



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for insulin degludec (rys)/insulin aspart (rys)

Proprietary Product Name: Ryzodeg 70/30 FlexTouch,
Ryzodeg 70/30 Penfill

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

May 2018

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

- 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
ACM	Advisory Committee on Medicines
ASA	Australian Specific Annex
$AUC_{0-6\text{ h}}$	Area under the drug concentration time curve from time zero to 6 hours
$AUC_{0-\text{inf}}$	Area under the drug concentration time curve from time zero to infinity
$AUC_{0-24\text{ h}}$	Area under the drug concentration time curve from time zero to 24 hours
$AUC_{(\text{IAsp } 0-12\text{ h})}$	Area under the IAsp concentration time curve from time 0 to 12 hours
$AUC_{(\text{IAsp } 0-2\text{ h})}$	Area under the IAsp concentration time curve from time 0 to 2 hours
$AUC_{(\text{IAsp } 0-6\text{ h})}$	Area under the IAsp concentration time curve from time 0 to 6 hours
$AUC_{\text{IDeg},\text{t},\text{ss}}$	Area under the drug concentration time curve for IDeg during 1 dosing interval at steady state
BIAsp	biphasic insulin aspart
BGL	Blood glucose level
C_{max}	Maximum serum concentration
$C_{\text{max,IAsp}}$	Maximum serum IAsp concentration
$C_{\text{max,IDeg ss}}$	Maximum serum IDeg concentration at steady state
CMI	Consumer Medicine Information
CPD	Certified Product Details
CV	Cardiovascular
DLP	Data lock point
EAC	Event Adjudication Committee
EMA	European Medicines Agency
EU	European Union

Abbreviation	Meaning
FDA	Food and Drug Administration (US)
FDC	Fixed dose combination
GIR	Glucose infusion rate
GIR _{max}	Maximum glucose infusion rate
GLP	Good Laboratory Practice
GLP-1	Glucagon like peptide-1 (agonist)
HbA1c	Glycated haemoglobin
IAsp	Insulin aspart
ICH	International Conference on Harmonisation
IDeg	Insulin degludec
IDegAsp	Insulin degludec and insulin aspart mixture
IGlar	Insulin glargine
ISS	Integrated Safety Summary
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
NPH	Neutral protamine Hagedorn (insulin)
PBRER	Periodic Benefit-Risk Evaluation Report
PI	Product Information
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SC	Subcutaneous
SGLT-2	Sodium-glucose cotransporter 2 (inhibitor)
SOC	System Organ Class
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

Abbreviation	Meaning
$t_{\max, IAsp}$	Time to peak serum concentration of IAsp
US	United States

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	24 November 2017
<i>Date of entry onto ARTG</i>	29 November 2017
<i>Active ingredients:</i>	Insulin degludec (70%); Insulin aspart (30%)
<i>Product names:</i>	Ryzodeg 70/30 FlexTouch; Ryzodeg 70/30 Penfill
<i>Sponsor's name and address:</i>	Novo Nordisk Pharmaceutical Pty Ltd PO Box 7586, Baulkham Hills, NSW, 2153
<i>Dose form:</i>	Solution for injection
<i>Strength:</i>	100 U/mL
<i>Container:</i>	Multidose cartridge
<i>Pack sizes:</i>	Ryzodeg 70/30 FlexTouch: Packs of 1 and 5 cartridge(s) Ryzodeg 70/30 Penfill: Pack of 1 cartridge
<i>Approved therapeutic use:</i>	<i>To improve glycaemic control in adult patients with diabetes mellitus requiring basal and prandial insulin.</i>
<i>Route of administration:</i>	Subcutaneous (SC) injection
<i>Dosage:</i>	Dosage is individualised according to patient need, related to patient's glycaemic control. See the Product Information (PI) for further details.
<i>ARTG numbers:</i>	Ryzodeg 70/30 FlexTouch: 280432 Ryzodeg 70/30 Penfill: 280433

Product background

This AusPAR describes the application by the sponsor to register Ryzodeg 70/30 FlexTouch and Ryzodeg 70/30 Penfill containing 70% insulin degludec (rys) and 30% insulin aspart (rys) solution for injection in the proposed dosage forms and strengths shown in Table 1 (below) for the following indication:

To improve glycaemic control in adult patients with diabetes mellitus requiring basal and prandial insulin.

Table 1: Proposed dosage forms/strengths

Active ingredients	Trade name	Dosage forms/strengths
70% Insulin degludec (rys)	Ryzodeg 70/30 FlexTouch	FlexTouch 100 U/mL, 3 mL solution for injection in prefilled pen
30% Insulin aspart (rys)	Ryzodeg 70/30 Penfill	Penfill 100 U/mL, 3 mL solution for injection in cartridge

Diabetes mellitus

Diabetes mellitus is associated with chronic hyperglycaemia due to either inadequate insulin production, insulin resistance or a combination of the two. Long term ocular, peripheral nervous system, renal and arterial damage can result.

There are predominantly 2 types of diabetes:

- Type 1: immune mediated pancreatic cell destruction results in insulin deficiency. Type 1 diabetes mellitus (T1DM) most commonly develops in childhood.
- Type 2: a combination of gradual insulin resistance and failure of the pancreas to produce sufficient insulin. Type 2 diabetes mellitus (T2DM) most commonly develops in adulthood.

In Australia, the estimated prevalence of adults with diabetes (both T1DM and T2DM) in 2011 to 2012 was 5.4% and in 2013, over 6000 children (aged 0 to 14 years) were estimated to have T1DM.¹ T2DM is by far the most common type of diabetes; an estimated 849,000 adults (4.7%) reported that they have T2DM in 2011 to 2012, although this is thought to be an underestimate. It is estimated that in 2011, 36,263 Australians started using insulin to treat T2DM (164 people per 100,000 population) and the incidence of insulin use for T2DM increases with age; it is estimated that there is a 5 fold increase in the use of insulin between the ages of 40 to 44 and 70 to 74 years.²

Current treatment options

Type 1 diabetes mellitus (T1DM)

Insulin is the cornerstone of treatment for T1DM.³ Insulin needs may be considered in terms of:

- Basal insulin, which is the background requirement of insulin and is independent of carbohydrate needs. This is usually administered via long or intermediate acting insulin once or twice a day; and
- Bolus insulin, which includes prandial insulin to cover oral carbohydrate intake and correction doses which are used to manage very high blood glucose levels. This is usually administered with short or very short acting insulin formations.

Type 2 diabetes mellitus (T2DM)

Initial treatment usually starts with addressing lifestyle factors. As per current Therapeutic Guidelines, if glycaemic targets are not met with addressing lifestyle factors, metformin is recommended as first line therapy.³ If glycaemic targets are still not met, current options include a sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor,

¹ Australian Institute of Health and Welfare (AIHW) webpage

² Incidence of insulin treated diabetes in Australia 2000 to 2011, Australian Institute of Health and Welfare Diabetes series number 22, AIHW webpage.

³ Diabetes: management; published November 2013. Melbourne: Therapeutic Guidelines Limited; July 2016.

glucagon like peptide-1 (GLP-1) agonist, sodium/glucose cotransporter-2 (SGLT-2) inhibitor, thiazolidinedione, acarbose or insulin. For patients with T2DM, insulin therapy is generally started as once daily basal insulin treatment; however some patients may require more intensive treatment. Insulin is usually started in combination to an oral hypoglycaemic therapy.

The following insulin formulations are available in Australia, as shown in Table 2.

Table 2: Australian Register of Therapeutic Goods (ARTG) registered basal insulin formulations in Australia

Type	(Relative) Duration of action	Active ingredient	Brand name(s)
Basal	Long acting	detemir	Levemir
		glargine	Lantus, Toujeo, Optisulin
	Intermediate acting	isophane (protamine suspension)	Humulin NPH, Protaphane, Hypurin Isophane

Adapted from Table 5.4 in 'Diabetes: management', Endocrinology, eTG Complete. Additional information from ARTG website (current as of 6 October 2016).

These products represent a new fixed dose combination (FDC) of insulin degludec (IDeg) and insulin aspart (IAsp). The combination of IDeg and IAsp may be referred to as IDegAsp.

IAsp is an active component of NovoRapid and NovoMix which are currently widely used in the treatment of diabetes in Australia.

IDeg is an ultra-long acting insulin proposed for use in diabetes. IDeg differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side chain consisting of glutamic acid and a C16 fatty acid has been attached. IDeg is produced by recombinant DNA technology using *Saccharomyces secrevisiae*.

IDegAsp has advantages over other premixed insulins in that it offers 24 hour basal coverage, has less late post prandial and nocturnal hypoglycaemia (but perhaps more earlier post prandial hypoglycaemia) and is soluble.

Other premixed FDC products approved in Australia are shown in Table 3 below.

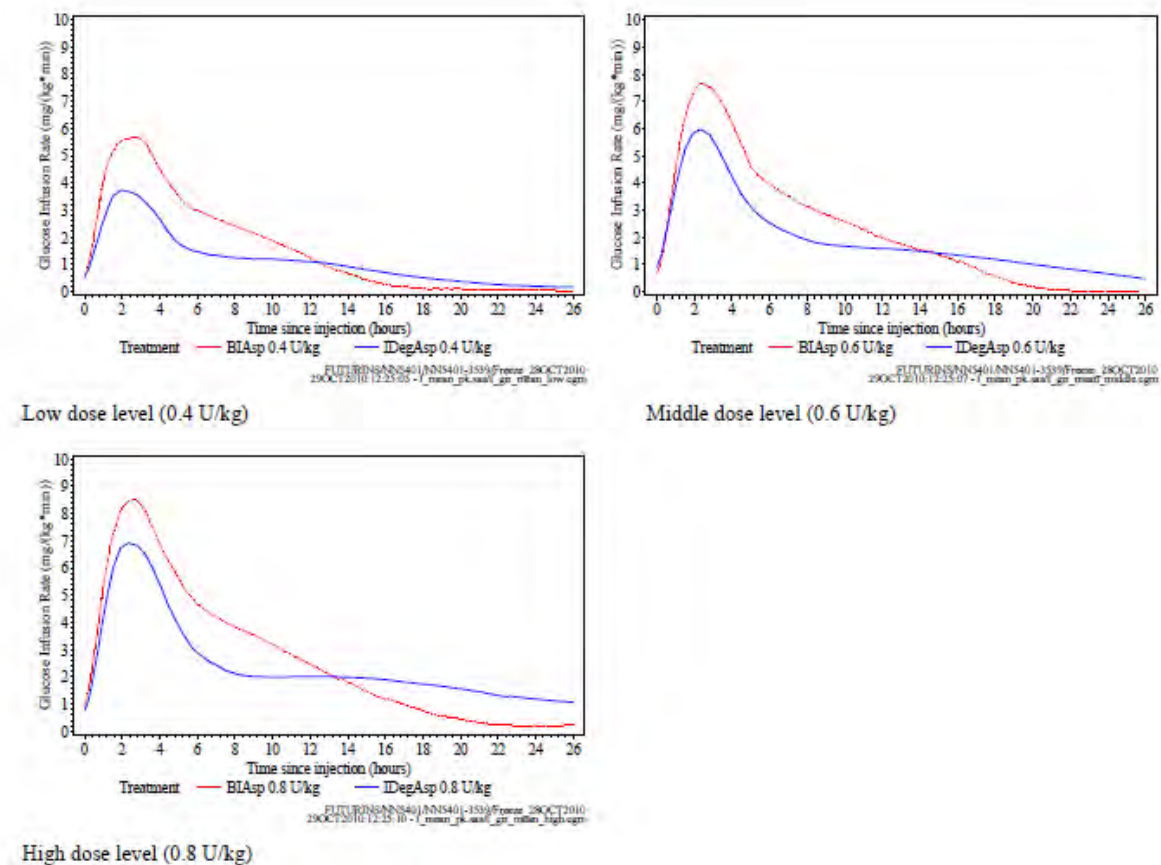
Table 3: Other pre-mixed insulins approved in Australia

Trade name	Components/active ingredients	Comments
NovoMix 30	Insulin aspart 30%/insulin aspart protamine 70%	Analogue
Humalog Mix 25	Lispro 25%/lispro protamine 75%	Analogue
Humalog Mix 50	Lispro 50%/lispro protamine 50%	Analogue
Mixtard 30/70 Humulin 30/70	Neutral 30%/isophane 70%	Human insulin

Trade name	Components/active ingredients	Comments
Mixtard 50/50	Neutral 50%/isophane 50%	Human insulin

Compared to NovoMix 30 (a FDC of 30% IAsp and 70% IAsp protamine), IDegAsp has lower and shorter post prandial insulin action and longer duration of action as shown in Figure 1, below.

Figure 1: Glucose infusion rate, mean smoothed profiles by dose level for IDegAsp and NovoMix (BiAsp) 30 after single dose



Regulatory status

Regulatory history

An application to register IDegAsp was previously submitted to the TGA in 2012. During the course of the evaluation, safety concerns regarding the cardiovascular (CV) risk of IDeg were identified by the United States (US) Food and Drug Administration (FDA). A meta-analysis identified that the use of IDeg could increase the risk of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, and unstable angina compared to comparators by up to 10%.

A meeting between the TGA and sponsor was held in September 2013 and the sponsor's application was subsequently withdrawn.

In relation to the current resubmission, a pre-submission meeting was held with the sponsor in June 2016. The TGA agreed to an abridged application based on interim results of the CV study and synopsis of other studies that had been submitted between the

original and subsequent evaluation. The sponsor had not proposed to include any information in the product information (PI) from the interim results of the CV safety study or other synopsis of clinical studies.

Overseas regulatory history

Ryzodeg was approved in the European Union (EU) by the European Medicines Agency (EMA) in 2013. The EMA was aware of the same data which raise concerns in the US, but considered that the low number of events, lack of confirmatory evidence from non-clinical data and limitations of post-hoc analysis meant that this data did not negate the otherwise positive risk-benefit analysis. IDeg has also been approved by Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. In the US, the initial application was in September 2011. The application was resubmitted in March 2015 and approved in September 2015.

IDegAsp has been approved in more than 55 countries and marketed in 5 countries (Denmark, Switzerland, India, Bangladesh and Mexico). The sponsor had proposed to resubmit an application for insulin degludec in Canada in 2016.

Similar submissions

A concurrent submission from the same sponsor for IDeg as a standalone product (Tresiba FlexTouch (prefilled pen) and Tresiba Penfill (cartridge)) was also under consideration by the TGA. As the IAsp component of Ryzodeg is currently widely used in the treatment of diabetes in Australia, and IDeg represents the novel component of this FDC, the Tresiba submission is also relevant to this submission. Further information can be found in the AusPAR for Tresiba on the TGA website.⁴

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. Registration timeline

Table 4: Registration timeline for Submission PM-2016-02723-1-5

Description	Date
Submission dossier accepted and 1st round evaluation commenced	31 October 2016
First round evaluation completed	7 April 2017
Sponsor provides responses on questions raised in first round evaluation	8 June 2017
Second round evaluation completed	7 July 2017

⁴ AusPAR for Tresiba FlexTouch/Tresiba Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2015-02721-1-5

Description	Date
Request for Advisory Committee advice and/or Delegate's Overview	30 August 2017
Sponsor's response to Delegate's Overview	20 September 2017
Advisory Committee meeting	5 and 6 October 2017
Registration decision	24 November 2017
Entry onto ARTG	29 November 2017
Number of TGA working days from commencement of evaluation to registration decision*	228

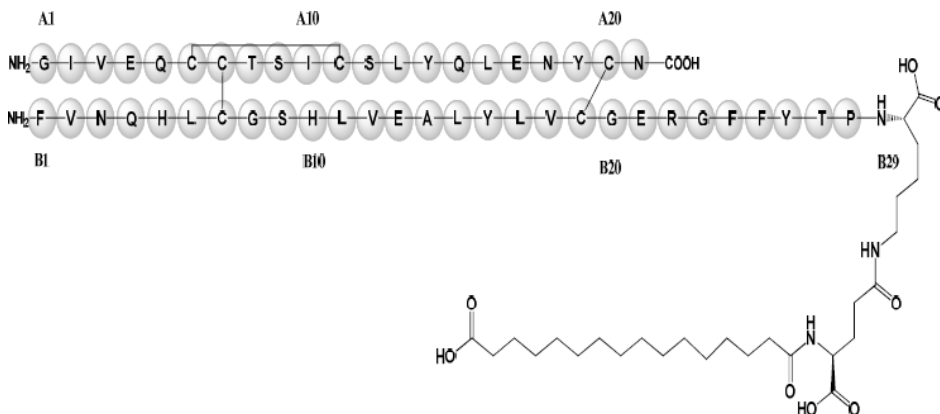
*Statutory timeframe: 255 working days.

III. Quality findings

Drug substance (active ingredient)

The drug structure of IDeg, the novel component of Ryzodeg, is shown in Figure 2, below. The molecular formula is $C_{274}H_{411}N_{65}O_{81}S_6$.

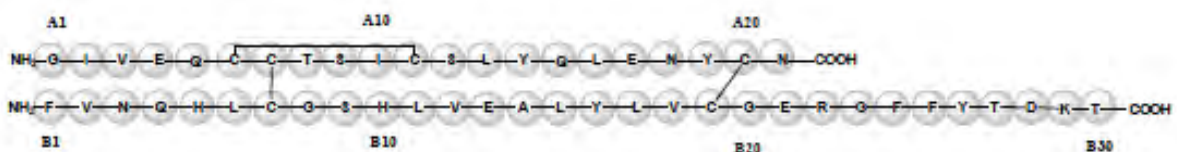
Figure 2: Insulin degludec (IDeg) structure



IDeg is an analogue of human insulin where threonine in position B30 has been omitted and where the ϵ -amino group of lysine B29 has been coupled with hexadecanedioic acid via a γ -glutamic acid spacer. IDeg is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification.

The drug structure of insulin aspart is shown in Figure 3, below.

Figure 3: Insulin aspart (IAsp) structure



IAsp (B28Asp human insulin) is a rapid acting prandial insulin, in which the amino acid proline in the β -chain of human insulin has been replaced by aspartic acid. IAsp is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification.

Drug product

The primary packaging is a Penfill 3 mL cartridge. The Penfill 3 mL cartridge can be assembled into a pre-filled disposable device, a PDS290 pen injector (FlexTouch). The PDS290 device is already approved for use with NovoRapid. The Penfill 3 mL cartridge is approved for use in other insulin products made by the same sponsor. It consists of Type I glass, with a plunger (halobutyl) and a stopper (halobutyl/isoprene). These materials have all been previously evaluated and found to be satisfactory.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The product is not photostable. However, the secondary packaging provides adequate protection.

The proposed shelf life is 30 months when stored at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. This is supported by adequate stability data.

In use stability data covering storage at 24 months at 2 to 8°C then 4 weeks at 30°C have also been submitted. The proposed shelf life and storage conditions for the opened product are 28 days when stored below 30°C or at 2 to 8°C .

Maximum temperature and duration of temperature excursion: Stability studies have been conducted in accordance with relevant International Conference on Harmonisation (ICH) guidelines.

Test samples of IDeg 100 U/mL, IDeg 200 U/mL and IDegAsp 100 U/mL drug products were tested in a temperature cycle study simulating temperature excursions outside 2 to 8°C during transportation and storage permitted by the sponsor. Test samples were exposed to all permitted excursions and subsequently test samples were placed for storage in a long term stability study at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ until end of shelf life.

Biopharmaceutics

The pharmacokinetic data for IDegAsp was evaluated in the previous withdrawn submission. The current dossier contained a synopsis for 1 additional pharmacokinetic/pharmacodynamic trial (Study NN5401-1979) as discussed below.

Pharmacokinetics in the target population

Study NN5401-1979

Study NN5401-1979 was a single centre, open label, multiple dose study to assess the pharmacodynamic and pharmacokinetic properties of IDegAsp (at steady state) in 22 adult subjects with T1DM.

All subjects received a fixed subcutaneous (SC) dose of IDeg (0.42 U/kg body weight) daily for 5 consecutive days (plus IAsp as bolus insulin as needed, dosage not specified) to achieve steady state for IDeg followed by a single fixed SC dose of IDegAsp (0.6 U/kg body weight, corresponding to 0.42 U/kg IDeg and 0.18 U/kg IAsp) on Day 6.

Pharmacokinetic properties were evaluated for 120 hours.

The mean total serum exposure of IDeg in IDegAsp at steady state during 1 dosing interval (area under the drug concentration time curve for IDeg during 1 dosing interval at steady state ($AUC_{IDeg,\tau,ss}$)) was 72084 pmol.h/L and the mean maximal concentration of IDeg at steady state ($C_{max,IDeg,ss}$) was 3938 pmol/L. Mean total serum exposure of IAsp in IDegAsp (area under the drug concentration time curve for IAsp from time 0 to 12 hours ($AUC_{IAsp,0-12h}$)) was 1087 pmol.h/L and mean maximal IAsp concentration ($C_{max,IAsp}$) was 326 pmol/L, with a median time to peak serum concentration of IAsp ($t_{max,IAsp}$) of 1.3 hours.

On visual inspection, the IAsp component of IDegAsp had a fast onset of appearance and a peak covering the prandial phase, whilst IDeg had a flat and evenly distributed pharmacokinetic profile over 24 hours. The mean ratio between $AUC_{IDeg,0-12h,SS}$ and $AUC_{IDeg,\tau,SS}$ was 0.51 indicating that exposure to IDeg in IDegAsp was similar for the first 12 hours compared to the following 12 hours of one dosing interval at steady state.

Biopharmaceutical evaluator's comments

The pharmacokinetics of IDeg at steady state in subjects with T1DM was determined in Studies NN5401-1991 and NN5401-1993 in the original withdrawn submission. The clinical evaluator for that submission noted IDeg exposure was similar for the first 12 hours compared to the following 12 hours of 1 dosing interval; the above results are consistent with these findings. However, as the half-life of IDeg is 25 hours, the pharmacokinetic parameters of the IDeg component of the IDegAsp would have been influenced by previous dosing of IDeg.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Ryzodeg FlexTouch and Ryzodeg Penfill 100 U/mL (insulin degludec (rys)/insulin aspart (rys)).

Recommended shelf life

30 months at 2 to 8°C. Store below 30°C or in the refrigerator between 2°C to 8°C for up to 28 days. Any remainder must then be discarded.

Proposed conditions of registration for the Delegate

Batch release testing and compliance with Certified Product Details (CPD)

It is a condition of registration that all batches of:

- Ryzodeg FlexTouch 100 U/mL (insulin degludec (rys)/insulin aspart (rys))
- Ryzodeg Penfill 100 U/mL (insulin degludec (rys)/insulin aspart (rys))

imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

It is a condition of registration that each batch of:

- Ryzodeg FlexTouch 100 U/mL (insulin degludec (rys)/insulin aspart (rys))
- Ryzodeg Penfill 100 U/mL (insulin degludec (rys)/insulin aspart (rys))

imported into/manufactured in Australia is 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 must supply:

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

IV. Nonclinical findings

Introduction

The submitted nonclinical dossier was in general accordance with the recommendations in the EU Guideline on the Nonclinical Development of Fixed Combinations of Medicinal Products (EMA/CHMP/SWP/258498/2005). The nonclinical dossier consisted of all nonclinical studies submitted for the registration of IDeg as a new biological entity (Tresiba; made simultaneously to this application) and a number of further studies to support the fixed dose combination.⁴ Only studies directly relevant to the proposed combination are discussed here.

Pharmacology

An additive effect of IDeg and IAsp was demonstrated in lipogenesis assays in rat adipocytes. In vivo in euglycaemic clamp studies in pigs, no interference in pharmacodynamic (or pharmacokinetic) profiles was found for a 1:8 or 1:1 combination of IAsp/IDeg when formulated with 6 Zn²⁺/6 IDeg (that is, the clinical zinc ratio). Significant interference in pharmacodynamic/ pharmacokinetic profiles was observed though with a 1:8 combination formulated with 3.38 Zn²⁺/6 IDeg. In a euglycaemic clamp study in pigs using the clinical ratio of 70:30 IDeg/IAsp (evaluated in the previous nonclinical report for Tresiba) a biphasic glucose infusion rate profile was found, comprising an early peak corresponding to IAsp and a flat basal action as a result of IDeg. IDeg did not blunt the response to insulin aspart.

Pharmacokinetics

No pharmacokinetic interactions between insulin degludec and insulin aspart were apparent in a series of single dose pharmacokinetic studies conducted in pigs with various dose ratios, strengths and zinc concentrations. These studies were designed to guide formulation development and did not include the final clinical formulation.

Pharmacokinetic data obtained in repeat dose toxicity studies in rats, conducted with the clinical formulation, indicated maintenance of the expected rapid SC absorption of insulin aspart and the more prolonged absorption of insulin degludec with co-formulation. No parallel single agent groups were included in the studies, hindering the assessment of potential pharmacokinetic interactions. Based on comparison with data obtained previously in other studies, there appears to be no effect on IDeg pharmacokinetics but some reduction in the peak exposure to IAsp. A similar finding in humans with the co-formulation is reported in the sponsor's Summary of Clinical Pharmacology Studies (referring to data obtained in Study NN5401-1959).

Toxicology

Two repeat dose toxicity studies with insulin aspart and insulin degludec in combination were submitted; a pilot 4 week study and a pivotal 13 week study in rats. Both were Good Laboratory Practice (GLP) compliant. Species selection and the route of administration (SC) were appropriate, as was the duration of the pivotal study. The clinical dose ratio (7:3 IDeg/IAsp) and vehicle formulation were used in both studies; another formulation of the combination (11:9 dose ratio) was also tested in the pilot study. NPH insulin was used as a comparator in the pivotal study.⁵ Exposure ratios (calculated as animal:human plasma area under the drug concentration time curve from time zero to 24 hours (AUC_{0-24h}) values) achieved in animals treated with 7:3 insulin degludec/insulin aspart are tabulated below. Human reference values relate to a daily dose of 1.08 U/kg, the highest reported mean clinical dose, observed in subjects with T2DM on a twice daily dose regime.

Table 4: Relative exposure in the repeat-dose toxicity studies

Species	Study duration	Dose(nmol/kg/day)		AUC _{0-24h} (nM·h)		Relative exposure	
		IDeg	IAsp	IDeg	IAsp	IDeg	IAsp
Rat (han Wistar)	4 weeks Study 208289	25	10.7	319	1.2	2	0.6
		75	32.1	944	10.9	6	5
		150	64.3	2285	24.3	13	12
	13 weeks Study 208337	25	10.7	494	3.1	3	1.6
		50	21.4	804	13.7	5	7
		75	32.1	1210	25.9	7	13
Human (diabetic patients)		4.54	1.94	170 ^a	2.0 ^a		
		(= 1.08 U/kg/day)					

a) Human AUC values for insulin degludec and insulin aspart have been calculated based on linear extrapolation of mean pharmacokinetic data obtained at 0.8 U/kg doses in clinical Studies NN1250-1993 (insulin degludec) and NN5401-3539 (combination), respectively.

Salient findings included clinical signs of hypoglycaemia (underactive behaviour, partially closed eyes), some changes in clinical chemistry (lower protein levels, as well as reduced blood glucose) and urinalysis (reduced volume with a subsequent darkening in colour and reduced pH), and reduced liver weights. Histopathological findings were limited to injection site reactions; generally mild and similar across all groups (including vehicle controls). No unanticipated toxicities were seen, and the findings are not considered adverse. A no observable adverse effect level of 75/32 nmol/kg/day is established for insulin degludec/insulin aspart in the pivotal combination study, associated with significant multiples of the clinical exposure for each insulin analogue (7 to 13).

Antibodies against both insulins developed in treated rats. This has been seen previously in studies with the individual components, are associated with a human protein

⁵ NPH (neutral protamine Hagedorn) insulin, also known as isophane insulin, is an intermediate acting human insulin.

administered to rats, and are not considered to be predictive of the clinical situation. Anti-drug antibodies were not seen to affect drug exposure.

Reproductive toxicity

Two rat embryofetal development studies with the combination were submitted; a pilot dose ranging study and a main study. Both were GLP compliant, and the pivotal study was appropriately designed and conducted. The clinical formulation and the clinical dose ratio (7:3 IDeg/IASp) were used, and NPH insulin was included as a comparator. Exposure ratios achieved in the animals are tabulated below. The same dose levels were used in both studies.

Table 5: Relative exposure in reproductive toxicity studies

Species	Study	Dose (nmol/kg/day)		AUC _{0-24 h} (nM·h)		Relative exposure	
		IDeg	IASp	IDeg	IASp	IDeg	IASp
Rat (Han Wistar)	Embryofetal development Studies 208333 and 208334	20	8.6	155	0.253	0.9	0.1
		80	34.3	765	21.8	5	11
		125	53.6	1300	47.4	8	24
Human (diabetic patients)		4.54	1.94	170 ^a	2.0 ^a		
		(= 1.08 U/kg/day)					

a) Human AUC values for insulin degludec and insulin aspart have been calculated as described in the preceding table.

Treatment at 125/53.6 nmol/kg/day insulin degludec/insulin aspart was associated with a decrease in mean fetal weight; this was also seen in the NPH insulin comparator group and is likely secondary to maternal hypoglycaemia. No treatment-related increase in fetal abnormalities was observed up to the highest dose tested (relative exposure, 8 to 24).

Pregnancy classification

The sponsor has proposed Pregnancy Category B3.⁶ This is considered appropriate. It is consistent with the finding of decreased fetal weight here and increased fetal abnormalities in rats seen in a study with insulin degludec alone (also see the nonclinical section of the AusPAR for Tresiba).⁴

Local tolerance

SC haemorrhage, inflammation and myofibre degeneration were seen at the injection site of treated rats in the toxicity studies. The incidence and severity were similar across all groups, including the controls, suggesting it is not associated with either insulin per se but likely associated with the vehicle in the clinical formulation and/or the injection procedure itself.

⁶ Australian categorisation system for prescribing medicines in pregnancy: Category B3; Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Nonclinical summary and conclusions

- The nonclinical dossier contained no major deficiencies. Nonclinical data of direct relevance to combination use comprised pharmacology, pharmacokinetic, repeat dose toxicity and embryofetal development studies, with all safety related studies conducted according to GLP.
- Pharmacology and pharmacokinetic data support the use of Ryzodeg as a basal bolus regimen for the treatment of diabetes mellitus. An additive effect of IDeg and IAsp was shown in lipogenesis assays in rat adipocytes. A biphasic glucose infusion rate profile, corresponding to the 2 insulins, was evident in a euglycaemic clamp study with the clinical dose ratio in pigs.
- No unanticipated toxicities were found for the combination in the submitted repeat-dose toxicity and embryofetal developments studies, conducted in rats. All findings were similar to those observed in controls treated with human insulin.
- The clinical formulation was seen to be well tolerated locally in rats.
- The proposed Pregnancy Category B3 is considered appropriate.⁶
- There are no objections on nonclinical grounds to the registration of Ryzodeg for the proposed indication.

V. 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.

Introduction

Clinical rationale

The sponsor's rationale for this new FDC (as stated in the submission cover letter dated 20 September 2016) is that there is: *'a need for an ultra long acting basal insulin which more closely mimics endogenous insulin secretion with low day to day variability of glucose lowering action, to deliver improved glycaemic control with a reduced risk of hypoglycaemia relative to premixed insulin'*.

Guidance

Relevant TGA adopted EMA guidelines are the following:

- Guideline on Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes Mellitus (14 May 2012; CPMP/EWP/1080/00 Rev. 1).
- Reflection Paper on Assessment of Cardiovascular Safety Profile of Medicinal Products (25 February 2016; EMA/CHMP/50549/2015).

Contents of the clinical dossier

The sponsor conducted a pre-submission meeting with the TGA on 20 June 2016, where it was agreed the dossier for IDegAsp would be resubmitted. In view of the previous evaluation, it was decided the dossier would be limited to data from Study EX 1250-4080 (also known as the DEVOTE trial), synopses of studies completed since the previous submission rather than full clinical trial reports, and addressing any outstanding issues from the previous submission.

The new studies comprised of:

- 10 new IDegAsp studies submitted (compared with the original submission) as synopses. These included 7 Phase III trials (including 1 extension part) and 3 clinical pharmacology trials.
- Additional information submitted in December 2016; this was the interim data from the cardiovascular outcomes DEVOTE trial (Study EX1250-4080).

Other key documents included:

- A Periodic Safety Update Report (PSUR)/Periodic Benefit-Risk Evaluation Report (PBRRER) for IDegAsp (dated 1 October 2014 to 30 September 2015).

The following documents were provided:

- An Introduction
- Quality Overall Summaries
- Nonclinical overview for both IDegAsp and IAsp
- Clinical overview for IDegAsp, IDeg and IAsp
- Nonclinical summaries for IDegAsp
- Clinical summaries for IDegAsp and IDeg (including Summary of Clinical Safety addendum, IDegAsp).

Paediatric data

No paediatric data was been submitted; as of 30 September, 2014, 1 paediatric trial was ongoing. No paediatric indication is being sought in Australia. Paediatric data is relevant for this medicine as diabetes also occurs in infants and children.

Good clinical practice

The newly submitted study synopses state the studies were conducted in accordance with the principles of Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

The pharmacokinetic profile of IDegAsp has been determined in the original withdrawn submission. The current dossier contained synopses for 1 additional pharmacodynamic/pharmacokinetic trial (Study NN5401-1979).

Evaluator's conclusions on pharmacokinetics

The pharmacokinetic characteristics of IDegAsp have been established in the original withdrawn submission.

The issue of bioequivalence has been addressed [see Attachment 2 for details]. It is recommended that the PI contain information as to the different pharmacokinetic parameters of IDegAsp compared to the individual components.

Pharmacodynamics

Studies providing pharmacodynamic data

The pharmacodynamic profile of IDegAsp has been described in the original withdrawn submission. The current submission included additional pharmacodynamic data for IDegAsp provided in Study NN5401-1979.

Evaluator's conclusions on pharmacodynamics

The pharmacodynamic effect of IDegAsp was determined in the original withdrawn submission.

The concern raised by the clinical evaluator of the previous submission regarding the effect during the first 2 hours of dosing with IDegAsp compared to separate injections of IDeg and IAsp is discussed in Attachment 2.

Efficacy

Studies providing efficacy data

There were 5 therapeutic confirmatory trials of similar design submitted and evaluated in the original withdrawn submission. The purpose of this evaluation is to address issues identified by the clinical evaluator of this submission, and discuss new data provided with the current submission.

The 5 therapeutic trials evaluated in the previous submission were:

- 1 study conducted in subjects with T1DM (Study NN5401-3594)
- 4 studies in subjects with T2DM who were either insulin naïve (Study NN5401-3590) or insulin treated (Studies NN5401-3592, NN5401-3593, and NN5401-3597).

All studies were of 26 weeks duration, with 2 trials (Studies NN5401-3594 and NN5401-3590) extended by an additional 26 weeks to provide long term safety data.

Synopses for 7 new studies providing efficacy data for subjects with T2DM were provided in the current dossier. Although defined as safety endpoints, some of the hypoglycaemic parameters are included in the study summaries below to facilitate comparison with those results in earlier studies. These studies were:

- Study NN5401-3726, the synopsis for the 26 week extension of pivotal Study NN5401-3590
- 2 additional studies investigating once daily dosing of IDegAsp (Studies NN5401-3844 and NN5401-3896)
- 4 additional studies investigating twice daily dosing of IDegAsp (Studies NN5401-3940, NN5401-3996, NN5401-3941 and NN5401-4003).

Evaluator's conclusions on efficacy

The efficacy of IDegAsp in terms of glycated haemoglobin (HbA1c) reduction was demonstrated in the pivotal studies evaluated in the original withdrawn submission (with non-inferiority of IDegAsp to comparators in subjects with both T1DM and T2DM demonstrated. Additional 52 week data for subjects with T2DM provided in the synopsis for Study NN5401-3726 demonstrate maintenance of effect in terms of HbA1c reduction.

Outstanding issues regarding efficacy identified in the original submission are considered to have been adequately addressed, with particular regard to the efficacy of twice daily dosing of IDegAsp in subjects with T2DM. The synopses provided in the current dossier for an additional 4 studies comparing IDegAsp twice daily and biphasic insulin aspart (BIAsp) 30 twice daily confirmed non-inferiority of IDegAsp to BIAsp 30 with respect to reduction in HbA1c in 2 studies. A reduction in HbA1c was observed, although non-inferiority of IDegAsp twice daily to BIAsp 30 twice daily not confirmed, in 1 study and the remaining study comprised a sample size too small to draw any meaningful conclusions. These findings need to be considered in accordance with safety data.

The external validity of the clinical trials is a major concern. The results of the clinical trials describe an average response for the population in terms of glycaemic control and hypoglycaemia. However, in clinical practice insulin doses are individualised based on type of diabetes, residual insulin secretion, insulin sensitivity, carbohydrate composition of meals, age and co-morbidities. Thus, the extrapolation of dosing regimens and outcomes need to be interpreted with caution.

Safety

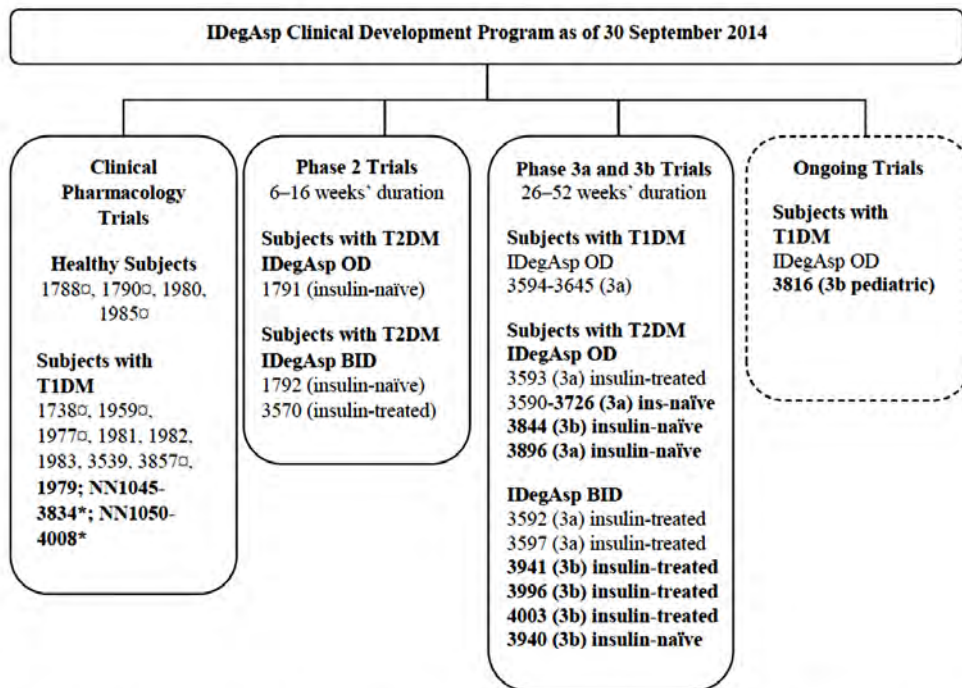
Studies providing safety data

Of the new studies which have been submitted, 2 have safety as the sole primary outcome:

- Study EX1250-4080 (the DEVOTE trial), a dedicated cardiovascular outcomes study. This study randomised subjects to either IDeg or Insulin glargine (IGlar) (an IDegAsp arm was not included). See Attachment 2 for this submission, and for the Tresiba submission for further details.⁴
- Study NN5401-3726 (the BOOST: START1 trial), an extension study (26 weeks) which continued to follow subjects with T2DM who were in Study NN 5401-3509 who received IDegAsp or IGlar. See Attachment 2 for further details

In the clinical evaluation report for the withdrawn submission, 5 therapeutic confirmatory studies and 3 exploratory studies (completed as of 31 January 2011) and ongoing studies (with a cut-off date as of 31 March 2011) provided evaluable safety data. The 5 pivotal/confirmatory studies counted for most of the overall exposure in the original submission. Of the additional data contained within this submission, 1 extension trial (Study NN5401-3726) for the original pivotal Study NN5401-3590 is included.

As of 30 September 2014, a total of 31 trials and extension trials have been completed with IDegAsp; one paediatric was trial ongoing, as shown below in Figure 5.

Figure 5: IDegAsp clinical development program as of 30 September 2014

Bold text: Trials not included in the original NDA. Trials marked with □ included both IDeg and IDegAsp. * Include different IDegAsp ratios. BID: twice daily, IDegAsp: insulin degludec/insulin aspart, OD: once daily, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus

This safety evaluation is mainly based on the Phase III trials; a complete list of the completed Phase III trials as of 30 September 2014 can be found below in Table 6. It should be noted that Study EX1250-4080 (the DEVOTE trial) is not included in this list since it is ongoing.

Table 6: Completed IDegAsp Phase III trials as of 30 September 2014

Trial ID	Type of subjects	Treatment duration (weeks)	Phase	Design Randomized (IDeg : Comp)	Test drug	Comparator	Exposed subjects
3594-3645	T1DM	26 + 26	3a	parallel (2:1) [#]	IDegAsp OD + IAsp at remaining meals	IDet OD/BID + IAsp at all meals	IDegAsp: 362 IDet: 180
3590-3726	T2DM	26 + 26	3a	parallel (1:1) [#]	IDegAsp OD + met	IGlar OD + met	IDegAsp: 265 IGlar: 261
3593	T2DM	26	3a	parallel (1:1)	IDegAsp OD + OADs	IGlar OD + OADs	IDegAsp: 230 IGlar: 233
3896 (Japan)	T2DM	26	3a	parallel (1:1)	IDegAsp OD ± OADs	IGlar OD ± OADs	IDegAsp: 147 IGlar: 149
3597	T2DM	26	3a	parallel (2:1)	IDegAsp BID ± met	BIAsp 30 BID ± met	IDegAsp: 279 BIAsp 30: 141
3592	T2DM	26	3a	parallel (1:1)	IDegAsp BID ± OADs	BIAsp 30 BID ± OADs	IDegAsp: 224 BIAsp 30: 222
3844	T2DM	26	3b	parallel (1:1)	IDegAsp OD ± met simple titration	IDegAsp OD ± met stepwise titration	IDegAsp simple: 134 IDegAsp stepwise: 140
3940	T2DM	26	3b	parallel (1:1)	IDegAsp BID + met	BIAsp 30 BID + met	IDegAsp: 196 BIAsp 30: 195
3941	T2DM	26	3b	parallel (1:1)	IDegAsp BID + met simple titration	IDegAsp BID + met stepwise titration	IDegAsp simple: 135 IDegAsp stepwise: 134
3996	T2DM	26	3b Repor-ting	parallel (1:1)	IDegAsp BID ± OADs	IDeg OD + IAsp TID ± OADs	IDegAsp: 136 IDeg: 135
4003	T2DM	26	3b	parallel (1:1)	IDegAsp BID + IAsp OD	IDeg OD + IAsp TID	IDegAsp: 20 IDeg: 20

Bold text: Trials not submitted as part of the original NDA. BID: twice daily; Comp: comparator; IAsp: insulin aspart; IDeg: insulin degludec; IDegAsp: insulin degludec/insulin aspart; BIAsp 30: biphasic insulin aspart 30; IDet: insulin detemir; IGlar: insulin glargine; met: metformin; OD: once daily; OAD, Ped: pediatric; TID: three times daily

[#]Randomization ratio at start of the main trial period – entry into extension required new informed consent.

Patient exposure

The following integrated patient exposure data is taken from the Summary of Clinical Safety Addendum and the Safety Update for IDegAsp, which contain data up until 30 September 2014. These 2 documents compare the updated data to data contained within the Integrated Safety Summary (ISS), with a cut-off of 31 January 2011.

Per the Summary of Clinical Safety Addendum which has a cut-off date of 30 September 2014:

- 3139 subjects have been exposed to IDegAsp in 31 completed clinical trials and extension trials, of which 10 trials have been completed since the 31 January 2011; 7 Phase III trials all in T2DM (1 extension part, 5 Phase III trials) and 3 clinical pharmacology trials. This has resulted in a 1,100 additional subjects compared to the original ISS (data up to 31 January 2011).
- The only ongoing IDegAsp trial as of 30 September 2014 is a paediatric trial.
- 10,773 subjects have been exposed to IDeg and/or IDegAsp in all completed IDeg/IDegAsp trials (a small number of subjects were exposed to both IDeg and IDegAsp). This includes an additional 167 subjects exposed in 6 Phase I trials completed with IDeg and IDegAsp since the ISS (data up to 31 January 2011).
- Subjects participating in the main and extension parts of a trial were counted only once in the subject exposure calculation.

Table 7 (shown below) is a summary of all subjects from completed trials for both IDeg and IDegAsp (from Summary of Clinical Safety Addendum IDegAsp).

Table 7: Exposure in all completed trials (IDeg and IDegAsp)

	IDeg* N	IDegAsp* N	IDeg + IDegAsp* N	Comparator N	Total N
Clinical Pharmacology Trials	1007	487	1295	723	1355
Healthy Subjects	256	76	332	26	358
Subjects with T1DM	608	351	760	549	793
Subjects with T2DM	143	60	203	148	204
Phase 2 trials	330	270	600	306	906
Subjects with T1DM	152	0	152	91	243
Subjects with T2DM	178	270	448	215	663
Phase 3 trials	6206	2382	8568	4098	12666
Subjects with T1DM	1102	362	1464	647	2111
Subjects with T2DM	5104	2020	7104	3451	10555
Insulin-naïve Subjects with T2DM	2911	882	3793	2375	6168
Insulin-treated Subjects with T2DM	2193	1138	3311	1076	4387
Other Therapeutic Trials	310	0	310	308	329
Subjects with T1DM	41	0	41	24	42
Subjects with T2DM	269	0	269	284	287
Total	7853	3139	10773	5435	15256

N = Number of subjects, Subjects from clinical pharmacology cross over trials may count in several treatment arms. For clinical pharmacology trials, comparator include placebo.
 * Includes all formulations. For Trials 3996 and 4003, exposure to IDeg and IDegAsp was included in the IDeg and IDegAsp columns, respectively, and none was included as 'comparator'. Subjects in main-extension trials only counted once. Similarly, subjects in Trials 4003 (coming from 3941) and 3948 (coming from 3579-3643) only counted once in each column. For Trial 3948, the non-randomized arm was included as IDeg.
 Trials: 1718 Part 1, 1718 Part 2, 1719, 1738, 1740, 1788, 1790, 1791, 1792, 1835, 1836, 1876, 1959, 1977, 1978, 1979, 1980, 1981, 1982, 1983, 1985, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 1996, 1999, 3538, 3539, 3569, 3570, 3579-3643, 3580, 3582-3667, 3583-3644, 3585-3725, 3586, 3587, 3590-3726, 3592, 3593, 3594-3645, 3597, 3668, 3672, 3678, 3718, 3724, 3762, 3765, 3769, 3770-main-ext, 3834, 3839, 3844, 3846, 3857, 3874, 3896, 3923, 3940, 3941, 3943, 3944, 3948, 3996, 3999, 4000, 4003, 4008, 4060

Table 8 (below) gives an indication of exposure to IDegAsp by exposure duration in the completed Phase III trials as of 30 September 2014.

Table 8. Exposure to IDegAsp in completed Phase III trials

	% of patients with any exposure (N)	% of patients with exposure ≥ 6 months	% of patients with exposure ≥ 12 months (N)	Total exposure in subject years
All subjects				
IDegAsp	100 (2382)	88.6	18.1 (431)	1340.3
Comparators	100 (1381)	89.1	23.7 (327)	815.8
T1DM				
IDegAsp	100 (362)	89.0	64.9 (235)	296.9
Comparators	100 (180)	87.2	63.3 (114)	145.5

	% of patients with any exposure (N)	% of patients with exposure ≥ 6 months	% of patients with exposure ≥ 12 months (N)	Total exposure in subject years
T2DM				
IDegAsp	100 (2020)	88.6	9.7 (196)	1043.4
Comparators	100 (1201)	89.4	17.7 (213)	670.3
Insulin naive T2DM				
IDegAsp	100 (882)	91.0	20.5 (181)	514.1
Comparators	100 (605)	91.4	35.2 (213)	398.9
Insulin treated T2DM				
IDegAsp	100 (1138)	86.6	1.3 (15)	529.3
Comparators	100 (596)	87.4	0	271.4

N = number of patients. Reference: Safety update IDegAsp (16 December 2014), includes Studies NN5401 3590-3726, 3592, 3593, 3594-3645, 3597, 3844, 3896, 3940, 3941, 3996 and 4003.

It is also noted that some trials included only IDeg and IDegAsp and no other comparator.

Compared to the ISS (cut-off date of 31 January 2011), an additional 930 subjects have been exposed to IDegAsp for 6 months, and additional 196 subjects for 12 months or more. The additional subjects who have been exposed for more than 6 months were enrolled on extension Study NN5401-3726 and therefore were all insulin naïve T2DM subjects receiving daily IDegAsp. It is noted that the maximum duration of the trials (per Figure 5, above) is 52 weeks therefore, even though a sizable proportion of the T1DM population and less percentages of the T2DM population are reported to have been exposed for ≥ 12 months, it is not expected that the subjects would have been exposed for any longer than 12 months. It is also noted that a very small number of insulin treated T2DM subjects have been treated for 12 months or more; the reason for this is not clear. Furthermore, of the subjects with T2DM who have been exposed for 12 months or more, the majority of these are in the comparator group. However, it is not clear why there is such a large difference in terms of those who have been exposed for ≥ 12 months (9.7% IDegAsp compared to 17.7% comparator) and this is not reflected as clearly in terms of completion of extension trials which showed that 92.4% of subjects completed the extension trials in the IDegAsp group compared to 93.9% of those in the comparator group. A question will be asked of the sponsor to clarify this.

In terms of subject disposition in the completed Phase III trials for IDegAsp, 87.5% of subjects on the IDegAsp group completed the main trials compared with 88.3% on the comparator group; the most common reason for withdrawal on the IDegAsp arm was 'other' (5.65%), Fulfilling withdrawal criteria (4.2%) and adverse events (1.4%). Similar rates were seen on the comparator arm except there were fewer (2.7%) withdrawing due to 'fulfilling withdrawal criteria'. Of the subjects included in the extension trials (446 on the IDegAsp, 343 on comparator arms), 92.4% completed the trial on IDegAsp and a slightly higher number on the comparator arm (93.9%). The most common reason for

withdrawal was 'other' (4% for IDegAsp and 3% for comparators); 1.3% withdrew due to adverse events on the IDegAsp compared to 0.9% on the comparator arm. It is noted that the sponsor has indicated that in some of the new completed trials, new withdrawal criteria have been included and this may have resulted in disproportionate reporting of withdrawals on the IDegAsp group since several trials had IDegAsp in both arms and there were no 'comparator' groups.

No new information was included regarding demographic characteristics in the Summary of Clinical Safety Addendum for IDegAsp.

Safety issues with the potential for major regulatory impact

The focus of this resubmission is CV safety. This is discussed in the benefit-risk assessments and Delegate's overview (below) and further evaluated in detail in Attachment 2.

Postmarketing data

The following summary is taken from the clinical evaluation report regarding postmarketing exposure and data; for further details, see Attachment 2.

Derived from the IDegAsp PSUR/PBRER (dated 1 October 2014 to 30 September 2015), with a start date immediately following the cut-off date for the Summary of Clinical Safety Addendum and therefore contains more updated data:

- IDegAsp has been approved in more than 55 countries and marketed in 5 countries (Denmark, Switzerland, India, Bangladesh and Mexico).
- Regulatory actions of note in the PSUR/PBRER period:
 - Singapore: marketing application for IDeg was withdrawn by sponsor, as the regulatory authority decided to wait for the results of the DEVOTE trial before making a final decision regarding the marketing application.
 - Malaysia: rejection (following appeals process) for IDegAsp; DEVOTE trial results are required to confirm the cardiovascular safety of the products.
- It is estimated that there has been 12,902 patient years of exposure to IDegAsp until 30 September 2015 ('cumulative exposure') and of these, 11,644 patient years of exposure have occurred during the current PSUR reporting period.
- Cumulatively, 91 adverse drug reactions have been reported in 41 spontaneous case reports, of which 4 reports were serious. 79 adverse drug reactions were reported in this PSUR period.
- 1 serious event of hypoglycaemia was received from non-interventional postmarketing studies and other solicited sources and is included as an adverse drug reaction.
- Most frequently reported events (5 events each) were injection site reactions (System Organ Class (SOC): general disorders and administration site conditions), hypoglycaemia, hyperglycaemia (both of SOC Metabolism and nutrition disorder) and blood glucose increased (SOC: investigations).
- No cases of major adverse cardiovascular event (MACE) or neoplasms have been reported.
- No fatal cases have been reported.
- Lack of efficacy: 3 reports were reported and all of these cases were associated with non-serious events of blood glucose increased or hyperglycaemia.

- Allergic reactions: 4 cases with 7 non-serious allergic reactions in the cumulative period; 4 events from this reporting period.
- Medication errors: 8 case reports with 9 non-serious events; 7 events (6 reports) from this reporting period: multiple use of single use product, wrong technique in administration (4 events), drug dose omission and incorrect storage of the product. No case of a mix up of bolus insulin with IDegAsp was reported in this reporting period; one has been reported cumulatively.
- The PSUR/PBRER states that *'no specific pattern or clustering of events was observed... single or few events (by preferred term) were reported'* and *'overall, no significant new safety concerns were identified with Ryzodeg from marketing experience, up until 30 Sep 2015.'*
- Off label use: Cumulatively, 6 case reports have been received relating to the use of IDegAsp in children, all of which are from this reporting period. One report was associated with an event of 'blood glucose abnormal'; the others had no adverse event reported. There are no reported post marketing cases of IDegAsp use in pregnant or lactating women.
- Data relating to IDegAsp components:
 - A discussion of the IDeg component is available in Attachment 2 for Tresiba.⁴
 - The most recent PSUR for IAsp was for the period of 1 October 2014 to 30 September 2015. According to the sponsor: *'Overall, the clinical trial safety data for IAsp remain in accordance with the cumulative experience as described in the current reference safety information. No reasons for new safety concerns were identified in connection with the administration of IAsp in clinical trials in the reporting period. No change was made to the existing safety concerns for IAsp.'*
- Other safety information; the PSUR states that:
 - *'No new nonclinical safety findings were reported during the period of this PSUR for Ryzodeg.'*
 - *'No new significant safety findings or concerns specifically for Ryzodeg were identified based on the results of the review of the scientific literature.'*
- It is noted that no non-interventional studies were initiated or completed for IDegAsp in this reporting period.
- Signal review and Evaluation of Authority Request:
 - 1 signal review of MACE is ongoing; MACE data from the dedicated CV outcomes trial, other clinical trials and postmarketing sources is included.
 - An Evaluation of Authority Request is ongoing of neoplasms and colon cancer as requested by SwissMedic and EMA's Committee for Medicinal Products for Human Use respectively. All potential events of neoplasms from all completed Phase IIIa and IIIb IDegAsp trials were sent to an external, independent and blinded consultant for classification into malignant, benign and unclassifiable neoplasms and post marketing data was analysed.

Summaries of safety concerns:

- No new potential or important risks have been identified in this PSUR period.

Evaluator's conclusions on safety

The important identified risks of IDeg Asp as noted in the PSUR/PBRER are hypoglycaemia and immunogenicity related events (allergic reactions). A safety concern

arising from the original withdrawn submission for IDegAsp related to CV outcomes and a core component of the safety data submitted in this resubmission of IDegAsp was the CV outcomes DEVOTE trial. This trial was of robust design and the primary endpoint comparing IDeg with insulin glargine (IGlar) was met for non-inferiority in an interim analysis; therefore the cardiovascular signal detected in the Phase III development program in the original submission was not supported. Nevertheless, it is noted that only interim results are presented and final results will provide stronger evidence. Further it is noted that DEVOTE trial does not provide data specific either to the T1DM population or patients receiving IDegAsp.

New integrated safety data with cut-off date of 30 September 2014 has been presented for IDegAsp in the current submission. This data has been compared in the submission documents to the Integrated Safety Summary with cut-off of 31 January 2011 from the FDA dossier. The evaluator has assumed that this data is the same as that in the original Australian dossier.

The updated dataset contained 10 new completed trials, of which 7 were Phase III trials, resulting in exposure of an additional 1100 subjects. There were no new Phase III data for T1DM (neither new nor ongoing patients). Of the Phase III trials relating to T2DM, 7 were new trials and one trial (a paediatric trial) was ongoing. In total, 3139 subjects have been exposed to IDegAsp in completed clinical trials as of 30 September 2014. It is noted that there were a variety of patient types included in this integrated dataset; subjects with T1DM and T2DM, and within the T2DM subset, subjects were either insulin naïve or insulin treated and received either a daily or twice daily dose. Similarly, the comparator group was an amalgamation of all comparators across a number of trials and patient populations. Therefore, as with all analyses of integrated data, data should be interpreted with some caution given that the population is a somewhat heterogeneous group. Nevertheless, this integrated data has the benefit of bringing together a large number of subjects who have received IDegAsp.

Based on the updated data presented, there do not appear to be any new significant safety signals that have emerged since the previous submission in terms of integrated safety data. Hypoglycaemia related adverse events continue to be the most frequently occurring possibly or probably related to study drug adverse events, serious adverse events and adverse event (preferred term) leading to withdrawal on the IDegAsp arm. This is not surprising, given the therapeutic action of IDegAsp; prescriber and patient education is important to ensure appropriate use. In general, the rate of hypoglycaemic events tended to be relatively similar in the IDegAsp group compared to the comparator group although there were some exceptions:

- preferred term of hypoglycaemia leading to withdrawal (although the rates are low, therefore the significance is unclear) was higher in the IDegAsp group.
- in terms of the specific hypoglycaemic analysis, confirmed hypoglycaemia episodes over 24 hours for T2DM insulin naïve, confirmed hypoglycaemia episodes over 24 hours in insulin treated subjects and documented symptomatic hypoglycaemic episodes over 24 hours for T2DM insulin naïve subjects were all higher in the IDegAsp group, all only in the group of subjects who received daily insulin.

In terms of nocturnal confirmed hypoglycaemia, IDegAsp had lower rates compared to the comparator group in all disease and dosing subgroups.

Subset analyses for T2DM are reported, although the T1DM dataset has not been updated. Overall, the rates seen for adverse events, overall serious adverse events, possibly/probably related serious adverse events and hypoglycaemic events were consistent with those seen in the overall population. It is noted that the proportion of subjects with the event of death was slightly higher on the T2DM IDegAsp arm compared

to the IDegAsp arm in the overall population; this is because all of the deaths that have occurred in IDegAsp trials have occurred in the T2DM population.

It is noted that in the updated data set, there is additional data with longer follow up (up to 52 weeks) than was available in the original submission. However, the proportion of subjects with T2DM in particular with data for 12 months remains limited and the majority of these are in the comparator group, although the reason for this discrepancy is not clear. More specifically, there are very few insulin treated subjects with T2DM were followed up for 12 months or more. Long term data is of relevance given that the use of IDegAsp in this population is expected to be administered for years rather than months in this population and highlights the importance of post marketing monitoring.

A number of specific analyses made by the sponsor such as immunological, MACE and neoplastic related events have not been discussed in detail the clinical evaluation report for this submission as only pooled data (IDegAsp + IDeg) was presented and this is presented in the IDeg clinical evaluation report [see Attachment 2 for Tresiba].⁴ Although reference was made to IDegAsp only data for MACE and neoplastic events, no data for IDegAsp relating to immunological events was presented for review.

Postmarketing experience is somewhat limited; the majority of the cumulative post marketing reports have been submitted in the year of the PSUR report. The paediatric study is noted and would be of interest for Australia in view of the relatively high prevalence of T1DM in children. It is also noted that there are two ongoing safety signal evaluations as detailed in the PSUR:

1. Neoplasms/colon cancer: See Attachment 2 for the Tresiba submission for specific discussion relating to pooled data.⁴ Ongoing monitoring should be maintained.
2. CV events: as previously discussed.

It has also been noted that medication errors due to a mix up with IDegAsp and bolus insulin is an Important potential risk, however several related cases have been reported, especially in the T2DM population.

First Round Benefit-Risk Assessment

First round assessment of benefits

Table 9 (below) summarises the assessment of benefits at the first round.

Table 9. First round assessment of benefits

Benefits	Uncertainties
Overall, non-inferior efficacy for glycaemic control compared to IDet, IGlax and BIAsp30.	The recommended dosing algorithm based on fasting plasma glucose only ignores the impact of the aspart component on post prandial blood glucose levels. Although fasting plasma glucose is the most important parameter, dosing considerations for the prandial component should also be considered.

Benefits	Uncertainties
The sponsor has proposed flexible dosing as a benefit. Although the glycaemic control in a clinical trial setting is similar for such a dosing regimen, the ability to extrapolate this to real life setting is unknown (see also risks).	Flexible dosing has potential to be of benefit if a dose is forgotten.
Rate of nocturnal hypoglycaemia generally lower compared to comparators	
Interim analysis of the DEVOTE trial provided supportive evidence for non-inferiority of CV endpoints	

First round assessment of risks

Table 10 (below) summarises the assessment of benefits at the first round.

Table 10. First round assessment of risks

Risks	Uncertainties
<p>Hypoglycaemia: Hypoglycaemia, and events related to hypoglycaemia, commonly occurred with the use of IDegAsp in the clinical trials. It is recognised that hypoglycaemia is an inherent risk associated with all insulins, however due to the 'ultra long' action, the period following a single dose in which hypoglycaemia may occur is longer than other insulins.</p> <p>However, it is also acknowledged that the aetiology of hypoglycaemia is multifactorial and the type of insulin used is only one important component. Thus education of prescribers and patients again will play an important part in mitigating this risk.</p>	
Exclusion of some oral anti-diabetic drugs in Phase III trials	<p>There is uncertainty regarding the use of some oral anti-diabetic drugs in combination with IDegAsp since glucagon like peptide-1 (GLP-1) receptor agonists, sulfonylureas, glinides and alpha glucosidase inhibitors were excluded from the Phase III trials. There were no studies with sodium-glucose cotransporter-2 (SGLT-2) inhibitors.</p> <p>This should be also noted in the PI.</p>
Routine use of flexible dosing is not consistent to overall approach to diabetes management and applicability into the 'real world' setting in unclear (see also benefits above).	

Risks	Uncertainties
<p>CV events (MACE): Although the outcomes of the interim analysis for the DEVOTE trials are reassuring with respect to the signal detected in the original evaluation, the final results from this study will allow more robust conclusions and provide long term data. Further monitoring should be continued (including the DEVOTE trial and the ongoing signal review).</p>	<p>IDegAsp was not used in the DEVOTE trial and therefore the specific cardiovascular risk in patients receiving IDegAsp is unknown and can only be extrapolated from the IDeg data.</p> <p>The DEVOTE trial did not include patients with T1DM and therefore the specific cardiovascular risk in this disease subset is unknown and can only be extrapolated from the T2DM data.</p>
<p>Dosing errors related to mixing basal and bolus insulin.</p> <p>It is noted that the dosing errors due to mixing basal and bolus insulin is an important potential risk, however there are a number of adverse events that have been reported relating to this in clinical trials.</p>	
	<p>Neoplasms/colon cancer: Neoplasms and colon cancer are the subject of an ongoing review as requested by SwissMedic and the EMA respectively. Further monitoring should be continued.</p>

First round assessment of benefit-risk balance

Overall, the benefit-risk balance is positive for IDegAsp provided appropriate steps for education of prescribers and patients are undertaken and consideration of the upgrade from important potential risk to identified risk should be made for dosing errors related to mixing basal and bolus insulin, as well as active ongoing monitoring for detected signals.

First Round Recommendation Regarding Authorisation

At this stage, the clinical evaluator has no major concerns for the approval of the registration of IDegAsp for the treatment of diabetes, providing the sponsor provide a suitable response to the questions and comments regarding the PI and the risk management plan (RMP).

Clinical Questions and Second Round Evaluation of clinical data submitted in response to questions

For details of the clinical questions, sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

No change to assessment of benefits (shown in Table 9, above).

Second round assessment of risks

In the first round report, hypoglycaemia was identified as a risk. Assessment of this risk is updated below in Table 11 (new text in *italics*); assessment of other risks identified in the first round remains unchanged.

Table 11. Second round assessment of risks

Risks	Uncertainties
<p>Hypoglycaemia: Hypoglycaemia and events related to hypoglycaemia, commonly occurred with the use of IDegAsp in the clinical trials. It is recognised that hypoglycaemia is an inherent risk associated with all insulins, however due to the 'ultra long' action, the period following a single dose in which hypoglycaemia may occur is longer than other insulins.</p> <p><i>It is also noted that hypoglycaemia episodes appear to occur around mealtimes in insulin naïve patients, even when IDegAsp is administered with the largest meal.</i></p> <p>However, it is also acknowledged that the aetiology of hypoglycaemia is multifactorial and the type of insulin used is only one important component. Thus education of prescribers and patients again will play an important part in mitigating this risk.</p>	

Second round assessment of benefit-risk balance

Overall, the benefit-risk balance is positive for IDegAsp provided appropriate steps for education of prescribers and patients are undertaken and active ongoing monitoring for detected signals is maintained.

Second round recommendation regarding authorisation

At this stage, the clinical evaluator has no major concerns for the approval of the registration of IDegAsp for the treatment of diabetes subject to PI comments.

VI. Pharmacovigilance findings

Risk management plan

- The sponsor submitted a Risk Management Plan (RMP): EU RMP version 5.2 (dated 1 August 2016; data lock point (DLP) 1 June 2015) and Australian Specific Annex (ASA) version 1 (dated 9 September 2016) in support of this application.
- The sponsor submitted an application to the TGA for this product in 2012, and the EU RMP (version 1.0; dated 8 September 2011) and the ASA (version 1.0; dated 6 February 2012) that accompanied this application were evaluated. However, the sponsor withdrew this application because the issues raised regarding CV safety of the product was not addressed at that time. The sponsor has made this current submission based on the original dossier submitted in 2012, with new/amended information to demonstrate CV safety.
- With the responses to evaluation reports and questions raised in the first round evaluations, the sponsor provided an updated ASA version 1.1 (dated 29 May 2017).
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in Table 12 below.

Table 12: Sponsor's summary of ongoing safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypoglycaemia	✓	-	✓	-
	Immunogenicity-related events (allergic reactions)	✓	-	✓	-
Important potential risks	Medication errors due to mix-up between Ryzodeg and bolus insulin	✓	-	✓	-
	Immunological events; formation of neutralising insulin antibodies	✓	-	✓	-
Missing information	Pregnant and lactating women	✓	-	✓	-
	Children < 2 years of age with diabetes mellitus	✓	-	✓	-
	Children and adolescents < 18 years ^a	✓	-	✓	-
	Hepatic impairment	✓	-	✓	-
	Moderate and severe renal impairment	✓	-	✓	-
	Elderly patients (> 75 years) with T1DM	✓	-	✓	-
	Co-administration of GLP-1 receptor agonists	✓	-	✓	-

a) Missing information of 'Children < 2 years of age with diabetes mellitus' has been replaced by 'Children and adolescents < 18 years' as recommended by the clinical evaluator.

Follow up questionnaires are proposed to be used to monitor the risk of medication error.

New and outstanding recommendations at the second round

The sponsor has adequately addressed the recommendations made during the first round RMP evaluation.

There are no outstanding issues from a RMP perspective.

Wording for conditions of registration for the Delegate

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

- Implement EU-RMP (version 5.2, date 1 August 2016, DLP 1 June 2015) with Australian Specific Annex (version 1.1, dated 29 May 2017) and any future updates as a condition of registration.

Other advice to the Delegate

The sponsor has not agreed to assign Identified Risk status to 'medication errors due to a mix up with IDegAsp and bolus insulin' as recommended by the clinical evaluator. The RMP evaluator has no objection to the sponsor's decision. This matter is raised for the Delegate's consideration.

VII. Overall conclusion and risk/benefit assessment

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

Quality and biopharmaceutics

There were no ongoing concerns from the assessment of the quality aspects of IDegAsp.

Nonclinical

There were no ongoing concerns from the assessment of the nonclinical aspects of IDegAsp. Also see Delegate's overview for Tresiba [available in the related Tresiba AusPAR].⁴

Clinical

This overview focuses on issues specific to the FDC. In relation to issues about IDeg, please refer to the Delegate's overview for Tresiba (available in the related Tresiba AusPAR).⁴

Table 13: Previously submitted data

Absorption	<p>Following subcutaneous injection:</p> <ul style="list-style-type: none"> • IDeg: Stable multi-hexamers are formed, resulting in a depot of IDeg. IDeg monomers gradually separate resulting in a slower and continual release into the circulation. Steady state concentrations are reached after 2 to 3 days of daily IDegAsp administration. • IAsp: there is rapid release of IAsp monomers into the circulation. Insulin aspart appears 14 minutes after injection and peak concentration occurs after 72 minutes.
Distribution	<ul style="list-style-type: none"> • IDeg: Plasma protein binding of > 99% in human plasma. • IAsp: Plasma protein binding of < 10% in human plasma.
Metabolism	Degradation of insulin degludec and insulin aspart is similar to that of human insulin.
Excretion	<p>IDeg half-life: 25 hours</p> <ul style="list-style-type: none"> • independent of dose • determined by rate of absorption from subcutaneous tissue.
Linearity	Total exposure with IDegAsp increases proportionally with increasing dose of the basal component (IDeg) and the mealtime component (IAsp) in T1DM and T2DM.
Special populations	No differences in pharmacokinetic parameters in hepatic and renal impairment compared to normal subjects. No differences in pharmacokinetic parameters between elderly and younger patients.

The clinical evaluator was concerned that the pharmacokinetic studies for the FDC IDegAsp were not bioequivalent to its components. There were substantial differences in the pharmacokinetic profile of IAsp and IDeg from Study NN5401-3857 which compared 0.5 U/kg of IDegAsp to 0.5 U/kg of IDeg and 0.5 U/kg of aspart. However, this is not a fair comparison as the dosing was not dose equivalent.

Study NN5401-1959 compared IDegAsp with similar molar doses of IDeg and IAsp. The C_{max} for IAsp was lower but the area under the drug concentration time curve from time zero to 6 hours (AUC_{0-6h}) was comparable. The C_{max} for IDeg was higher but the area under the drug concentration time curve from time zero to infinity (AUC_{0-inf}) was comparable.

The pharmacokinetic endpoints from Study NN5401-1959 were:

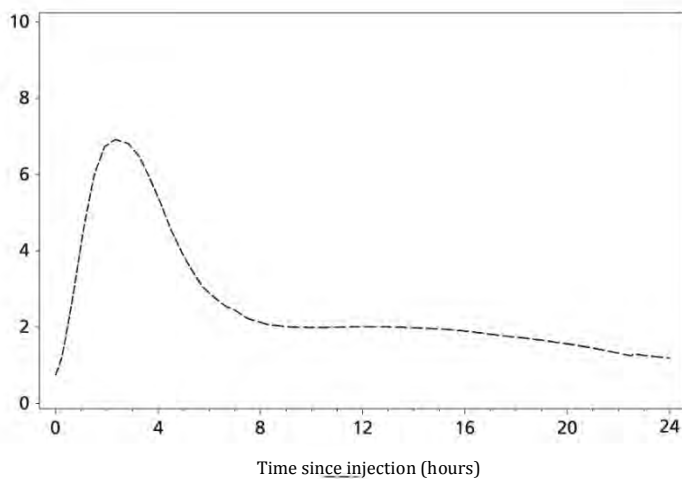
- Area under the IAsp concentration time curve from time 0 to 2 hours ($AUC_{(IAsp\ 0-2h)}$): 0.68 (95% CI 0.61 to 0.75)
- Area under the IAsp concentration time curve from time 0 to 6 hours ($AUC_{(IAsp\ 0-6h)}$): 0.89 (95% CI 0.83 to 0.95)
- C_{max} (IAsp): 0.72 (0.64 to 0.79)
- IDeg $AUC_{(0-inf)}$: 1.03 (95% CI 0.93 to 1.14)
- C_{max} (IDeg): 1.13 (95% CI 1.02 to 1.25)

The glucose infusion rate of IDegAsp was comparable to separate injections of molar equivalent doses of IDeg and IAsp.

Pharmacodynamic endpoints from Study NN5401-1959:

- Glucose infusion rate (GIR) maximum/average ($AUC_{(GIR\ 0-24)}$): 0.91 (0.84 to 0.99)
- $AUC_{(0-24\ h)}$ for GIR: 1.04 mg/kg (0.94 to 1.14)
- $AUC_{(0-6\ h)}$ for GIR: 0.97 mg/kg (0.88 to 1.06)
- $AUC_{(0-2\ h)}$ for GIR: 0.74 mg/kg (0.64 to 0.86)
- Maximum glucose infusion rate (GIR_{max}): 0.94 mg/kg/min (0.86 to 1.03)

Figure 6: Mean glucose infusion rate profile of Ryzodeg after a single dose administration of 0.8 U/kg in T1DM (Study NN5401-3589)



Clinical Studies

In the initial submission there were 5 clinical studies, 1 in T1DM and 4 in T2DM. The studies compared IDegAsp to levemir, IGlax, or NovoMix. Patients were not blinded due to difference in pens for comparator insulins. The clinical studies excluded patients using insulin secretagogues, alpha glucosidase inhibitors or GLP-1 agonists.

All the therapeutic confirmatory trials were conducted with a treat-to-target principle; the dose was adjusted for each individual subject with the aim of achieving identical glycaemic targets for IDegAsp and comparator products. The overall treatment goal in all therapeutic confirmatory trials was to achieve HbA1c < 7% and a pre-breakfast (fasting) blood glucose level (BGL) of < 5.0 mmol/L. In trials with twice daily dosing an additional titration target of BGL < 5.0 mmol/L before the main evening meal was applied for adjustment of the morning dose. In subjects with T1DM (Study NN5401-3594), IAsp as a separate bolus (for both treatment groups) were titrated based on the mean pre-prandial BGL.

Non inferiority was established in comparison to other basal and mixed insulins in terms of HbA1c. There was a difference in the relative rates of hypoglycaemia between the studies, reflective of the different comparators, patient populations and dosing regimens.

The clinical evaluator had concerns about the choice of comparators. The Delegate considers the choice of comparators reasonable as they are all options for use in patients with diabetes in Australia. However, IGlax, levemir and NovoMix all have different pharmacokinetic/pharmacodynamic profiles, thus differences in the outcomes of the trials would be expected.

Table 14. Comparison of IDegAsp studies and study endpoints

Parameter	Study 3594	Study 3590	Study 3593	Study 3592	Study 3597					
Design	26 week (+ 26 week extension) efficacy and safety study comparing IDegAsp OD with IDet OD in adult subjects with T1DM.	26 week efficacy and safety study comparing IDegAsp OD with IGlax OD in insulin naïve adult subjects with T2DM currently treated with metformin.	26 week efficacy and safety study comparing IDegAsp OD and IGlax OD in insulin treated adult subjects with T2DM in combination with OADs (metformin ± pioglitazone ± DDP-4I).	26 week efficacy and safety study comparing IDegAsp BD and BIAsp 30 BD in adult subjects with T2DM treated with insulin ± OADs (± metformin ± DDP-4I ± pioglitazone)	26 week Pan-Asian efficacy and safety study comparing IDegAsp BD and BIAsp 30 BD in adult subjects with T2DM treated with insulin ± metformin.					
Treatment	IDegAsp 100 U/mL OD with main meal + IAsp with remaining meals; or IDet OD according to local label + IAsp as meal time insulin. A second dose of IDet could be added after 8 weeks if inadequate glycaemic control.	IDegAsp 100 U/mL OD with morning meal; or IGlax OD according to local label metformin.	IDegAsp 100 U/mL OD with any meal (evening meal or largest meal; same meal throughout study); or IGlax OD according to local label metformin ± pioglitazone ± DDP-4I.	IDegAsp 100 U/mL BD with breakfast and main evening meal; or BIAsp30 BD with breakfast and main evening meal ±metformin ± DDP-4I. ± pioglitazone	IDegAsp 100 U/mL with breakfast and main evening meal; or BIAsp 30 BD with breakfast and main evening meal ± metformin.					
Primary efficacy endpoint	Mean change from baseline in HbA1c after 26 weeks of treatment (%)									
	IDegAsp	IDet	IDegAsp	IGlax	IDegAsp	IGlax	IDegAsp	BIAsp 30	IDegAsp	BIAsp 30
	-0.75	-0.70	-1.72	-1.75	-0.98	-1.00	- 1.31	- 1.29	-1.39	-1.44
	Non-inferiority confirmed. Reduction in HbA1c maintained after 52 weeks	Non-inferiority confirmed	Non-inferiority confirmed	Non-inferiority confirmed	Non-inferiority confirmed	Non-inferiority confirmed	Non-inferiority confirmed	Non-inferiority confirmed	Non-inferiority confirmed	
Secondary efficacy endpoint	Proportion of subjects with HbA1c < 7.0% without confirmed hypoglycaemic episodes (%)									
	IDegAsp	IDet	IDegAsp	IGlax	IDegAsp	IGlax	IDegAsp	BIAsp 30	IDegAsp	BIAsp 30
	4.5	3.0	23.6	30.7	20.9	23.5	21.8	14.9	21.9	13.2

Parameter	Study 3594	Study 3590	Study 3593	Study 3592	Study 3597					
Safety endpoint	Rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE									
	IDegAsp	IDet	IDegAsp	IGlar	IDegAsp	IGlar	IDegAsp	BIAsp 30	IDegAsp	BIAs p 30
	371	572	19	46	82	101	74	253	111	155
Safety endpoint	Rate of confirmed hypoglycaemic episodes per 100 PYE									
	IDegAsp	IDet	IDegAsp	IGlar	IDegAsp	IGlar	IDegAsp	BIAsp 30	IDegAsp	BIAs p 30
	3917	4434	423	185	431	320	972	1396	956	952

OD = once daily; BD = twice daily

In the T1DM trials, severe hypoglycaemia was lower in the IDegAsp group than the comparator group with Levemir. However there were more withdrawals due to hypoglycaemia in the IDegAsp group, this may have been because the study was not blinded and patients taking IDegAsp were treated with more caution.

In T2DM, the rate of severe hypoglycaemia was lower or similar to comparators. More hypoglycaemia occurred during the day, particularly after meals, compared to the night.

New data

CV study

For the DEVOTE trial see Delegate's overview for Tresiba (available in the related AusPAR).⁴

Updated safety to 30 September 2014 for Ryzodeg

In comparison to the 5 efficacy studies, 3 exploratory studies and ongoing studies in the original submission, the new summary of safety data contained 31 studies, with 3193 subjects exposed. There have been 431 patients exposed for > 12 months in Phase III clinical studies.

In the DEVOTE trial that the patients who received IAsp developed a higher rate of Event Adjudication Committee (EAC) confirmed hypoglycaemia compared to those not receiving IAsp, more than 3 times the rate. In terms of the individual arms, the IDeg + IAsp arm had a lower rate (7.23 events per 100 patient years of observation) compared to the IGlar + IAsp arm (11.16 events per 100 patient years of observation) although it is noted that the actual proportion of subjects affected were similar (2.7% on IDeg and 3.0% on IGlar).

The most frequently reported adverse events were headache, nasopharyngitis and upper respiratory tract infection. The most frequently reported treated related adverse events were hypoglycaemia and injection site reactions. There were a total of 15 deaths, with no significant treatment imbalance.

The rate of MACE+ in the IDeg Asp group was 1.9% per 100 subject years of exposure, compared to 1.5% in the comparator group.

In relation to neoplasms, there were varying rates of discrepancies between the rates of different types of neoplasms and between T1DM and T2DM, with no pattern.

RMP

See the Summary of safety concerns in Table 12, above.

Risk-benefit analysis

Delegate's considerations

Delegate issues specific for IDeg/Asp

The usual requirement for new fixed dose combination products is to assess the benefits of the FDC in comparison to the components. Although a comparison of IDegAsp to IDeg would be appropriate for T2DM, the use of IDeg or IAsp alone is not appropriate in T1DM, and the use of IAsp alone would rarely be appropriate in T2DM. There is a large variability in insulin needs among patients with diabetes. Relative efficacy of one insulin preparation over another in a clinical trial does not always match relative efficacy in an individual patient.

Efficacy

Non inferiority in change in HbA1c was seen with IDegAsp and IAsp at other meals was compared with IDeg and aspart at all meals with T1DM.

Non inferiority compared to other basal insulins was demonstrated in T2DM.

In clinical practice, the role of this medicine is questionable. It may reduce 1 injection per day in patients with T1DM if the ratio of IAsp to IDeg suits the patients' insulin requirement. It may also be useful in T2DM if a patient eats a high carbohydrate meal once a day and needs short acting insulin to cover this meal only.

The main advantage of this over using separate injections of IDeg and IAsp is a reduction in the number of injections. The main disadvantage is that it is not possible to adjust the ratio of IDeg and IAsp individualised dose titration of IDeg and IAsp would minimise the risk of hypoglycaemia.

The PI does not contain adequate information about how to dose the fast acting component of this FDC.

Safety

Although there were less nocturnal hypoglycaemic events, there was a trend towards more episodes of hypoglycaemia after meals. This risk could be reduced by better information in the PI around dosing.

Labelling

The trade name needs to include the proportion of IDeg and IAsp in the FDC product. This would be consistent with the tradename in the US of Ryzodeg 70/30.⁷

Use in paediatrics

The TGA has evaluated data from a pharmacokinetic study in children and adolescents (Study NN5401-1982). The concentration of IAsp and IDeg were higher in children than in adults after a single injection of IDegAsp.

In the US, IDeg Asp is not indicated in children < 18 years.

In Europe, IDeg Asp is indicated in children > 1 year. The PI includes data from a clinical study in children aged 2 to 17 years with T1DM.

⁷ Ryzodeg 70/30 compared to original planned product tradename of Ryzodeg.

There was no synopsis of a clinical efficacy study in paediatrics submitted with this dossier. The TGA would require the full study report of the clinical study in paediatrics before an extension of indication for use in children could be considered.

Summary of issues

The issues are the same as the Tresiba submission.⁴

In addition:

1. The clinical evaluator was concerned that IDegAsp was not 'bioequivalent' to its components. The Delegate is not concerned about this issue. Bioequivalence is not as relevant as the pharmacodynamic profile and clinical efficacy. The pharmacodynamic profile of IDegAsp is as would be expected from a FDC of the two products.
2. The use of this medicine in the clinical trials may not replicate how it would be used in clinical practice. In particular, dosing of a combination product should take into consideration the effects of both basal component (fasting BGL) and post prandial component (2 hour post prandial BGL). This needs to be reflected in the PI to minimise daytime hypoglycaemia.

Proposed action

The Delegate has no reason to say, at this time, that the application for Ryzodeg should not be approved for registration (with appropriate changes to the PI, labelling and RMP).

Request for ACM advice

1. Would the committee support modifying the dosing section of the PI to include advice about how to titrate the IAsp component and when to consider another form of insulin therapy.

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

Response from sponsor

Issues in common with Tresiba FlexTouch/Penfill

Please refer to the responses to the issues raised for the Tresiba submission (available in the related AusPAR).⁴

Summary of issues: Issue 2

'The use of this medicine in the clinical trials may not replicate how it would be used in clinical practice. In particular, dosing of a combination product should take into consideration the effects of both basal component (fasting BGL) and post prandial component (2 hour post prandial BGL). This needs to be reflected in the PI to minimise daytime hypoglycaemia'.

Sponsor's response

Different dosing regimens were investigated in the clinical trial programme, with the result that once daily and twice daily regimens were both found to be effective and hypoglycaemia was minimised by dosing Ryzodeg with the main meal(s). It is proposed that Ryzodeg should be dosed in clinical practice in a similar way to how it was dosed in the clinical trials. The recommendations for dose adjustments in the label are therefore designed to reflect the dosing instructions in the later clinical trial protocols.

Since Ryzodeg is a fixed combination product of 70% IDeg and 30% IAsp, the primary consideration when performing dose adjustments should be the pre-meal plasma

glucose measurements, however, the physician should also take into consideration other factors such as the individual patient's history of hypoglycaemic episodes, diet, exercise and lifestyle. This ensures an appropriate dose of the basal component (IAsp) is administered.

In order to minimise the risk of post-prandial hypoglycaemia, Ryzodeg should be administered at a main meal (that is, the meal(s) with the largest carbohydrate content). The proposed Australian PI includes instructions to the prescriber regarding recommended dosing time of Ryzodeg under the Dosage and Administration section: 'Ryzodeg can be administered once or twice daily with the main meal(s)'. This wording is also used in the European Summary of Product Characteristics for Ryzodeg.

Advisory Committee Considerations

The Advisory Committee on Medicines (ACM) agreed with the Delegate on the proposed conditions of registration and advised that implementation by the sponsor of the recommendations outlined below to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of these products.

Delegate's request for specific advice

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

1. *Would the committee support modifying the dosing section of the PI to include advice about how to titrate the aspart component and when to consider another form of insulin therapy?*

The ACM noted that modifying the dosing section of the PI to include advice about how to titrate the aspart component would be challenging. The ACM agreed that the onus was more on the learnt experience of the treating doctor and patient together as there is considerable inter-patient variation and intra-patient variation.

The ACM noted that the fixed ratio is an issue but not more so than for all other fixed dose combination insulins which are still very useful.

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

Outcome

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

- Ryzodeg 70/30 FlexTouch 70% insulin degludec (rys)/30% insulin aspart (rys) 100 U/mL solution for injection cartridge; and
- Ryzodeg 70/30 Penfill 70% insulin degludec (rys)/30% insulin aspart (rys) 100 U/mL solution for injection cartridge.

The approved indication for these therapeutic goods is:

'To improve glycaemic control in adult patients with diabetes mellitus requiring basal and prandial insulin'.

Specific conditions of registration applying to these goods

- The insulin degludec/insulin aspart (Ryzodeg) EU Risk Management Plan (RMP), version 5.2, dated 1 August 2016 (data lock point 1 June 2015) with Australian Specific

Annex, version 1.1, dated 29 May 2017, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

- The Consumer Medicines Information must be included with the products as a package insert.
- Batch release testing and Compliance with Certified Product Details (CPD)

All batches of Ryzodeg 70/30 FlexTouch 100 U/mL (insulin degludec (rys)/insulin aspart (rys)) and Ryzodeg 70/30 Penfill 100 U/mL (insulin degludec (rys) / insulin aspart (rys)) solution for injection multidose cartridge imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

Each batch of Ryzodeg 70/30 FlexTouch 100 U/mL (insulin degludec (rys)/insulin aspart (rys)) and Ryzodeg 70/30 Penfill 100 U/mL (insulin degludec (rys) / insulin aspart (rys)) solution for injection multidose cartridge imported into/manufactured in Australia is 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 must supply:

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

Attachment 1. Product Information

The PI for Ryzodeg 70/30 FlexTouch and Ryzodeg 70/30 Penfill 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>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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