



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for insulin glargine (rbe)

Proprietary Product Name: Toujeo / Edomlus /
Lambeto

Sponsor: Sanofi Aventis Australia Pty Ltd

January 2017

TGA Health Safety
Regulation

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- 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 <<https://www.tga.gov.au>>.

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- An Australian Public Assessment Report (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; it provides 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.

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Common abbreviations

Abbreviation	Meaning
AE	adverse event
AUC	area under curve
AUC ₀₋₂₄	area under curve from 0 to 24 hours
AUC _{0-∞}	area under curve from 0 to infinity
BMI	body mass index
CGM	continuous glucose monitoring
CI	confidence interval
CMI	consumer medicine information
CV	coefficient of variation
EU	European Union
FPG	fasting plasma glucose
GCP	good clinical practice
GIR	glucose infusion rate
HbA1c ¹	haemoglobin A1c
PD	Pharmacodynamics
PI	product information
PK	Pharmacokinetic
RMP	risk management plan
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
SMPG	Self-monitored plasma glucose
TGA	Therapeutic Goods Administration
U100	Insulin glargine 100U/mL

¹ The HbA1c test is a blood test that provides information about a person's average levels of blood glucose, also called blood sugar, over the past 3 months. The HbA1c test is based on the attachment of glucose to haemoglobin.

Abbreviation	Meaning
U300	Insulin glargine 300U/mL
USA	United States of America

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New strength
<i>Decision:</i>	Approved
<i>Date of decision:</i>	22 June 2015
<i>Date of entry onto ARTG</i>	30 June 2015
<i>Active ingredient:</i>	Insulin glargine (rbe)
<i>Product names:</i>	Toujeo / Edomlus / Lambeto
<i>Sponsor's name and address:</i>	Sanofi Aventis Australia Pty Ltd
<i>Dose form:</i>	Injection solution
<i>Strength:</i>	300 units/mL
<i>Container:</i>	Prefilled pen injector
<i>Pack sizes:</i>	1, 3 and 5 pen injectors
<i>Approved therapeutic use:</i>	<i>Treatment of diabetes mellitus in adults</i>
<i>Route of administration:</i>	Subcutaneous
<i>Dosage:</i>	Individualised dose, once daily
<i>ARTG numbers:</i>	223457, 223466, 223467

Product background

This AusPAR describes a submission by Sanofi Aventis Australia Pty Ltd (the sponsor) to register an additional strength, 300 units/mL (U/mL) of insulin glargine (rbe) with the trade names; Toujeo, Edomlus and Lambeto,² (also referred to as U300). The new strength contains 300 IU/mL insulin glargine compared to the 100 IU/mL strengths currently registered (as Lantus and Optisulin also referred to as U100).

A more restrictive indication for the new strength, excluding use in children is proposed. The existing, approved indication for insulin glargine is:

Treatment of type 1 diabetes mellitus in adults and children and type 2 diabetes mellitus in adults who require insulin for the control of hyperglycaemia.

The proposed indication for the new U300 product is:

Treatment of diabetes mellitus in adults.

The proposed presentation of Toujeo is in a 1.5 mL Solostar prefilled injector.

² Future reference in this AusPAR will only use the trade name Toujeo or U300, but will apply to all three trade names.

Like most insulin preparations, the product is intended for subcutaneous injection, in this case once daily, usually by the patient. Time of day is not specified. As usual for insulin, the quantum of dosage is individualised. The product information (PI) states that injections can be given up to 3 hours before or after the usual administration time, this being a significant change from the existing recommendation for Lantus.

In both Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) there is a place for a long acting insulin preparation suitable for once daily administration, either as the basal component of a basal/bolus regimen or, in the majority of T2DM patients requiring insulin, used alone. The existing approved formulation of insulin glargine (Lantus) has been widely used in this role both in Australia and overseas, particularly since the earlier long acting formulations crystalline insulin zinc suspension (Ultralente) and protamine zinc insulin were withdrawn from the market.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 30 June 2015.

Registration of the U100 strength of insulin glargine (Lantus) in Australia was in February 2001.

A summary of the regulatory status at the time this submission was reviewed is provided in Table 1 below.

Table 1: International regulatory status

Country	Submission Date	Status
European Union (EU)	April 2014	Positive CHMP opinion (received 26 February 2015)
USA	April 2014	Approved (25 February 2015)
Canada	June 2014	Pending
Switzerland	May 2014	Pending
Japan	July 2014	Pending
Brazil	August 2014	Pending

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Drug substance (active ingredient)

Insulin glargine (rbe) is a recombinant analogue of human insulin used in the treatment of T1DM and T2DM and is produced in *Escherichia coli*. Insulin glargine is designed to have a low solubility at neutral pH. At pH 4, insulin glargine is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralised leading to formation of a precipitate from which small amounts of insulin glargine are continuously released.

Drug product

The Lantus series of product containing 100 U/mL of insulin glargine is supplied in:

- 10 mL vials (AUST R 122335 Lantus insulin glargine (rbe) 100 U/mL 10 mL injection vial),
- 3 mL injection cartridges (AUST R 77737 Lantus insulin glargine (rbe) 100 U/mL 3 mL injection cartridge) and
- injection pens (AUST R 128468 Lantus Solostar insulin glargine (rbe) 100 U/mL 3 mL solution for injection pen).

Identical products with the additional trade name Optisulin have also been registered. These products are all administered by subcutaneous injection.

Toujeo, Endomlul and Lambeto (300 units/mL) are each available in a Solostar pre-filled pen. The 1.5mL cartridge is sealed in a disposal pen injector.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data: the product is not photostable. The proposed shelf life is 18 months when stored at +2°C to +8°C.

In-use stability data have also been submitted. The proposed shelf life and storage conditions for cartridges assembled in the pen injector are 42 days when stored at up to +30°C.

Insulin Glargine, 300 IU/mL is stable for repeated temperature excursions to +25°C from +2°C to +8°C. Based on the data supplied the only excursions allowed during transit are: 4 x 4 days at +25°C from +2°C to +8°C during a period of 28 days.

Bio-pharmaceutics

This submission is to register injection pens containing a 1.5 mL cartridge which contains 300 U/mL solution of insulin glargine. The application letter states that due to the higher concentration, precipitation of the insulin glargine occurs after subcutaneous injection and this leads to slower release into the blood stream and thus increases the time of the glucose lowering effect beyond 24 hours so that the new product may be dosed once daily in a more flexible manner compared to registered products.

The submission included clinical study data to support registration.

The submission also included 2 bioequivalence studies (PKD10086 and PKD13560). Each of these compared pharmacokinetic (PK) endpoints (that is, they were bioequivalence

studies) and clinical endpoints (the glucose infusion rate (GIR), that is, they were biopharmadynamic equivalence studies).

PKD13560 compared 2 formulations of the proposed U300 product: 1 formulated with 0.02 mg/mL of polysorbate 20 and the other formulated without this excipient. The results are stated to indicate bioequivalence. The relevance of this study was not apparent to the evaluator as the information provided by the sponsor indicates that the formulation used in the clinical studies was the same as that proposed for supply in Australia (the formulation without polysorbate 20).

PKD10086 compared the proposed U300 product to the registered U100 product. The results indicated that the products were not bioequivalent.

The evaluator repeated the calculations of the PK parameters and the associated confidence intervals (CIs) from 1 study (PKD13560) to ensure that the results of both studies are accurate.

Evaluator's recalculations of pharmacokinetic parameters and statistics

Determination of pharmacokinetic parameters

The PK parameters (C_{max} , C_{min} , DF, T_{max} , $t_{1/2}$, area under curve (AUC), AUC_{0-24}) have been recalculated based on the nominal sampling times; using the concentration versus time datasets. Recalculation was performed on Test and Reference datasets for 6 subjects (12%).

The recalculation results for parameters C_{max} , C_{min} , DF and T_{max} were identical to those of the sponsor and those for AUC_{0-24} differed by less than 1%. There were however some $t_{1/2}$ values that were significantly different, but this will be due to the number of points used in the calculations and is not an issue for this steady state study.

Statistical analysis

The TGA evaluator could not do a true repeat of the sponsor's statistical calculations as the TGA program must have equal numbers in each of test and reference. The calculations of the 90% CIs were therefore repeated without one set of results for Subject 22 (which could be included in the sponsor's calculations).

The TGA calculations showed no significant period, treatment or sequence effects.

The statistical analyses carried out by the evaluator produce 90% CI for C_{max} and $AUC_{0-\infty}$ that compare as below with the company's calculation.

Table 2: Comparison of for C_{max} and $AUC_{0-\infty}$ with the company's calculation

	C_{max} (Recalculated)	C_{max} (Company results)	AUC_{0-24} (Recalculated)	AUC_{0-24} (Company results)
	ratio	ratio	ratio	ratio
Test versus Reference Estimate	0.98	1.02	1.01	1.00
90% CI	0.91-1.06	0.91-1.14	0.95-1.07	0.95-1.06

The AUC_{0-24} results compare favourably. The slight differences in the C_{max} results are likely to be due to the omission of the data for Subject 22.

Before the calculations performed by the company can be confirmed as correct, the following issues relating to Study PKD13560 should be addressed by the sponsor.

1. *Subject 22 had no measurable levels of insulin glargine after the reference treatment. Please give a logical explanation of why this should be the case given that the GIR data for this subject and treatment is not dissimilar to GIR data for other subjects and treatments?*

Sponsor's response

Sanofi-Aventis cannot explain why this subject had very low levels, but incurred sample reanalysis indicated that this was indeed the case. It was also stated that this subject only had 1 result in the other arm above the limit of quantification (LOQ) of 5.00 µU/mL. Further there was another Subject (13) that also had low results, though not below the LOQ. Finally, a further calculation was performed assuming Subject 22 had a constant concentration of 50% of the LOQ for the 24 hour period. This did not affect the conclusion that the 2 treatments are bioequivalent.

2. *It is usual for these types of studies to adjust the measured amounts of insulin (total insulin) for the amounts of endogenous insulin to give the amounts due to the Drug insulin. The amount of endogenous insulin in turn being estimated with the C peptide concentration data using Owens method (Owens 1986³). The calculation is thus:*

$$\text{Drug insulin} = \text{total insulin} - F * C \text{ peptide}$$

where F is the average of the ratios of insulin to C peptide at baselines (-1, -0.5 and 0 hour) for both periods.

You do not appear to have used this approach here in Study PKD13560. If you have used this approach please give an assurance that this is the case. If you have not used this approach, please justify your own approach, and, (if possible) recalculate the PK parameters and 90% CIs (AUC₀₋₂₄ and C_{max}) on drug insulin levels after performing this adjustment?

Sponsor's response

Subjects were chosen that had no endogenous insulin levels so that a baseline correction is not required.

3. *There appears to be a transcription error between the tables of data for free insulin concentrations (in µU/mL) in the bio-analytical Report and the tables of data for free insulin concentrations. The errors only appear to be in the results at time 0.*
 - a. *If this was a deliberate act, please justify your approach.*
 - b. *If this was not a deliberate act, please check that the calculations of the PK parameters (C_{max}, C_{min}, DF, T_{max}, t_{1/2}, AUC₀₋₂₄) for each subject and each treatment were calculated using the correct primary data. If this is the case, please provide an assurance to that effect. If this was not the case, please provide revised PK results and revised statistical results.*

Sponsor's response

The approach was deliberate. Due to problems with interference in the 0 hour results at the same time as starting the glucose clamp, the 24 hour results from the end of Day 6 were used as the 0 hour results. Although not ideal, given the similarity in the results, this should not affect the outcomes of the study.

³ Owens DR. Human Insulin: Clinical Pharmacological Studies in Normal Man. New York: Springer Publishing; 1986.

Conclusion

With respect to the 2 bioequivalence studies included in the submission (PKD10086 and PKD13560), the PK and statistical results cited by the sponsor can be taken as correct.

PKD13560 compared 2 formulations of the proposed U300 product: 1 formulated with 0.02 mg/mL of polysorbate 20 and the other formulated without this excipient. The results are stated to indicate bioequivalence. The relevance of this study is not apparent to this evaluator as the formulation used in the clinical studies was the same as that proposed for supply in Australia (the formulation without polysorbate 20).

PKD10086 compared the proposed U300 product to the registered U100 product. The results indicated that the products were not bioequivalent.

Summary of quality evaluation and issues of importance

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The Microbiology Evaluator has raised the following issue:

“The application to register insulin glargine 300 units/mL solution for injection injector pen included an open shelf life of 42 days rather than 28 days, which is the maximum open shelf life period approved for injectable medicines intended for multi-dose use in a single patient. The company indicated that the extended shelf life fulfilled a clinical need.

The company argued that healthcare professionals recommend that patients use more than one pen in parallel to ensure an accessible supply of medically critical insulin; and also there are patients who use less than 12 U per day (low dose users). This leads to partially used pens at the end of a 28 day in-use period. The company has argued that the longer in-use time will “avoid excessive product waste through unused product needing to be discarded.” The company’s argument as to the clinical need for the 48 day open shelf life therefore appears to be based on patient convenience and pharmaco economic factors rather than a real clinical requirement. There is no compelling justification in the company’s response for a 42 day open shelf life.

The company has also referred to ease of access to the internet which means that patients can source information approved from overseas regulators, meaning that patients will use the pens for more than 28 days regardless. This is not considered sufficient reason to allow extended use periods.

It has been noted by Laboratories Branch; Microbiology that Sanofi currently has 100 U/mL products registered under the trade names Lantus and Optisulin which contain 3 mL of product solution. Using the above example of a low dose patient on 12 U per day; the 100 U/mL 3mL product would be sufficient for 25 days of use. It is acknowledged that the dosed amount vary over time, however it appears that it may be appropriate for low dose patients to potentially be using the 100 U/mL presentation to avoid as many partially used pens after reaching the 28 day open shelf life. [Information redacted].

As stated previously, Laboratories Branch Microbiology has never approved an open shelf life of greater than 28 days for a multidose injectable intended for use in one patient because of microbiological safety concerns, as detailed in the original question to the company. Provision of experimental data that shows a product can pass a simulated use test over an extended period is not sufficient justification for a prolonged open shelf life unless there are extremely compelling clinical reasons for doing so.

The results provided by the company may provide some assurance that there is a satisfactory level of safety over the proposed shelf life if the product is prepared and administered according to appropriate practices. However, as stated previously, the product is intended to be administered by patients in their own home (or wherever the patient is when their daily dose is required to be administered) and although it is acknowledged that these patients are instructed to use proper technique, there is a greater risk for these processes to be performed incorrectly than if it was performed by a trained healthcare practitioner.

It is therefore recommended that the application to register Insulin Glargine 300 units/mL solution for injection injector pen be rejected”.

Quality summary and conclusions

The quality evaluators recommend that:

TOUJEO insulin glargine 300 units/mL solution for injection injector pen AUST R 223457

ENDOMLUS insulin glargine 300 units/mL solution for injection injector pen AUST R 223466

LAMBETO insulin glargine 300 units/mL solution for injection injector pen AUST R 223467

should be rejected on the grounds of open shelf-life.⁴

Batch release conditions of registration for clinical Delegate

Should the product be approved, the following conditions of registration should be applied.

Batch Release Testing by Laboratories Branch

It is a condition of registration that, as a minimum, the first five independent batches of;

- TOUJEO insulin glargine 300 units/mL solution for injection injector pen AUST R 223457
- ENDOMLUS insulin glargine 300 units/mL solution for injection injector pen AUST R 223466
- LAMBETO insulin glargine 300 units/mL solution for injection injector pen AUST R 223467

imported into Australia are not released for sale until samples and/or the manufacturer’s release data have been assessed and endorsed for release by the TGA Laboratories Branch.

III. Nonclinical findings

Introduction

The new strength contains 300 U/mL insulin glargine also features a corresponding 3 fold increase in zinc chloride levels.

⁴ The open shelf life was reduced to 28 days prior to approval for registration.

According to the Clinical Overview and Summaries, the 100 and 300 U/mL strengths are not bioequivalent as the 300 U/mL strength has a reduced bioavailability and a slower, more prolonged absorption profile.

The nonclinical data comprised of 1 study on local tolerance, conducted in rabbits. The study was GLP compliant and of high quality. It revealed generally minimal or mild injection site reactions with administration of the 300 U/mL strength (commercial formulation) by the intended route (subcutaneous) and by potential accidental routes (intramuscular, intravenous and paravenous), which were comparable in incidence and severity compared with equal volumes of both the existing 100 U/mL formulation and saline. In patients, the injection volume (and in some individuals the number of injections) will be reduced with the new strength compared with the existing one, which may further reduce the potential for adverse local reactions.

Nonclinical summary and conclusions

- The new 300 U/mL strength was shown to be well tolerated locally in rabbits, with no appreciable difference in injection site reactions compared with the same volume of either the existing 100 IU/mL formulation (Lantus) or saline.
- There are no nonclinical objections to registration of the new higher strength.

The nonclinical evaluator also made recommendations with regard to the PI and the risk management plan (RMP) but these are beyond the scope of the AusPAR.

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 (extract from the clinical evaluation report).

Clinical rationale

The use of injectable insulin is essential in the management of T1DM and is well established as a treatment option for T2DM, particularly in those patients with secondary failure of oral hypoglycaemic therapy in whom there is usually evidence of loss of beta cell function. Despite the development of alternative therapeutic options such as incretin based therapies, there remains a population of T2DM patients for whom insulin is a safe and effective treatment either alone or in combination with other agents.

In both T1DM and T2DM applications, there is a place for a long acting insulin preparation suitable for once daily administration, either as the basal component of a basal/bolus regimen or, in the majority of T2DM patients requiring insulin, used alone. The existing approved formulation of insulin glargine (Lantus) has been widely used in this role both in Australia and overseas, particularly since the earlier long acting formulations crystalline insulin zinc suspension (Ultralente) and protamine zinc insulin were withdrawn from the market.

Contents of the clinical dossier

The clinical dossier documents a development program of pharmacodynamic (PD) / PK studies and pivotal clinical/efficacy studies beyond what would be expected simply for the registration of a new strength, relating to the sponsor's claim of an improved benefit/risk ratio for the use of the product by comparison with the existing U100 strength, based on maintenance of equivalent efficacy (blood glucose and HbA1c reduction¹) and associated with improved safety in terms of a reduction in hypoglycaemic episodes, particularly at

night. The submission places particular emphasis on the hypoglycaemic aspect of safety, relating improvements in this to alterations in the PK and PD properties of the product observed in the submitted clinical pharmacology studies. It draws a distinction between this and what it calls non hypoglycaemic safety, claiming, quite reasonably in the view of this evaluation, that evidence on this aspect can be extrapolated from the extensive documented use of the U100 Lantus product.

Comment: While hypoglycaemia is always a safety issue with regard to insulin administration, clinicians treating diabetes look upon the avoidance of hypoglycaemia as an efficacy issue: an effective insulin preparation is one which achieves good glycaemic control with the least possible incidence of hypoglycaemia.

The submission contained the following clinical information:

- 6 clinical pharmacology studies, all of which provide both PK and PD data.
- 4 pivotal efficacy/safety studies comparing the U300 product with U100 Lantus as comparator.
- An exploratory Phase II study (PDY12777) undertaking the same comparison utilising continuous glucose monitoring (CGM).
- 2 other studies (sub-studies of 2 of the pivotal studies) evaluating the efficacy and safety of varying the dosing interval by plus 3 hours.

Paediatric data

The submission did not include paediatric data, consistent with the proposed indication specifying adult use.

Good clinical practice

All submitted studies contained certifications regarding compliance with established codes of good clinical practice (GCP) and the protocols and other documentation examined by this evaluation appear consistent with these.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each pharmacokinetic (PK) topic and the location of each study summary.

Table 3: Submitted pharmacokinetic studies

PK Topic	Subtopic	Study ID	Summary page
PK in healthy adults	Bioequivalence ¹ – Single dose	PKD10086	47
PK in special populations	Target population ² – Single dose	PKD11627 PKD12270	51 54

PK Topic	Subtopic	Study ID	Summary page
	Multi dose	PKD13560	49
		PDY12335	56
		TDR11626	58

¹ Bioequivalence of different formulations. ² Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The PK studies have been well conducted and present robust evidence that the proposed U300 formulation has a reliable absorption profile quantitatively similar to that of the existing Lantus product but with delayed onset of action, a lower and later peak level and more sustained maintenance of insulin levels over the later part of the 24 hour dosing interval. Although this does not result in significant accumulation with prolonged administration, steady state insulin levels do take 3 to 4 days to achieve by comparison with 1 to 2 days with the existing approved U100 Lantus formulation.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 4 shows the studies relating to each PD topic.

Table 4: Studies relating to each pharmacokinetic topic

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on insulin action as measured by GIR during euglycaemic	PKD10086*
		PKD11627
		PKD12270
		PKD13550
		TDR11626
	Effect on glycaemic profile measured by CGM	PDY12335

*Conducted on healthy subjects; remainder of studies conducted on subjects who would be eligible to receive the drug if approved for the proposed indication.

These studies containing PD data are the same set as those presented above in the section on PK. None had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The PD properties of the new U300 glargine insulin formulation are qualitatively similar to those of the existing U100 formulation but with a delayed onset, prolonged duration of action and reduced variation during the dosing interval consistent with its altered PK properties. There is suggestive evidence, not confirmed by the statistical analysis, that

intra-individual variation in PD response during the dosing interval may be reduced with the new formulation.

Dosage selection for the pivotal studies

Dosage of insulin therapy is generally individualised along a continuous scale and usually, as in these studies, to a therapeutic target. The starting dose in this instance, for either the test product or the comparator (U100, Lantus), was defined as the subject's existing insulin dose, or in the case of insulin naïve subjects (patients) in Study EFC12347, 0.2 U/kg. In Studies EFC11628 and EFC11629, the administration device used necessitated a lower limit of 42 units for basal insulin dose at recruitment.

Efficacy

Studies providing efficacy data

Efficacy is supported by 4 pivotal Phase III studies, Studies EFC12456, EFC11628, EFC11629 and EFC12347. These were conducted using a common protocol. Additionally there was a Phase II exploratory study (PDY12777), and 3 month sub-studies conducted during the main study period of 2 of the pivotal studies (EFC11628 and EFC11629).

Evaluator's conclusions on efficacy

Parameters of hypoglycaemia incidence, particularly nocturnal hypoglycaemia, were included as efficacy variables in the pivotal studies and will therefore be taken into consideration in these conclusions. An effective insulin preparation is one which achieves good glycaemic control with the least possible incidence of hypoglycaemia.

The included studies clearly demonstrate non-inferiority of the U300 formulation by comparison with U100 Lantus in terms of the principal efficacy parameter, change in HbA1c¹ from baseline to 6 months, in the most relevant clinical setting of improving glycaemic control by stepwise insulin titration. The numerical comparison of efficacy by this criterion was very close between the 2 formulations, as was the comparison of the secondary glycaemic parameters fasting plasma glucose (FPG) and pre-injection self-monitored plasma glucose (SMPG). All of the above comparisons were successfully demonstrated in each pivotal study.

The first specified secondary efficacy parameter was the incidence of nocturnal hypoglycaemia. A reduced incidence of this was found in all 3 of the pivotal studies carried out on T2DM patients, but not in Study EFC12456 carried out on T1DM patients. In 2 of the T2DM studies, EFC11628 and EFC11629, the risk reduction for nocturnal hypoglycaemia was statistically significant.

Variation of the timing of daily insulin injection by up to 3 hours was shown, in sub-studies of EFC11628 and EFC11629 to have no effect on glycaemic control or hypoglycaemia incidence in T2DM patients using the U300 formulation.

A number of the studies show reduced glycaemic variability with the U300 formulation, particularly across the time course of its action. None of these findings achieve statistical significance, but the fact that the phenomenon has been observed more than once and is supported by similar pharmacodynamic data suggests that this is a real finding.

The above conclusions concur with those on which the sponsor bases claims for the use of the U300 formulation. This evaluation, however, finds a number of important caveats in relation to these conclusions, as follows:

- The finding of reduced hypoglycaemia incidence which, as the sponsor acknowledges, is restricted to use in T2DM, is also only supported for evening injection of U300. Not to have included a morning injection arm in the T2DM studies, as was done for the T1DM Study EFC12456, is a flaw in the design of the trials. There is every possibility that morning injection would not be associated with such reduced incidence of nocturnal hypoglycaemia, or might even result in an increase, as was observed in Study EFC12456 although not statistically confirmed. The possibility of such an outcome is also supported by the data from the PD studies, which were all performed with morning administration.
- The demonstration of non-inferior clinical efficacy of U300 with respect to U100 comes at the cost of increased dose of insulin; from baseline to 6 months, U300 dose increased 1.5 to 2.5 fold more than U100, resulting in final doses 10% higher for the T2DM patients and 17% higher for T1DM.
- The finding supporting flexibility of dosage timing by plus 3 hours is only supported for T2DM patients, in whom it was shown. It should not be assumed that this tolerance would extend to use in T1DM. It has also not been confirmed that this property is specific to the U300 formulation as the U100 Lantus patients in Studies EFC11628 and EFC11629 were not included in the sub-studies. Demonstration of a difference between the treatment arms would have added more weight to the finding.

Apart from the matter of increased insulin dosage, these restrictions on the relevance of the supporting data are not recognised or acknowledged in any of the summary documents in the submission.

Safety

Throughout this submission, a distinction is quite reasonably drawn between safety relating to hypoglycaemia, and general safety. Hypoglycaemia is an inevitable safety issue with any form of insulin therapy, and its avoidance is a parameter of efficacy as already discussed above with particular relevance to the proposed new U300 formulation.

Other new safety issues seem unlikely to arise as the drug substance and excipient composition of the formulation are identical with the U100 Lantus formulation currently in use. Referring to the clinical development program for U300, the sponsor's letter of application states: "*The program has been built on the hypothesis that the efficacy and general, non-hypoglycaemia safety profile of U100 can be extended to insulin glargine in the U300 formulation*". This evaluation supports that proposal. The general safety information collected in the clinical trials and summarised briefly below provides, as might be expected, no evidence of difference between the 2 formulations.

Studies providing safety data

All of the included studies, as listed in the exposure table below (Table 5), provided safety data.

Patient exposure

Overall exposure to the test drug and comparator is shown in the following table.

Table 5: Exposure to U300 and comparator (U100 Lantus) in clinical studies

Phase/Study	Treatment duration	HOE901-U300	Lantus	Total
Phase I program				
Healthy subjects		23	24	24
T1DM		140	91	142
Total Phase I		163	115	166
Phase II/III program				
Studies in T1DM				
PDY12777	16 weeks	30	29	59
EFC12456	6 months	274	275	549
Total T1DM		304	304	608
Studies in T2DM				
EFC11628	6 months	404	402	806
EFC11629	6 months	403	406	809
EFC12347	6 months	435	438	873
Total T2DM		1242	1246	2488
Total Phase II/III T1DM and T2DM		1546	1550	3096

Phase III studies: completed 6 month main study periods

Post marketing data

None is available as the product is not yet marketed in any jurisdiction.

Evaluator's conclusions on safety

The evidence that use of the U300 formulation by T2DM patients, by comparison with U100 Lantus, results in a clinically significant reduction in the risk of nocturnal hypoglycaemia, is accepted. As already noted in the conclusions on efficacy, this conclusion is subject to the product being used under the same conditions as in the supporting trials, specifically as an evening injection.

Safety data other than that relating to hypoglycaemia support the sponsor's contention that the general safety profile of U100 Lantus can be extended to the new U300 formulation (Toujeo). A possible association of insulin glargine with malignancy incidence has been the subject of attention in the literature although concern has diminished, as reflected in a recent review.⁵ There is no evidence of such concerns in the data submitted with this application.

First round benefit-risk assessment

The benefits and risks listed below are postulated as those which would apply to use of Toujeo (300 U/mL insulin glargine) in place of U100 Lantus, the product with which it was compared in the included clinical trials and which is also the product it would most likely replace in clinical use in Australia.

First round assessment of benefits

The benefits of Toujeo in the proposed usage are:

- Maintenance, for both T1DM and T2DM patients, of an equivalent level of blood sugar control.
- Reduction of the risk of hypoglycaemia occurring at night. On the evidence provided, this benefit is restricted to T2DM patients given Toujeo as an evening injection. However, the proposed usage as defined by the dosing instructions in the draft PI does not specify this, so unless that is changed this benefit is uncertain.
- Ability to vary the time of daily injection by up to 3 hours. This has only been shown for T2DM patients and it has not been clearly shown that the benefit only applies to U300.
- A reduced injection volume. This would be an advantage for patients on large doses but is partially offset by the need, according to the trial data, to increase the dose.

First round assessment of risks

The risks of Toujeo in the proposed usage are:

- Necessity to use a higher dose of insulin. There is a largely hypothetical risk, of minor degree, related to the suggestion that increased exposure to insulin, whether exogenous or endogenous, is associated with some health risks. An additional "disadvantage", as opposed to "risk", would be increased resource or economic costs associated with increased insulin usage.
- Potential for dosing error. As noted above, this is offset by presentation of the product in a dedicated, disposable injection device. However, approval of this application might open the way to availability of other presentations (for example, cartridge or vial) which would carry this risk if used with standard insulin syringes. Appropriate warnings do appear in the draft Consumer Medicine Information (CMI).

First round assessment of benefit-risk balance

The benefit risk balance of Toujeo is unfavourable given the proposed usage, but would become favourable if the recommended changes are adopted. This comment relates entirely to the finding of this evaluation that the recommendations regarding timing of dose in the draft PI are not consistent with the supporting evidence and have the potential

⁵ Home P: Insulin therapy and cancer. *Diabetes Care* 2013 Aug; 36 Suppl 2

to put patients at risk, or at least be denied the potential benefits of the product, unless appropriately changed.

First round recommendation regarding authorisation

The clinical evaluator stated that approval of the submission in its present form is not recommended. The sponsor should be asked to consider changes to the draft PI particularly those which would align the recommendations regarding dosage timing with the evidence in the pivotal trials. The clinical evaluator emphasised that the evidence itself is not in question and that the submission was in other respects satisfactory.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a risk management plan (RMP); RMP EU-RMP (Version: 4.0, dated 3 April 2014) with an Australian Specific Annex (ASA) Version: 1.2, dated May 2014 which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 6.

Table 6: Sponsor's summary of ongoing safety concerns

Summary of ongoing safety concerns	
Important identified risks	Hypoglycaemia Medication errors (insulin mix ups) Injection site reactions Hypersensitivity reactions
Important potential risks	Malignancies Antigenicity Medication error (inappropriate dose injected, following needle blocked in absence of compliance with instructions for use)
Missing information	Use in pregnancy (U300 only) Use in paediatric population (U300 only)

Comment: The above ongoing safety concerns differ from those previously accepted for Lantus as follows:

- The addition of the important potential risk: 'Medication error (inappropriate dose injected, following needle blocked in absence of compliance with instructions for use)'.
- The addition of the missing information: 'Use in paediatric population (U300 only)', to reflect the lack of paediatric data for the higher concentration formulation and to capture any such off label use.

- Specifying the missing information: 'Use in pregnancy' is applicable only to the U300 presentation to reflect the significant exposure of pregnant women to the marketed U100 dosage form and the limited use in pregnancy during clinical development with U300.

Notwithstanding the evaluation of the nonclinical and clinical aspects of the Safety Specification, the above summary of the Ongoing Safety Concerns is considered acceptable.

Reconciliation of issues outlined in the RMP report

Table 7 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

Table 7: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>1. The sponsor should provide copies of the targeted structured forms used to follow up ICSRs related to the important identified risk: 'Medication errors (insulin mix ups)' and to the important potential risk: 'Medication error (inappropriate dose injected, following needle blocked in absence of compliance with instructions for use)' as attachments to a revised ASA.</p>	<p>The sponsor has provided copies of the targeted structured forms as specified and stated: "Please note there are no proposed targeted structured forms to follow up ICSRs related to the 3 new important potential risks incorporated in the updated AUS-RMP (v 1.3): 1. Medication error (unnecessary re calculation of the units needed); 2. Medication error (inappropriate use, i.e., extraction of insulin from the pen using a syringe); and 3. Medication error (substitution with product with inadequate concentration dispensed). Routine surveillance activities are considered adequate for monitoring these new important potential risks."</p>	<p>This is acceptable</p>
<p>2. Routine risk minimisation is proposed for all the specified ongoing safety concerns, except for the important potential risk: 'Malignancies' for which no risk minimisation activities are proposed. Routine risk minimisation in the form of information in the sub section: 'Carcinogenicity' in the Precautions section of the Australian PI for Lantus was previously accepted for the important potential risk: 'Malignancies'. Given this text still appears in the draft Australian PI submitted with this application the sponsor should provide an</p>	<p>The sponsor states: "This oversight has been corrected in the revised ASA (v 1.3). Further details are provided in Table 2 and Table 3 of the ASA."</p>	<p>This is acceptable</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>explanation for this discrepancy or correct this oversight by revising the ASA.</p>		
<p>3. The assurance in the ASA should be amended as follows: "Final versions of the tools as intended to be used to support product launch will be made available provided in a timely manner to the TGA for review before their implementation."</p>	<p>See Recommendation 4.</p>	<p>See Recommendation 4.</p>
<p>4. In principle there are no objections to sponsor proposing to provide a specific 6 monthly safety focused report for 3 years following the commercialisation of U300 to evaluate the incidence and root cause and assess the effectiveness of minimisation activities on the different types of medication errors. However, this activity is reliant upon data from spontaneous ADRs which are unlikely to be sufficient in measuring the effectiveness of these proposed additional risk minimisation activities. This is due to the under reporting and the lack of reliable exposure (usage) data associated with spontaneous reporting systems, not to mention the information gained from adverse reaction reporting is often incomplete. Consequently the sponsor should plan appropriate alternative methods to assess the educational materials for HCPs and patients as a measure to reduce risk of medication errors and include such detail in a revised ASA. For example periodic market research of the Australian target audience of the educational materials could be planned for the post market period for as long as these additional risk minimisation activities are still considered necessary and therefore continue to be implemented.</p>	<p>The sponsor states: "During evaluation in the EU the proposed tools included in the RMP were deemed to be standard educational items reflecting information included in the product labelling, rather than specific risk mitigation measures. Routine pharmacovigilance activities, including ICSR review, periodic safety reports, proactive safety review/signal detection and continuous monitoring of the safety profile/benefit risk assessment, were considered adequate for monitoring the safety concerns. As a consequence the tools and the plan to provide a specific 6 monthly safety focused report as a measure of their effectiveness, no longer form part of the EU RMP. To align with the EU-RMP (v 4.1), the AUS-RMP (v1.3) has been updated and reference to the proposed tools and measures of effectiveness have also been removed from the ASA (v1.3). In Australia the tools will be made available to healthcare professionals and patients as part of the standard educational materials delivered at time of product launch to ensure Quality use of Medicines."</p>	<p>This is acceptable.</p>

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

In their response to the TGA request for information the sponsor provided an updated EU-RMP (Version 4.1, dated 14 November 2014) with an updated ASA (Version 1.3, dated December 2014). Key changes from the versions evaluated at Round 1 are summarised in Table 8.

Table 8. Key changes in the updated RMP

Document	Changes implemented
EU-RMP	<p>The potential risks: 'Medication error (unnecessary re-calculation of the units needed)', 'Medication error (inappropriate use, i.e. extraction of insulin from the pen using a syringe)' and 'Medication error (substitution with product with inadequate concentration dispensed) were added.</p> <p>No additional risk minimisation activities were deemed necessary for any of the risks by the CHMP. Consequently the additional risk minimisation activities previously proposed for the important identified risk: 'Medication errors (insulin mix-ups)' and for the important potential risk: 'Medication error (inappropriate dose injected, following needle blocked in absence of compliance with instructions for use)' were removed.</p>
ASA	<p>The ASA has been updated to incorporate the changes resulting from the revised EU-RMP (see above).</p> <p>The sponsor has advised that references to the previously proposed tools and measure of effectiveness have been removed from the ASA to align with the updated EU-RMP. During evaluation in the EU, the proposed tools were deemed to be standard educational items reflecting information included in the product labelling, rather than specific risk mitigation measures. As a consequence, the tools and the plan to provide a specific 6 monthly safety-focused report as a measure of their effectiveness, no longer form part of this RMP. In Australia the tools will be made available to healthcare professionals and patients as part of the standard educational materials delivered at time of product launch to ensure quality use of medicines.</p>

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

The European Risk Management Plan (Version 4.1, dated 14 November 2014), as qualified by the Australian Specific Annex (Version 1.3, dated December 2014), must be implemented.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The application to register insulin glargine 300 U/mL solution for injection injector pen included an open shelf life of 42 days rather than 28 days.

28 days is the maximum open shelf life period approved for injectable medicines intended for multi dose use in a single patient. For example, Lantus Australian PI specified an open shelf life of 28 days. The EU SmPC for Lantus also specifies an open shelf life of 28 days.

The sponsor has provided:

The latest negotiated EMA SmPC; the open shelf life is given as 4 weeks.

The latest negotiated FDA PI; the open shelf life is given as 28 days.

Nonclinical

There are no nonclinical objections to registration of the new higher strength.

Clinical

Submitted studies

- 6 PK/PD studies
- 1 Phase II study comparing U300 formulation with U100 formulation, using continuous glucose monitoring (CGM)
- 4 pivotal Phase III, therapeutic equivalence studies of the U300 formulation versus the U100 formulation, powered on an inferiority margin for HbA1c of 0.4%
- 2 sub-studies of 2 of the pivotal Phase III studies that assessed varying the time of administration by + or - 3 hours

PK/PD studies

The PK/PD studies are summarised in the clinical evaluation report (see Attachment 2). Selected results are given below.

- The U300 formulation is not bioequivalent, unit for unit, to the U100 formulation: AUC: 0.62, 90% CI (0.57, 0.66).
- The U300 formulation has a delayed onset of action, lower and later peak, and more sustained levels in the latter part of the 24 hour dosing interval.
- This is due to different absorption rates from the subcutaneous precipitate; although the mechanism for this is unclear.
- There is no accumulation, but steady state levels are achieved after 3 to 4 days, compared to 1 to 2 days with the U100 formulation.

Efficacy

Results are from 4 pivotal Phase III therapeutic equivalence studies.

Study designs

Study characteristics and baseline participant characteristics are given in Attachment 2.

In all studies the comparator was U100 (Lantus); they were all open label (U300 had a reduced injection volume) and study participants were all older than 18 years, with a

screening HbA1c between 7 to 10% for patients already on (pre-treated with) basal insulin (12456, 11628, 11629); and 7 to 11% for patients who were insulin naïve (12347). There was 1 study in T1DM (12456) and 3 studies in T2DM (11628, 11629, 12347); in 1 of the T2DM studies, patients were also on mealtime insulin (11628) plus or minus oral anti diabetes agents.

In all studies, doses of U300 and U100 were titrated to pre-specified glucose targets over the 6 months of the studies, using a self-performed insulin adjustment protocol that is typical of that used in many outpatient diabetes clinics (treat to target). In the T2DM studies all insulin doses were given in the evening; whereas in the T1DM study, patients were stratified into morning or evening doses.

Results

Primary endpoint

Table 8: Primary endpoint (6 month change in HbA1c)

Study	N U300 U100	Baseline HbA1c% U300 U100	6 month HbA1c% U300 U100	Change U300 U100	Difference 95% CI
12456	273	8.13	7.70	-0.40	0.04
T1DM	273	8.12	7.68	-0.44	(-0.098, 0.185)
11628	404	8.13	7.23	-0.90	-0.03
T1DM	400	8.14	7.27	-0.87	(-0.144, 0.083)
Basal insulin experienced Mealtime insulin +/- oral agents					
11629	403	8.27	7.47	-0.73	-0.03 (-0.168, 0.099)
T2DM	405	8.22	7.49	-0.70	
Basal insulin experienced also on oral agents					
12347	432	8.49	7.08	-1.42	0.04
T2DM	430	8.58	7.05	-1.46	(-0.090, 0.174)
Insulin naïve Also on oral agents					
Pooled	835	8.38	7.27	-1.08	0.01
12347/11629	835	8.40	7.27	-1.09	(-0.083, 0.106)
Also on oral agents					

Comment: All results met the pre-specified non-inferiority margin of 0.4%. That is, none of the upper 95% confidence limits were above 0.4%. There is an argument that the non-inferiority margin should be 0.3%, p11 of the EMA Guideline on medicinal product for diabetes: (CPMP/EWP/1080/00 Rev. 1 2012); this margin was also met.

*Insulin dose***Table 9: Insulin dose**

Study	Baseline	6 month	Increase
	U300	U300	U300
	U100	U100	U100
12456 T1DM	33.5U	40.5U	21%
	31.5U	34.1U	8%
11628 T2DM	70.3U	103.3U	47%
	70.9U	93.6U	32%
11629 T2DM	62.1U	91.0U	47%
	63.9U	81.9U	28%
12347 T2DM Insulin naïve	18.3U	59.4U	225%
	18.6U	52.0U	180%

Comment: Compared to U100, higher doses of U300 were needed to achieve the pre-specified plasma glucose targets. That is, although U300 has a reduced injection volume, this is partially offset by the need for larger doses (approximately 10 to 18% higher). The clinical relevance of the need for higher doses is unclear. In theory it could result in more weight gain and more hypoglycaemia, but the available data (arguably short term; 6 months) do not support this.

Secondary endpoints

Severe and or confirmed nocturnal hypoglycaemia (a main secondary efficacy endpoint)

Definition: occurring between midnight and 5:59 am and symptomatic and requiring correction, or confirmed by self-monitored plasma glucose (SMPG) < 4.0 mmol/L; between Week 9 and Month 6.

Table 10: Secondary efficacy endpoint, number of patients with at least 1 severe or confirmed episode of nocturnal hypoglycaemia between Week 9 and Month 6

Study	N	n (n/N%)	Risk difference	Relative risk
	U300	U300	U100 - U300	U300/U100
	U100	U100		95% CI
12456 T1DM	273	162 (59.3%)	-3.3%	1.06 (0.92, 1.23)
	273	153 (56.0%)		
11628 T2DM	404	146 (36.1%)	9.9%	0.79 (0.67, 0.93)
	400	184 (46.0%)		
11629 T2DM	403	87 (21.6%)	6.3%	0.77 (0.61, 0.99)
	405	113 (27.9%)		
12347	432	67 (15.5%)	1.9%	0.89 (0.66, 1.20)

Study	N		n (n/N%)		Risk difference	Relative risk
	U300	U100	U300	U100	U100 - U300	U300/U100
						95% CI
T2DM Insulin naïve	430		75 (17.4%)			
Pooled 12347/11629 Also on oral agents	835		154 (18.4%)		4.1%	0.82 (0.68, 0.99)
	835		188 (22.5%)			

Comment: Compared to U100, U300 was associated with less nocturnal hypoglycaemia in the 2 T2DM studies where the patients were already on (pre-treated with) insulin glargine at recruitment. For T2DM patients, who were insulin naïve, the point estimates (risk difference: 1.9%; relative risk: 0.89) suggested less nocturnal hypoglycaemia, but this was not statistically significant (that is, the CI for the relative risk included 1.0); and based on the upper limit of the 95% CI (1.20), the risk of hypoglycaemia could be 20% higher. In all 3 of the T2DM studies, the insulin glargine was given in the evening.

In the T1DM study, the results did not show any reduction in nocturnal hypoglycaemia with U300: the point estimates were in the direction of more hypoglycaemia (risk difference: -3.3%, relative risk: 1.06); the CI for the relative risk included 1.0, with an upper limit of 1.23.

In this T1DM study, patients were stratified according to whether they took the insulin glargine in the morning or evening. The results for nocturnal hypoglycaemia were: morning U300: 60%, U100: 55% [an approximately 5% higher risk of nocturnal hypoglycaemia with U300]; evening U300: 59%, U100: 57% [an approximately 2% higher risk of nocturnal hypoglycaemia with U300]. That is, there is no evidence that U300 resulted in a decrease in nocturnal hypoglycaemia for patients with T1DM, whether given in the morning or evening, and might even result in an increase (especially when given in the morning); although this concern about the morning dose is based on results that are not definitive, given this is a subgroup analysis.

Other secondary endpoints

Change in pre-injection Self-monitored plasma glucose from baseline to Month 6

In all 4 pivotal studies, the least square (LS) mean change from baseline to endpoint (Month 6) in average pre injection SMPG was similar in the U300 and Lantus groups. Similar results were also seen in the meta-analysis on the pooled data from the 2 T2DM studies (12347/11629) with oral hypoglycaemics as background therapy.

Change in variability of pre-injection self-monitored plasma glucose from baseline Month 6

The variability of pre-injection SMPG, calculated as mean of coefficient of variation (CV) over at least 3 SMPG measurements during the 7 days preceding the visit, decreased from baseline to Month 6.

HbA1c below 7% and no severe or confirmed hypoglycaemia

In all 4 studies, similar percentages of U300 and Lantus treated patients reached HbA1c levels below 7.0% at Month 6 overall and without reporting severe and/or confirmed hypoglycaemia with the low threshold of < 3.0 mmol/L (54 mg/dL) during the last 3 months of study treatment.

Fasting plasma glucose

Fasting plasma glucose (FPG) (measured in the central laboratory) showed decreases in both treatment groups in the 4 studies with most of the decrease seen in the first 3 months of study treatment. Although the difference in the LS mean change of FPG in study of insulin naïve T2DM patients was in favour of Lantus, it was not associated with a greater HbA1c reduction in this study.

Adaptable (+/- 3 hours) versus fixed dosing interval for T2DM; sub-studies of 11628 & 11629

After the completion of the 6 months of follow up in Studies 11628 and 11629, patients on U300 had the possibility of being re-randomised to a flexible dosing interval versus a fixed dosing interval. Follow up was 3 months; sample size: 11628: 106; 11629: 78. The results suggested that there was no difference in HbA1c and risk of hypoglycaemia for flexible versus fixed dosing. However, these studies had some deficiencies:

- They were not powered (n=106, 78) to show equivalence/non-inferiority of flexible versus fixed dosing on HbA1c or hypoglycaemia.
- The studies only went for 3 months.
- The studies were only in T2DM patients, who are more tolerant of flexible dosing than T1DM patients because T2DM patients have endogenous residual insulin
- The studies only considered flexible dosing for an evening dose of U300
- There was no assessment of (or comparison to) flexible dosing for U100.

Safety

The safety evaluation was based on 1,544 patients exposed to U300, of whom only 100 were exposed for at least 1 year.

Hypoglycaemia

As the clinical evaluator has pointed out, an effective insulin preparation is one which achieves good glycaemic control with an acceptably low incidence of hypoglycaemia. Severe or confirmed nocturnal hypoglycaemia was a pre-specified main secondary efficacy endpoint.

The sponsor also conducted various safety analyses using multiple (standard) definitions of hypoglycaemia (for example: severe, documented, symptomatic, asymptomatic, probable, et cetera), periods (0 to 6 months, 2 to 6 months, 0 to 2 months), time (nocturnal, any, daytime, et cetera), analysis method (at least 1, number of episodes, episode rate). There was no safety signal for increased hypoglycaemia; however, these analyses cannot be used as evidence that U300 leads to less hypoglycaemia than U100 because of the problem multiple statistical comparisons. That is, they can be used to reduce concerns that U300 leads to more hypoglycaemia (given a higher dose is needed), but they do not provide conclusive evidence that U300 leads to less hypoglycaemia.

Non hypoglycaemic safety profile

The sponsor makes the point that the non-hypoglycaemic safety profile of U100 can be extended to U300 because the active pharmaceutical ingredient and the excipients are identical.

No safety signals emerged from the clinical development program; in particular, no safety signals emerged for injection site reactions, hypersensitivity reactions, malignancy, or cardiovascular events. Given that the studies were open label, interpretation of any safety signal might be problematic. Analyses of serious adverse events (SAE), deaths, and discontinuations were unremarkable.

Potential for dosing errors

Given this is a new strength of insulin, a safety concern worthy of consideration is the potential for dosing errors. "Dosing errors related to the availability of multiple strengths of insulin was a common problem prior to the worldwide adoption of 100 U/mL as a single standard strength in the 1980s. The proposal of this submission to now reintroduce an additional strength does raise this concern once again, although the specific presentation applied for does not constitute a risk as the insulin is contained in a prefilled injection device specifically designed to deliver the correct dose."

Risk management plan

The RMP evaluator accepted the sponsor's list of ongoing safety concerns (Table 6).

Additional pharmacovigilance measures (beyond routine measures) in Australia are based on those proposed in the EU and comprise the delivery of a specific 6 monthly safety focused report for 3 years following the commercialisation of U300 to evaluate the incidence and root cause and assess the effectiveness of minimisation activities on the different types of medication errors.

Risk-benefit analysis

Delegate's considerations

U300 is a different strength of insulin glargine. It is not bioequivalent, on a same dose basis, with the currently registered and marketed U100 strength. It has a delayed onset of action, and a lower and later peak. That is, it has a different PK/PD profile.

Current EMA guidelines (adopted by TGA) do not specifically discuss the evidential basis for registration of a different strength of insulin. The discussion of insulin analogues in the guideline,⁶ states that insulin analogues are usually developed for their novel PK properties. It goes on to say that differences in PK parameters alone cannot be used to support claims in the PI. Benefits/superiority needs to be established on clinical endpoints such as HbA1c, weight, or hypoglycaemia.

The sponsor has provided good evidence that, although it is not bioequivalent (on a same dose basis), U300 can be titrated, such that HbA1c levels are similar to those achieved with U100, after 6 months. On average, to achieve the same HbA1c, a higher dose of U300 is needed, compared to U100 (10 to 18% higher). That is, U300 can be titrated to be non-inferior to U100 on the endpoint of HbA1c.

For these HbA1c results and in other respects, U300 is similar to Lantus U100. The different PK profile (with a delayed onset of action, lower and later peak, and more sustained levels in the latter part of the 24 hour dosing interval) is a theoretical advantage, but the clinical trials failed to show major clinical advantages.

Possible advantages

Reduction in injection volume

This could be important for patients who require large amounts of insulin. However, the limitation to 80 units per injection requires these patients to still use more than 1 injection, removing the most obvious advantage. There may be advantages of less pain

⁶ CPMP/EWP/1080/00 Rev1 (2012) Guideline on clinical investigation of medicinal products for treatment and prevention of diabetes.

associated with a smaller injection volume. The reduction in injection volume is offset slightly by the requirement, on average, for a higher dose.

Hypoglycaemia

Severe/confirmed nocturnal hypoglycaemia was “a main secondary efficacy endpoint”. The data show that for T2DM patients who take an evening dose of either U300 or U100, the risk of severe or confirmed nocturnal hypoglycaemia is lower on U300.

However, for insulin naïve T2DM patients there was no conclusive evidence of a reduction in severe or confirmed nocturnal hypoglycaemia on U300. The insulin naïve T2DM patients (Study 12347) were at the point in their disease progression where they are just developing what could be regarded as an indication to start insulin therapy. They had a much shorter duration of diabetes (median 8.5 years) than patients pre-treated with insulin in Study 11628 (15.2 years). Because of this, they would have had more residual beta cell function, more intact counter regulatory mechanisms, a lesser requirement for insulin, and for all these reasons would be less prone to the development of hypoglycaemia, hence the lower incidence of hypoglycaemia in this study; and less possibility of showing a clinically important decrease with U300.

For T1DM, the point estimate suggested an absolute increase of 3.3% in the risk of severe or confirmed nocturnal hypoglycaemia. The 95% CI for the relative risk did not rule out the possibility of a relative increase in the risk of 23%. In the T1DM study, insulin glargine dosing was stratified to morning or evening. The absolute increase in risk of hypoglycaemia for U300 versus U100 was 4.8% (59.6% to 54.8%), when dosing was in the morning; and 1.9% (59.1% to 57.2%) when dosing was in the evening.

The clinical evaluator has suggested that because of its delayed onset of action, U300, when given in the evening, causes less nocturnal hypoglycaemia than U100. However, this might not apply to T1DM patients who are more insulin sensitive.

Flexible dosing

These studies had several limitations (for example, they were only for 3 months, there was no formal statistical power calculation, the sample sizes were relatively small, they were only in T2DM patients who took an evening dose, there was no comparison to U100, there was no comparison to other basal insulins). On theoretical grounds, occasional flexibility should be safe for both the U300 and U100 (Lantus) formulations (and other basal insulins). The data from the studies on flexible dosing are exploratory and there are no established differences from Lantus (U100) or other basal insulins.

Possible disadvantages

Hypoglycaemia

The higher dose raises concerns about increased risk of hypoglycaemia; however, the currently available data show no evidence of this.

Dosing errors

The pen device mitigates this risk. If, in the future, the sponsor was to market a vial, then the risk might be greater.

Questions

1. Information about reduced risk of hypoglycaemia in the Clinical Trials section of the PI

The sponsor’s proposed PI has 6 paragraphs on the claim of less hypoglycaemia and a large table that includes the various safety analyses using multiple (standard) definitions of hypoglycaemia (for example, severe, documented, symptomatic, asymptomatic, probable, et cetera), periods (0 to 6 months, 2 to 6 months, 0 to 2 months), time

(nocturnal, any, daytime, et cetera), analysis method (at least 1, number of episodes, episode rate). These safety results provide reassurance that Toujeo does not increase the risk of hypoglycaemia (in spite of the need for an increased dose; on average: 10% to 18%). However, any claim of reduced hypoglycaemia must rest on the main secondary efficacy endpoint: at least 1 episode of severe or confirmed nocturnal hypoglycaemia between 9 weeks and 6 months.

In response to TGA's request for information about why the reduction in severe or nocturnal hypoglycaemia (between 9 weeks to 6 months) was not seen for T1DM, the sponsor has argued that for T1DM patients, mealtime insulin, physical activity, and meal intake are potential confounders. It is possible that even in a randomised study there is some confounding (given the sample size is finite and randomisation only provides probabilistic protection against confounding, on average). However, the result for T1DM is the best data we currently have for this pre-specified main secondary endpoint.

The sponsor has also argued that the caveat of "evening dose" should be omitted from the information on T2DM because of the flat and prolonged PK profile of Toujeo. However, the EMA guidelines for diabetes products (adopted by the TGA) require that claims in the PI are supported by clinical endpoint studies, in addition to the PK characteristics.

In short, it seems reasonable to conclude that U300 causes less severe or confirmed nocturnal hypoglycaemia in T2DM patients who take an evening dose. It is accepted that for T2DM patients who were insulin naïve, the risk of hypoglycaemia is comparatively low and it can be difficult to show clinically meaningful differences.

The section in the draft EMA SmPC (under: clinical efficacy and safety) is:

Results from clinical trials demonstrated that the incidence of confirmed hypoglycaemia (at any time of the day and nocturnal) was lower in patients treated with Toujeo compared to insulin glargine 100 U/mL treated patients, in patients with T2DM treated in combination with either noninsulin anti hyperglycaemic medicinal product or mealtime insulin.

The superiority of Toujeo over insulin glargine 100 U/mL in lowering the risk of confirmed nocturnal hypoglycaemia was shown in patients with T2DM treated with basal insulin in combination with either noninsulin anti hyperglycaemic medicinal product (18% risk reduction) or mealtime insulin (21% risk reduction) during the period from Week 9 to end of study period.

Overall, these effects on hypoglycaemia risk were consistently observed whatever the age, gender, body mass index (BMI) and duration of diabetes (< 10 years and ≥ 10 years) in Toujeo treated patients compared to insulin glargine 100 U/mL treated patients.

In patients with T1DM, the incidence of hypoglycaemia was similar in patients treated with Toujeo compared to insulin glargine 100 U/mL treated patients (Table 11).

Table 11: Summary of the hypoglycaemic episodes of the clinical study in patients with T1DM and T2DM

Diabetic population	T1DM		T2DM		T2DM	
	Patients previously treated with basal insulin		Patients previously treated with basal insulin		Patients previously Insulin naïve or on basal insulin	
Treatment in combination with	Meal time insulin analogue		Meal time insulin analogue +/- metformin		Noninsulin anti hyperglycaemic medicinal products	
	Toujeo	IGlar	Toujeo	IGlar	Toujeo	IGlar
Incidence (%) of severe ^a hypoglycaemia (n/Total N)						
Entire study period ^d	6.6 (18/274)	9.5 (26/275)	5.0 (20/404)	5.7 (23/402)	1.0 (8/838)	1.2 (10/844)
	RR*: 0.69 [0.39;1.23]		RR: 0.87 [0.48;1.55]		RR: 0.82 [0.33;2.00]	
Incidence (%) of confirmed ^b hypoglycaemia (n/Total N)						
Entire study period	93.1 (255/274)	93.5 (257/275)	81.9 (331/404)	87.8 (353/402)	57.6 (483/838)	64.5 (544/844)
	RR: 1.00 [0.95;1.04]		RR: 0.93 [0.88; 0.99]		RR: 0.89 [0.83; 0.96]	
Incidence (%) of confirmed nocturnal ^c hypoglycaemia (n/Total N)						
From Week 9 to end of study period	59.3 (262/273)	56.0 (153/273)	36.1 (146/404)	46.0 (184/400)	18.4 (154/835)	22.5 (188/835)
	RR: 1.06 [0.92;1.23]		RR: 0.79 [0.67;0.93]		RR: 0.82 [0.68;0.99]	

IGlar: Insulin glargine 100 U/mL ^a Severe hypoglycaemia: Episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. ^b Confirmed hypoglycaemia: Any severe hypoglycaemia and/or hypoglycaemia confirmed by plasma glucose value \leq 3.9 mmol/L. ^c Nocturnal hypoglycaemia: Episode that occurred between 00:00 and 05:59 hours ^d 6 month treatment period *RR: estimated risk ratio; [95% CI]

The FDA PI does not seem to have any information about hypoglycaemia under “Clinical Studies”. The following information is provided under “Adverse Reactions”.

Hypoglycaemia

Hypoglycaemia is the most commonly observed adverse reaction in patients using insulin, including Toujeo. In the Toujeo program, severe hypoglycaemia was defined as an event requiring assistance of another person to administer a resuscitative action and documented symptomatic hypoglycaemia was defined as an event with typical symptoms of hypoglycaemia accompanied by a SMPG value equal to or less than 54 mg/dL.

The incidence of severe hypoglycaemia in patients with T1DM receiving Toujeo as part of a multiple daily injection regimen was 6.6% at 26 weeks. The incidence of documented symptomatic hypoglycaemia was 69% at 26 weeks. There were no clinically important differences in hypoglycaemia between Toujeo and Lantus among T1DM patients.

The incidence of severe hypoglycaemia in patients with T2DM was 5% at 26 weeks in patients receiving Toujeo as part of a multiple daily injection regimen, and 1.0% and 0.9% respectively at 26 weeks in the 2 studies where patients received Toujeo as part of a basal insulin only regimen. The incidence of documented symptomatic hypoglycaemia in patients with T2DM receiving Toujeo ranged from 8% to 37% at 26 weeks and the highest risk was again seen in patients receiving Toujeo as part of a multiple daily injection regimen.

(In the EMA SmPC hypoglycaemia is listed in the table of adverse reactions, but is not otherwise mentioned.)

Flexible dosing

Given the weaknesses in this evidence (for example, the studies were only for 3 months, there was no formal statistical power calculation, the sample sizes were relatively small, they were only in T2DM patients who took an evening dose, there was no comparison to U100, there was no comparison to other basal insulins), the information in the proposed Australian PI (2 paragraphs and a table) is arguably unhelpful to prescribers. One reasonable option is that it is omitted because prescribers already know that some flexibility in timing of the dose is acceptable for all basal insulins.

The section in the draft EMA SmPC is:

Flexibility in dosing time

The safety and efficacy of Toujeo administered with a fixed or flexible dosing time were also evaluated in 2 randomised, open label clinical studies for 3 months. T2DM patients (n = 194) received Toujeo once daily in the evening, either at the same time of the day (fixed time of administration) or within 3 hours before or after the usual time of administration (flexible dosing time). Administration with a flexible dosing time had no effect on glycaemic control and the incidence of hypoglycaemia.

The FDA PI does not seem to contain any information about flexible dosing (sponsor to confirm).

Conditions of registration

Implement the European Risk Management Plan (Version 4.1, dated 14 November 2014), as qualified by the Australian Specific Annex (Version 1.3, dated December 2014).

Notify the TGA of the results of any relevant studies as soon as they become available.

Proposed action

The Delegate has no reason to say, at this time, that the application for Toujeo should not be approved for registration.

Request for ACPM advice

1. Information about reduced risk of hypoglycaemia in the Clinical Trials section of the PI

The sponsor's proposed PI has 6 paragraphs on the claim of less hypoglycaemia and a large table that includes the various safety analyses using multiple (standard) definitions of hypoglycaemia (for example, severe, documented, symptomatic, asymptomatic, probable, et cetera), periods (0 to 6 months, 2 to 6 months, 0 to 2 months), time (nocturnal, any, daytime, et cetera), analysis method (at least one, number of episodes, episode rate). These safety results provide reassurance that Toujeo does not increase the risk of hypoglycaemia (in spite of the need for an increased dose; on average: 10% to 18%). However, any claim of reduced hypoglycaemia must rest on the main secondary

efficacy endpoint: at least one episode of severe or confirmed nocturnal hypoglycaemia between 9 weeks and 6 months

The sponsor has argued that the caveat of “evening dose” should be omitted from the information on T2D because of the flat and prolonged PK profile of Toujeo. However, the EMA guidelines for diabetes products (adopted by the TGA) require that claims in the PI are supported by clinical endpoint studies, in addition to supporting data on the PK characteristics.

It seems reasonable to conclude that U300 causes less severe or confirmed nocturnal hypoglycaemia in T2D patients who take an evening dose. It is accepted that for T2D patients who were insulin-naïve, the risk of hypoglycaemia is comparatively low and it can be difficult to show clinically meaningful differences; pooling of the two T2D studies (12347, 11629) where patients were not on mealtime insulin is reasonable.

Therefore, there could be a short statement in the Clinical Trials section along the lines of: “Randomised clinical trials (parenthetical phrase identifying trials) showed that, in T2DM patients, who take their insulin glargine in the evening, Toujeo resulted in less severe or confirmed nocturnal hypoglycaemia than Lantus. There are no randomised data on the risk of hypoglycaemia when Toujeo is given to T2DM patients in the morning. Randomised clinical trials of T1DM patients (parenthetical phrase identifying trials) showed no reduction in the risk of severe or confirmed nocturnal hypoglycaemia with Toujeo versus Lantus. There are no data comparing Toujeo with basal insulins other than Lantus.” (The sponsor could include results from the trials, but must include both the absolute risk difference and relative risk. This should be done ‘in line/in text’ in the paragraph.)

The ACPM is asked to provide advice on the amount of information provided in the Clinical Trials section of the PI about the reduction in hypoglycaemia and whether the claim of reduced severe or confirmed nocturnal hypoglycaemia should be restricted to T2DM patients who take an evening dose. The ACPM is asked to comment on the use of multiple safety endpoints for hypoglycaemia to support a claim of reduced hypoglycaemia.

2. Flexible dosing

Given the weaknesses in this evidence (for example, the studies were only for 3 months, there was no formal statistical power calculation, the sample sizes were relatively small, they were only in T2DM patients who took an evening dose, there was no comparison to U100, there was no comparison to other basal insulins), the information in the proposed Australian PI (2 paragraphs and a table) is arguably unhelpful to prescribers. One reasonable option is that it is omitted because prescribers already know that some flexibility in timing of the dose is acceptable for all basal insulins.

The ACPM is asked to advise on whether a statement about flexible dosing is warranted in the PI.

Response from sponsor

The sponsor agrees with the preliminary assessment of the Delegate that the application is considered approvable and provides the following information in response to the matters outlined in the Delegate’s Overview to assist the Committee with its discussion:

Delegate’s question 1. Information about reduced risk of hypoglycaemia in the Clinical Trials section of the PI

Management of hypoglycaemia in diabetic patients is a key aspect for optimising long term clinical outcomes and a comprehensive evaluation of Lantus versus Toujeo was therefore incorporated into study protocols. This robust approach is reinforced by the (clinical) evaluator in the Clinical Evaluation Report who notes that while hypoglycaemia is always a safety issue with regard to insulin administration, clinicians treating diabetes look upon

the avoidance of hypoglycaemia as an efficacy issue: an effective insulin preparation is one which achieves good glycaemic control with the least possible incidence of hypoglycaemia. The sponsor acknowledges the Delegates reference to the regulatory guidelines in considering information to be included in the PI, however does not consider this precludes providing ready access to a broader set of information on safety aspects that will assist a practicing clinician in optimizing product use. The sponsor has also consolidated the information in the PI to reduce the number of individual paragraphs from the 6 noted by the Delegate in the Overview.

Assessment of hypoglycaemia was included as the first main secondary efficacy endpoint being defined as percentage of patients with at least 1 severe and/or confirmed nocturnal hypoglycaemia (nocturnal: 00:00 to 05:59am; confirmed: SMPG \leq 70 mg/dL, 3.9 mmol/L) reported during Week 9 to Month 6. In addition a thorough hypoglycaemia analysis was pre-specified in the study protocols included in the safety analysis in order to allow a comprehensive assessment of the consistency of the results. These pre specified analyses included:

- Different categories of hypoglycaemia as suggested by the American Diabetes Association (ADA) work group on hypoglycaemia ^{7, 8}
- Analysis of % patients with at least 1 hypoglycaemia
- Hypoglycaemia event rate per patient year exposure
- Assessment during different time periods such as the entire study period; the first 8 weeks of study treatment; Week 9 to Month 6 as well as the distribution of the hypoglycaemia events over the 24 hour period.

In considering assessments over different time periods, the early experience of managing hypoglycaemia when initiating insulin therapy or switching insulins is important from a clinical practice perspective. Enabling patients to gain confidence with managing their diabetes helps to ensure optimal clinical outcomes can be achieved. This is especially important for older patients who are at higher risk of T2DM.

Whilst it is correct that in the 3 studies in T2DM, Toujeo and Lantus were injected in the evening, as shown in patients with T1DM in Study EFC12456 including randomisation of patients to morning and evening injections of Toujeo and Lantus, morning and evening injection of Toujeo show similar efficacy and safety. These results are fully in line with the PK/PD studies, showing an even distribution of the glucose lowering activity over 24 hours and beyond. Considering the available clinical study and PK/PD data, the efficacy and safety results, including the risk of hypoglycaemia obtained with once daily evening injection of Toujeo and Lantus justify extrapolation to any regular injection time of the day. Restricting statements in the PI to T2DM patients taking an evening dose is therefore not considered warranted.

Overall, based on the multiple safety assessments completed, the sponsor considers that inclusion of comprehensive information in the PI relating to hypoglycaemic episodes is important for prescribers and will help to guide optimal use to ensure quality use of medicines.

Delegate's question 2. Flexible dosing

The sponsor acknowledges the Delegate's comments and has significantly revised this section of the PI by simplifying the text and removing the table to align with the information included in the EU SmPC as noted in the Overview. Providing a "window" with

⁷ American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes. *Diabetes Care* 2005;28:1245-1249

⁸Seaquist ER, et al. Hypoglycemia in diabetes. A report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384-1395

a defined timeframe for flexible dosing is considered relevant and important information for prescribers and patients; this window drives quality use of medicines and enhances patient compliance to optimise clinical outcomes.

The supporting data based on the results of the 2 independent sub studies investigating the occasional injection of Toujeo up to 3 hours earlier or later than the regular once daily injection time, show similar efficacy as fixed injection intervals every 24 hours and without more hypoglycaemia events in patients receiving Toujeo in combination with short acting (mealtime) insulin or in combination with oral anti-hyperglycaemic drugs.

Although the sub-study populations were limited in sample size ($n = 106$, $n = 78$), they cover the full spectrum of insulin treatment regimens as they include both patients treated with basal and mealtime insulin, and patients receiving basal insulin in combination with oral anti-diabetic medications. The demographic characteristics were comparable to those of the main study populations. In both injection groups, most patients were compliant to the assigned flexible or fixed dosing interval regimens. All analyses were pre-specified in the substudy protocols. The results can therefore be considered representative of the patient population on insulin treatment and hence support inclusion of the revised statement about flexible dosing in the PI.

Open shelf life

The Delegate has requested the sponsor to advise on the proposed open shelf life of 42 days versus 28 days recommended by the evaluator and notes that Lantus includes a shelf life of 28 days being the historically maximum open shelf life period approved for an injectable multi dose medicine.

The sponsor had requested an open shelf life of 42 days based on the available in use simulation stability test data, including sterility and preservative efficacy testing that confirmed the product remained sterile and all critical quality attributes remained within specification at the end of the 42 days. The medical rationale for supporting a 42 day in use period was to reflect real world clinical practice. In particular the sponsor notes that in the management of diabetes, healthcare professionals including diabetic educators routinely recommend to patients that they use more than 1 pen in parallel (for example, keep 1 at home and another at work). This practice ensures an accessible supply of insulin which is medically critical in order to avoid the significant risks and serious long term clinical sequelae of poor management of insulin levels. As a consequence each individual pen is in use for a longer period than 28 days.

This evaluator had noted that regardless of the supporting data available, risks from microbiological contamination do not support an open shelf life longer than 28 days, in the absence of a compelling clinical rationale and provided feedback that interchanging Toujeo and Lantus could potentially be utilised by patients for parallel use of multiple pens to avoid wastage. However given the 2 presentations are not bioequivalent, and the potential for SAEs resulting from this practice, this was not considered appropriate or relevant by the sponsor. In addition the EU RMP (version 4.4) was specifically updated to include switching between 100 U/mL and 300 U/mL without dose adjustment as an important potential risk. This is reflected in the updated Australian Specific Annex included as part of the pre ACPM response.

The sponsor considers that the simulated in use studies conducted following long term storage of both assembled pens and individual cartridges under 'home use' conditions, with product withdrawn daily under non sterile conditions, with and without further protection of the pen, provide a robust assessment of the risk for microbial contamination over the in use period.

- In use stability studies for assembled pen injectors following 12 months of long term storage at various temperatures confirm that after 4, 5, 6 and 8 weeks of use, critical

quality attributes are all within the acceptance criteria and support a 42 day in use period at 30°C. Specifically:

- Sterility testing performed up to 6 weeks after in use simulation confirms the product remains sterile over the full 42 day period
- Preservative concentrations remained at levels confirmed to be effective over the full 42 day period of in use testing

Additional in use stability testing carried out on cartridges stored separately for 20 months and then to assembled into the pen injector just prior to each testing, confirmed that after 4, 5 and 6 weeks of use, the critical quality attributes all remained within the acceptance criteria and support a 42 day in use period at 30°C. Importantly, cartridges stored in this way during stability testing represented a higher contamination risk than when protected by the proposed commercial pen configuration where the cartridge remained in the pen assembly, and the product tested remained sterile over the entire 42 day period during which use was simulated. Similarly preservative efficacy levels were also maintained over this in use test period providing further confidence that in the commercial presentation, the cartridges are permanently integrated into the proposed pen.

In summary, the critical quality attributes over the in use period have been thoroughly evaluated during in use stability testing after long term storage of both assembled pens and cartridges. The microbiological safety of the proposed product out to a 42 day open shelf life has been demonstrated by maintenance of sterility and preservative efficacy over the in use period, and is required to meet the practical daily needs of diabetes patients to ensure optimal clinical outcomes. The sponsor therefore considers the scientific evidence supports approval of a 42 day open shelf life for Toujeo.

Risk management plan

As part of finalisation of evaluation in the EU, an updated EU-RMP version 4.4 dated 6 February 2015 has been made available and is included as part of the pre ACPM response. The Australian Specific Annex (v1.4) has been revised to align with the EU-RMP and the statements relating to the RMP as part of the conditions of registration will therefore need to reflect the updated document versions.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Toujeo Solostar [and multiple trade names] presented in a 1.5 mL prefilled injector containing 300 U/mL of insulin glargine, to have an overall positive benefit risk profile for the indication;

Toujeo (U300) is indicated for the treatment of diabetes mellitus in adults.

In making this recommendation the ACPM noted that:

- on average, Toujeo requires a higher dose than Lantus (10% to 18%);
- the claimed severe/confirmed nocturnal hypoglycaemic advantage was only in a subgroup of the target population (T2DM, evening dose);
- the evidence presented in the sponsor's dossier did not include paediatric data.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI and CMI amendments

The ACPM advised on the proposed amendments to the PI and CMI in the answers to the specific questions below.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Information about reduced risk of hypoglycaemia in the Clinical Trials section of the PI*

The sponsor's proposed PI has 6 paragraphs on the claim of less hypoglycaemia and a large table that includes the various safety analyses using multiple (standard) definitions of hypoglycaemia (for example, severe, documented, symptomatic, asymptomatic, probable, et cetera), periods (0 to 6 months, 2 to 6 months, 0 to 2 months), time (nocturnal, any, daytime, et cetera), analysis method (at least 1, number of episodes, episode rate). These safety results provide reassurance that Toujeo does not increase the risk of hypoglycaemia (in spite of the need for an increased dose; on average: 10% to 18%). However, any claim of reduced hypoglycaemia must rest on the main secondary efficacy endpoint: at least 1 episode of severe or confirmed nocturnal hypoglycaemia between 9 weeks and 6 months.

The sponsor has argued that the caveat of "evening dose" should be omitted from the information on T2DM because of the flat and prolonged PK profile of Toujeo. However, the EMA guidelines for diabetes products (adopted by the TGA) require that claims in the PI are supported by clinical endpoint studies, in addition to supporting data on the PK characteristics.

It seems reasonable to conclude that U300 causes less severe or confirmed nocturnal hypoglycaemia in T2DM patients who take an evening dose. It is accepted that for T20 patients who were insulin naïve, the risk of hypoglycaemia is comparatively low and it can be difficult to show clinically meaningful differences; pooling of the 2 T2DM studies (12347, 111629) where patients were not on mealtime insulin is reasonable.

Therefore, there could be a short statement in the Clinical Trials section along the lines of: "Randomised clinical trials (parenthetical phrase identifying trials) showed that, in T2DM patients, who take their insulin glargine in the evening, Toujeo resulted in less severe or confirmed nocturnal hypoglycaemia than Lantus. There are no randomised data on the risk of hypoglycaemia when Toujeo is given to T2DM patients in the morning. A randomised clinical trial of T1DM patients (parenthetical phrase identifying trial) showed no reduction in the risk of severe or confirmed nocturnal hypoglycaemia with Toujeo versus Lantus. There are no data comparing Toujeo with basal insulins other than Lantus." (The sponsor could include results from the trials, but must include both the absolute risk difference and relative risk. This should be done "in line/in text" in the paragraph.)

The ACPM is asked to provide advice on the amount of information provided in the Clinical Trials section of the PI about the reduction in hypoglycaemia and whether the claim of reduced severe or confirmed nocturnal hypoglycaemia should be restricted to T2DM patients who take an evening dose.

The ACPM was concerned at the slant of the sponsor's proposed statements on the data concerning hypoglycaemia. For T2DM, the ACPM accepted the claim of lower rates of hypoglycaemia (pre-specified main secondary efficacy endpoint of severe/confirmed nocturnal hypoglycaemia) for U300 versus U100, when taken in the evening. For T1DM, the ACPM noted that on the pre-specified main secondary efficacy endpoint of nocturnal hypoglycaemia, the point estimate favoured lower rates of severe/confirmed nocturnal

hypoglycaemia for U100 although the CI crossed the null value. The ACPM advised that it was not appropriate to list series of different hypoglycaemia endpoints as in Table 3 of the proposed PI; especially for T1DM, but also for T2DM.

2. Flexible dosing

Given the weaknesses in this evidence (for example, the studies were only for 3 months, there was no formal statistical power calculation, the sample sizes were relatively small, they were only in T2DM patients who took an evening dose, there was no comparison to U100, there was no comparison to other basal insulins), the information in the proposed Australian PI (2 paragraphs and a table) is arguably unhelpful to prescribers. One reasonable option is that this information is omitted because prescribers already know that some flexibility in timing of the dose is acceptable for all basal insulins

The ACPM is asked to advise on whether a statement about flexible dosing is warranted in the PI.

The ACPM advised that the timing of the dosing for all basal insulins can be occasionally varied without the patient coming to any harm; however, the ACPM also agreed with the clinical evaluator that the quality of evidence for flexible dosing for U300 was poor.

The ACPM advised that the finding supporting flexibility of dosage timing by plus 3 hours is only supported for T2DM patients, in whom it was shown. It should not be assumed that this tolerance would extend to use in T1DM.

3. The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application.

In reference to the proposed open shelf life of the product, the ACPM was concerned that if a 42 day open shelf life for Toujeo was accepted, then this could cause confusion among diabetes educators and patients because a standard open shelf life of 28 days applied to all the other insulin products. The ACPM noted that a 42 day open shelf life for this product had not been accepted by the EMA and advised that the open shelf life should be 28 days.

The ACPM expressed concern at the possibility of dosing errors with this proposed U300 presentation compared to all other insulins of U100. The pen presentation mitigated this risk; however, the ACPM advised that approval should be only for the pen device and that if a vial was proposed for approval, then this should be brought back to ACPM for clinical advice as a new registration.

Outcome

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

- Toujeo insulin glargine 300 U/mL solution for injection injector pen
- Edomlul insulin glargine 300 U/mL solution for injection injector pen
- Lambeto insulin glargine 300 U/mL solution for injection injector pen

The approved indication for these therapeutic goods is:

Treatment of diabetes mellitus in adults

Specific conditions of registration applying to these goods

- The insulin glargine (Toujeo/Edomlul/Lambeto) EU Risk Management Plan (RMP), Version 4.5, dated 31 March 2015, as qualified by the Australian Specific Annex, Version 1.5, dated June 2015, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

- Notify the TGA of the results of any relevant studies as soon as they become available.
- As a minimum, the first 5 independent batches of Toujeo/Endomlul/Lambeto insulin glargine 300 U/mL solutions for injection injector pen imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

The sponsor should supply:

1. Certificates of Analysis of all active ingredient (drug substance) and final product.
2. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
3. Evidence of the maintenance of registered storage conditions during transport to Australia.
4. 5 vials of each batch for testing by the Therapeutic Goods Administration Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Samples and data should be forwarded to the Biochemistry Section, Laboratories Branch before release of each batch and with sufficient lead time to allow for Laboratories Branch testing.

This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition to remain in place until the sponsor is notified in writing of any variation.

Attachment 1. Product Information

The PI for Toujeo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>. The PIs for Endomlul and Lambeto are identical except for the product name.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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