detemir and NPH, respectively. No malformations were associated with abortions (spontaneous or induced) or ectopic pregnancies. One malformation was fatal; it concerned a case of 'pulmonary hypoplasia' in a child who also had 'Dandy-Walker syndrome'. The mother was pregnant at randomisation and was treated with NPH during organogenesis and the death was recorded as a perinatal death. Among the 25 subjects who were exposed to trial treatment who were withdrawn from the trial while pregnant, only one major malformation was reported (in the NPH group); this was a pelvic kidney, diagnosed after the mother was withdrawn due to HbA1c > 8.0% at confirmation of pregnancy.

Secondary to the initial evaluation, cases of malformations based on the subgroup of subjects who became pregnant after randomisation to detemir and NPH were evaluated and reclassified (post-hoc) by an independent specialist. This data,

published by Hod M *et al*, 2013[16], are referenced by the Delegate. According to the post-hoc evaluation, the risk of major malformations was higher for subjects treated with NPH (3.9%) than for subjects treated with detemir (2.4%) during organogenesis (Table 12). There were some differences between the primary and post-hoc classifications, overall however, the evaluations showed a similar frequency of malformations in both treatment groups.

Table 12: Summary of congenital malformations by randomised treatment and treatment during organogenesis for children delivered during Trial 1687

Group	Expert 1 classification				Expert 2 (blinded *post hoc*) classification			
Randomized treatment	IDet ($n=142$)		NPH ($n=145$)		IDet ($n=142$)		NPH ($n=145$)	
	n	%	*n*	%	*n*	%	*n*	%
Children with congenital malformations	8	5.6	8*	5.5	5	3.5	4*	2.8
Minor	3	2.1	7	4.8	0	0.0	1	0.7
Major	5	3.5	1	0.7	5	3.5	3	2.1
Treatment during organogenesis†	IDet ($n=84$)		NPH ($n=154$)		IDet ($n=84$)		NPH ($n=154$)	
	n	%	*n*	%	*n*	%	*n*	%
Children with congenital malformations	4	4.8	11	7.1	2	2.4	6	3.9
Minor	1	1.2	8	5.2	0	0.0	0	0.0
Major	3	3.6	3	1.9	2	2.4	6	3.9

*There was one additional malformation (preferred term: pelvic kidney; treatment during organogenesis: NPH; randomized treatment: NPH; classification: major), that was diagnosed after the mother was withdrawn from the trial (detail in Table 2). As this table is based only on those women who gave birth during the trial, this malformation is not included.
†Those subjects treated with a basal insulin other than IDet or NPH ($n=35$) or who were unclassifiable ($n=14$; i.e. used more than one basal insulin or had missing information about their basal insulin) were not included in the treatment during organogenesis calculations. The woman treated with insulin glargine during organogenesis (detail in Table 2) is not included.
IDet, insulin detemir; NPH, neutral protamine Hagedorn.

T1DM and T2DM during pregnancy are associated with a two to five fold increase in congenital anomalies compared to the general population[17]. The types of malformations reported in Trial 1687 reflect those previously observed in the diabetic population, and also in the general population[18]. There were few major malformations in Trial 1687 and the incidence based on treatment during organogenesis was within the reported incidence for the background population of pregnant women with diabetes for both detemir and NPH. Furthermore, the malformations were not clustered to specific organ systems which could be indicative of a drug-induced teratogenic effect. Therefore, NN does not consider the incidence of malformations in Trial 1687 to indicate an increased risk associated with the use of detemir during pregnancy compared to NPH. The clinical evaluator concluded that the "rates and patterns of congenital malformations for both populations were consistent with the known patterns of malformations in infants of diabetic mothers".

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Levemir Flexpen / Levemir Penfill / Levemir Innolet solution for injection containing 100 U/mL of insulin detemir (rys) to have an overall positive benefit–risk profile for the proposed Pregnancy Category A**.**

[16] Hod M, Mathiesen ER, Jovanovič L, McCance DR, Ivanisevic M, Durán-Garcia S, Brøndsted L, Nazeri A, Damm P. 2013. A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes. *J Matern Fetal Neonatal Med.* 2013 Jun 5.

[17] Zabihi S, Loeken MR. 2010. Understanding diabetic teratogenesis: where are we now and where are we going? *Birth Defects Res A Clin Mol Teratol*; 88(10):779-790.

[18] Department of Health FC. Reviewer. 2005. Guidance Evaluating the Risks of Drug Exposure in Human Pregnancies.

In making this recommendation the ACPM expressed concern that the animal studies were inadequate to provide reassurance, including that the species was an inappropriate choice. The studies were considered to be inadequate to provide data to fulfil the Pregnancy Category B3 and suggested that B2 may have been a more appropriate initial classification.

The committee was requested to provide advice on the following specific issues:

- Advice on suitability of change from the current Pregnancy category B3 to Pregnancy category A for this long-acting (basal) insulin analogue, in particular whether sufficiently large data is considered to be available supporting this change.

  The ACPM advised that in light of;

  – The evidence from the trial with insulin detemir during pregnancy submitted

  – The clinical experience reported,

  – The more extensive prospective cohort study planned in Europe.

  The ACPM advised that a there is sufficient evidence for the change in pregnancy classification applied for.

Proposed conditions of registration:

The ACPM agreed with the delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA,
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM advised that the amendments to the Product Information (PI) and Consumer Medicine Information (CMI) should include the following:

- The required change in Pregnancy Category from the current B3 to A.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the variation to the registration of:

- Levemir Penfill insulin detemir (rys) 100 U/mnL solution for injection cartridge AUST R 172213
- Levemir Flexpen insulin detemir (rys) 100 U/imL solution for injection cartridge AUST R 172234
- Levemir Innolet insulin detemir (rys) 100 U/mL solution for injection cartridge AUST R 172235

With these PI updates:

- Inclusion of clinical trials information on co-administration with liraglutide (Victoza).

- Inclusion of longer term (24 months) safety data (antibody formation and glycaemic control) for the use of Levemir in adolescents and children (two to 16 years) with T1DM.
- Allow use of Levemir in pregnancy, that is, change in Pregnancy category from current B3 to Pregnancy category A.
- Align with the CCDS, as well as various editorial changes.

Attachment 1: Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2: Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au