▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

TRESIBA® FlexTouch® (insulin degludec) solution for injection
TRESIBA® FlexPen® (insulin degludec) solution for injection
TRESIBA® Penfill® (insulin degludec) solution for injection

1. NAME OF THE MEDICINE

insulin degludec

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tresiba is an ultra-long acting basal insulin analogue, for once-daily subcutaneous administration at any time of the day.

Tresiba FlexTouch 100 U/mL solution for injection
1 mL of the solution contains 100 U insulin degludec (equivalent to 3.66 mg salt-free anhydrous insulin degludec). One prefilled pen contains 3 mL equivalent to 300 U. The prefilled FlexTouch pen can provide a maximum dose of 80 U in a single injection in dose increments of 1 U.

Tresiba FlexTouch 200 U/mL solution for injection
1 mL of the solution contains 200 U insulin degludec (equivalent to 7.32 mg salt-free anhydrous insulin degludec). One prefilled pen contains 3 mL equivalent to 600 U. The prefilled FlexTouch pen can provide a maximum dose of 160 U in a single injection in dose increments of 2 U.

Tresiba FlexPen 100 U/mL solution for injection
1 mL of the solution contains 100 U insulin degludec (equivalent to 3.66 mg salt-free anhydrous insulin degludec). One prefilled pen contains 3 mL equivalent to 300 U. The prefilled FlexPen pen can provide a maximum dose of 60 U in a single injection in dose increments of 1 U.

Tresiba Penfill 100 U/mL solution for injection
1 mL of the solution contains 100 U insulin degludec (equivalent to 3.66 mg salt-free anhydrous insulin degludec). One cartridge contains 3 mL equivalent to 300 U.

For the full list of excipients, see Section 6.1 List of excipients.

The potency of insulin analogues including insulin degludec is expressed in units (U). One unit (U) of insulin degludec corresponds nominally to one IU (international unit) of human insulin and to one unit of most other insulin analogues.

Insulin degludec is produced by recombinant DNA technology using *Saccharomyces cerevisiae*.

3. PHARMACEUTICAL FORM

Tresiba is a clear, colourless, neutral solution. Tresiba has a pH of approximately 7.6.
Tresiba is a solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.

4.2 Dose and Method of Administration

Dosage

Tresiba is an ultra-long acting basal insulin for once daily subcutaneous administration at any time of the day, preferably the same time every day.

Tresiba is to be dosed in accordance with the individual patient's needs. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose.

As with all insulin products adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Regardless of which Tresiba product is used, the dose is dialled in units. Tresiba FlexTouch 200 U/mL prefilled pen provides the dose in half the volume of standard basal insulin products of strength 100 U/mL and can provide doses up to 160 U in a single injection.

The dose counter shows the number of units regardless of strength and no dose conversion should be done when transferring a patient to a new strength.

Tresiba can be used in elderly patients (≥65 years old). As with all insulin products, glucose-monitoring is required and the insulin dose adjusted on an individual basis (see Section 5.2 Pharmacokinetic Properties).

Tresiba can be used in patients with renal and hepatic impairment. As with all insulin products, glucose-monitoring is to be intensified and the insulin dose adjusted on an individual basis (see Section 5.2 Pharmacokinetic Properties).

When changing basal insulin to Tresiba, dose reduction of basal and bolus insulin needs to be considered on an individual basis, in order to minimise the risk of hypoglycaemia (see Section 4.4 Special Warnings and Precautions for Use).

Initiation of Tresiba

For patients with type 1 diabetes mellitus, Tresiba is to be used once daily with mealtime insulin and requires subsequent individual dosage adjustments. Tresiba must be combined with short and/or rapid acting insulin to cover mealtime insulin requirements.

For insulin naïve adults with type 2 diabetes mellitus, the recommended daily starting dose of Tresiba is 10 U, followed by individual dosage adjustments. Tresiba can be administered alone, in addition to oral anti-diabetic drugs and/or in addition to bolus insulin.

Transfer from other insulins

For most patients with type 1 diabetes mellitus, a dose reduction of 20% based on the previous basal insulin dose, or basal component of a continuous subcutaneous insulin infusion regimen, should be considered with subsequent individual dosage adjustments based on the glycaemic response.

For patients with type 2 diabetes mellitus taking once daily basal, basal-bolus, premix or self-mixed insulin therapy, changing the basal insulin to Tresiba can be done unit-to-unit based on the previous basal insulin dose followed by individual dosage adjustments.

A dose reduction of 20% based on the previous basal insulin dose followed by individual dosage adjustments should be considered when:
- transferring to Tresiba from twice-daily basal insulin
- transferring to Tresiba from insulin glargine (300 units/mL).

As with all insulin products, close glucose monitoring is recommended during the transfer and following weeks. Doses and timing of concurrent rapid-acting or short-acting insulin products or other concomitant antidiabetic treatment may need to be adjusted.

Flexibility in dosing time
Tresiba has a slow consistent rate of absorption which provides a flat and stable glucose-lowering-effect with a low variability. Tresiba allows for some flexibility in the timing of insulin administration. When needed the patient has the option of changing the once daily injection time from day-to-day. Patients who forget a dose are advised to take it upon discovery and then resume their usual once daily dosing schedule. Ensure a minimum of 8 hours between injections. There is no clinical experience with flexibility in dosing time of Tresiba in children and adolescents.

Avoidance of accidental mix-ups
To avoid accidental mix-ups between the two different strengths of Tresiba as well as between Tresiba and other insulin products, patients must be instructed to always check the label for the right type of insulin before each injection.

Use of Tresiba in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus
When adding Tresiba to GLP-1 receptor agonists, the recommended daily starting dose is 10 units followed by individual dosage adjustments.

When adding GLP-1 receptor agonists to Tresiba, it is recommended to reduce the dose of Tresiba by 20% to minimise the risk of hypoglycaemia. Subsequently, dosage should be adjusted.

Method of Administration
Tresiba is for subcutaneous administration only. Tresiba must not be administered intravenously as it may result in severe hypoglycaemia. Tresiba must not be administered intramuscularly as it may change the absorption. Tresiba must not be used in insulin infusion pumps.

Tresiba is administered subcutaneously by injection in the thigh, the upper arm or the abdominal wall. Injection sites should always be rotated within the same region in order to

reduce the risk of lipodystrophy and cutaneous amyloidosis (see Sections 4.4 Special Warnings and Precautions for Use and 4.8 Adverse Effects (Undesirable Effects)).

Instructions for use and handling
Tresiba FlexTouch, Tresiba FlexPen and Tresiba Penfill must not be used if the solution does not appear clear and colourless. Tresiba which has been frozen must not be used.

Tresiba FlexTouch, Tresiba FlexPen and Tresiba Penfill are for use by one person only.

Tresiba FlexTouch
The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling. Please note that insulin is not delivered if the patient reverse dials the insulin pen by returning the dose selector to zero after inserting the needle. Patients should be instructed that insulin injection only occurs when the pushbutton is depressed.

The cartridge inside Tresiba FlexTouch must not be refilled. NovoFine® disposable needles up to a length of 8 mm are designed to be used with Tresiba FlexTouch. The patient should be advised to discard the needle after each injection.

Tresiba FlexPen
The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling. Please note that insulin is not delivered if the patient reverse dials the insulin pen by returning the dose selector to zero after inserting the needle. Patients should be instructed that insulin injection only occurs when the pushbutton is depressed.

The cartridge inside Tresiba FlexPen must not be refilled. NovoFine disposable needles up to a length of 8 mm are designed to be used with Tresiba FlexPen. The patient should be advised to discard the needle after each injection.

Tresiba Penfill
The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling. The leaflet refers to the instructions for using the accompanying Novo Nordisk insulin delivery system, such as NovoPen® (durable device for repeated use).

Tresiba Penfill cartridges must not be refilled. Tresiba Penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems, such as NovoPen, and NovoFine disposable needles. The patient should be advised to discard the needle after each injection.

4.3 Contraindications
Hypersensitivity to insulin degludec or any of the excipients.

4.4 Special Warnings and Precautions for Use

Hypoglycaemia
Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see Sections 4.5 Interactions with Other Medicines and Other Forms of Interactions, 4.8 Adverse Effects (Undesirable Effects) and 4.9 Overdose).

In children, care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimise the risk of hypoglycaemia.

Patients whose blood glucose control is greatly improved, for example by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia, and must be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes mellitus.

Concomitant illness, especially infections and fever, usually increases the patient's insulin requirements. Concomitant diseases in the kidney, liver or diseases affecting the adrenal, pituitary or thyroid gland may require changes in the insulin dose.

As with other basal insulin products, the prolonged effect of Tresiba may delay recovery from hypoglycaemia.

Hyperglycaemia
Administration of rapid-acting insulin is recommended in situations of severe hyperglycaemia.

Inadequate dosing or discontinuation of treatment in patients requiring insulin, may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Furthermore concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement.

Usually the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, and loss of appetite as well as acetone odour of breath. In type 1 diabetes mellitus, untreated hyperglycaemic events may lead to diabetic ketoacidosis, which is potentially lethal.

Antibodies
Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Eye disorder
Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term glycaemic control decreases the risk of progression of diabetic retinopathy.

Weight gain
Weight gain can occur with any insulin therapy, including Tresiba, and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

Administration
Tresiba is for subcutaneous administration only. Tresiba must not be administered intravenously as it may result in severe hypoglycaemia. Tresiba must not be administered intramuscularly as it may change the absorption. Tresiba is not to be used with insulin infusion pumps.

Skin and subcutaneous tissue disorders
Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

Transfer of patients between insulin types
Transferring a patient to another type, brand or manufacturer of insulin must be done under medical supervision and may result in the need for a change in dosage.

Avoidance of accidental mix-ups
To avoid accidental mix-ups between the two different strengths of Tresiba as well as between Tresiba and other insulin products, patients must be instructed to always check the label for the right type of insulin before each injection.

Patients must be able to visually verify the dialled number of units on the dose counter of the pen. Therefore, it is a prerequisite to be able to self-inject that patients have sufficient sight to read the dose counter. Patients who are blind or visually impaired must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device.

Use in hepatic impairment
Tresiba can be used in patients with hepatic impairment. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis (see Section 5.2 Pharmacokinetic Properties).

Use in renal impairment
Tresiba can be used in patients with renal impairment. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis (see Section 5.2 Pharmacokinetic Properties).

Use in the elderly
Tresiba can be used in elderly patients. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis (see Section 5.2 Pharmacokinetic Properties).

Paediatric use
Tresiba has been studied in adolescents and children from the age of 1 year with type 1 diabetes mellitus. The efficacy and safety of Tresiba has not been evaluated in children below the age of 1 year (see Section 5.1 Pharmacodynamic Properties).

When changing basal insulin to Tresiba, dose reduction of basal and bolus insulin needs to be considered on an individual basis, in order to minimise the risk of hypoglycaemia. There have been no studies in infants less than 1 year or children with type 2 diabetes mellitus.

Effects on laboratory tests
No data available.

4.5 Interactions with Other Medicines and Other Forms of Interactions

A number of medicinal products are known to interact with the glucose metabolism. Possible interactions must therefore be taken into account by the physician.

The following substances may reduce the patient's insulin requirements:
Oral anti-diabetic agents (OADs), GLP-1 receptor agonists, monoamine oxidase inhibitors (MAOIs), non-selective beta-adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids (except danazol and oxymetholone), alpha-adrenergic blocking agents, quinine, quinidine and sulfonamides.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone, diazoxide, asparaginase, nicotinic acid, oxymetholone and danazol.

Beta blockers may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify and prolong, or reduce, the hypoglycaemic effect of insulin.

Combination of thiazolidinediones and insulin
Cases of cardiac failure have been reported when thiazolidinediones were used in combination with insulin, especially in patients with risk factors for development of cardiac failure. This should be kept in mind if treatment with the combination of thiazolidinediones and Tresiba is considered. If the combination is used, patients should be observed for signs and symptoms of cardiac failure, weight gain and oedema. Thiazolidinediones must be discontinued if any signs of deterioration in cardiac function occur.

Incompatibilities
Substances added to Tresiba may cause degradation of insulin degludec. Tresiba must not be added to infusion fluids. Tresiba must not be mixed with other insulin products or solutions.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility
Animal reproduction studies with insulin degludec have not revealed any adverse effects on fertility.

In a combined fertility and embryofetal study in male and female rats, treatment with subcutaneous doses of insulin degludec up to 21 U/kg/day (yielding 5-6 times the AUC in humans at a dose of 0.8 U/kg/day) prior to mating and in female rats during gestation had no effect on mating performance or fertility.

Use in pregnancy
Pregnancy Category: A
Treatment with Tresiba may be considered during pregnancy, if clinically needed.

The use of Tresiba in pregnant women with diabetes has been investigated in an interventional trial (see Section 5.1 Pharmacodynamic Properties, Clinical trials). A moderate

amount of clinical trial and post-marketing data in pregnant women (more than 400 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity.

In rats, treatment with insulin degludec at subcutaneous doses ≥13 U/kg/day (resulting in 2.6 times the AUC in humans at a dose of 0.8 U/kg/day) caused an increase in the incidence of fetal skeletal abnormalities. Similar effects were seen with human insulin, and these are probably secondary to maternal hypoglycaemia. No adverse effects on embryofetal development were observed in rabbits at subcutaneous doses up to 3 U/kg/day (resulting in 9 times the human AUC at a dose of 0.8 U/kg/day).

In general, intensified blood glucose control and careful monitoring of pregnant women with diabetes mellitus are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually decrease in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements normally return rapidly to pre-pregnancy values. Careful monitoring of glucose control is recommended, and the insulin dose should be adjusted on an individual basis.

Use in lactation
There is no clinical experience with Tresiba during breast-feeding. In rats, insulin degludec and its metabolites were secreted in milk; the peak concentration of insulin degludec in milk was less than half of that in plasma. It is unknown whether Tresiba is excreted in human milk. No metabolic effects of Tresiba are anticipated in the breast-fed newborn/infant.

4.7 Effects on Ability to Drive and Use Machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (for example, driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or who have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Adverse Effects (Undesirable Effects)

Summary of the safety profile
More than 5600 patients have been exposed to insulin degludec in the clinical development programme. Hypoglycaemia is the most commonly observed adverse reaction in patients using insulin, including Tresiba.

Tabulated list of adverse events
Table 1: Treatment-emergent adverse events (excluding hypoglycaemia) in patients with type 1 diabetes mellitus (adverse events with frequency ≥ 5%) comparing Tresiba with insulin glargine from trials 3583 and 3770

Adverse Event Term	**Tresiba, % (n=801)**	**IGlar, % (n= 315)**
Nasopharyngitis	25.5	22.2
Upper respiratory tract infection	13.6	11.4
Headache	11.7	12.4
Sinusitis	6.5	6.3
Oropharyngeal pain	5.4	7.6

Nausea	5.2	5.7
Gastroenteritis	5.2	2.9
Influenza	4.6	5.1
Cough	4.2	6.7
Diarrhoea	3.7	5.1

Table 2: Treatment-emergent adverse events (excluding hypoglycaemia) in patients with type 1 diabetes mellitus (adverse events with frequency ≥ 5%) comparing Tresiba with insulin detemir from trial 3585

Adverse Event Term	**Tresiba, % (n=301)**	**Insulin detemir, % (n=152)**
Nasopharyngitis	19.6	22.4
Headache	12.0	6.6
Upper respiratory tract infection	7.3	7.2
Cough	4.3	5.3

Table 3: Treatment-emergent adverse events (excluding hypoglycaemia) in patients with type 2 diabetes mellitus (adverse events with frequency ≥5%) comparing Tresiba with insulin glargine with concomitant use of 1 or 2 OADs from trials 3579, 3672 and 3668

Adverse Event Term	**Tresiba, % (n=1450)**	**IGlar, % (n= 714)**
Nasopharyngitis	14.1	10.9
Headache	10.0	8.1
Diarrhoea	7.4	7.7
Upper respiratory tract infection	6.3	6.6
Back pain	5.4	4.3

Table 4: Treatment-emergent adverse events (excluding hypoglycaemia) in patients with type 2 diabetes mellitus (adverse events with frequency ≥5%) following basal-bolus therapy from trial 3582

Adverse Event Term	**Tresiba, % (n=753)**	**IGlar, % (n=251)**
Nasopharyngitis	14.2	13.9
Upper respiratory tract infection	14.2	12.7
Headache	8.6	7.2
Diarrhoea	6.1	8.0
Oedema peripheral	6.0	5.6
Cough	5.8	6.4
Influenza	5.6	6.0
Hypertension	5.4	5.2
Back Pain	5.4	7.2
Pain in extremity	5.0	5.6
Arthralgia	4.2	8.0

Table 5: Treatment-emergent adverse events (excluding hypoglycaemia) in patients with type 2 diabetes mellitus (adverse events with frequency ≥5%) comparing Tresiba with sitagliptin from trial 3580

Adverse Event Term	**Tresiba, % (n=226)**	**Sitagliptin, % (n=228)**
Headache	10.6	6.6
Diarrhoea	5.8	8.3
Nasopharyngitis	5.8	7.9
Nausea	3.5	6.1

Adverse reactions from clinical trials

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA System Organ Class. Frequency categories are defined according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).

System Organ Class	**Preferred Term**	**Frequency**
Immune system disorders	Hypersensitivity	Rare
	Urticaria	Rare
Metabolism and nutrition disorders	Hypoglycaemia	Very common
Skin and subcutaneous tissue disorders	Lipodystrophy	Uncommon
General disorders and administration site conditions	Injection site reactions	Common
	Peripheral oedema	Uncommon

Adverse reactions from post-marketing sources

Adverse reactions listed below are based on post-marketing source data and classified according to MedDRA System Organ Class.

System Organ Class	**Preferred Term**	**Frequency**
Skin and subcutaneous tissue disorders	Cutaneous amyloidosis	Not known

Description of selected adverse reactions

Immune system disorder

As with any insulin therapy, allergic reactions may occur. Immediate type allergic reaction to either insulin itself or the excipients may potentially be life threatening.

With Tresiba hypersensitivity (manifested with swelling of tongue and lips, diarrhoea, nausea, tiredness and itching) and urticaria were reported with rare frequency.

Hypoglycaemia

As with any insulin therapy, hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

Injection site reactions
As may occur with any insulin therapy, injection site reactions (including injection site haematoma, pain, haemorrhage, erythema, nodules, swelling, discolouration, pruritus, warmth and injection site mass) occurred in patients treated with Tresiba. These reactions are usually mild and transitory and they normally disappear during continued treatment.

Skin and subcutaneous tissue disorders
As with any insulin therapy, lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see Section 4.4 Special Warnings and Precautions for Use).

Peripheral oedema
Insulin, including Tresiba, may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Antibody production
There was no clinically relevant development of insulin antibodies after long-term treatment with insulin degludec.

Paediatric population
Tresiba has been administered to children (6-11 years) and adolescents (12-18 years) for the investigation of pharmacokinetic properties (see Section 5.2 Pharmacokinetic Properties). Safety and efficacy have been demonstrated in a long-term trial in children aged 1 to less than 18 years. The frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population (see Section 5.1 Pharmacodynamic Properties).

Other special populations
Based on results from clinical trials, the frequency, type and severity of adverse reactions observed in the elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

A specific overdose cannot be defined. However, hypoglycaemia may develop over sequential stages if doses are administered which are too high relative to the patient's requirements:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or other products containing sugar. It is therefore recommended that the patient always carries glucose-containing products. Adjustments in drug dosage, meal patterns, or exercise, may be needed.

- Severe hypoglycaemic episodes, including where the patient is not able to treat themselves, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person or with glucose given intravenously by a health care professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. After apparent clinical recovery from hypoglycaemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycaemia.

For information on the management of overdose (in non-emergency situations), contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

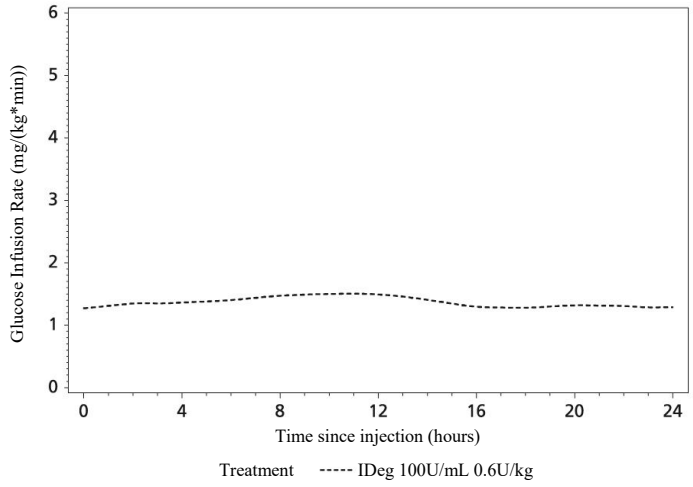
ATC code: A10AE06.

Mechanism of action

Insulin degludec binds to the human insulin receptor resulting in the same pharmacological effects as human insulin. The blood glucose lowering effect of Tresiba is due to the facilitated uptake of glucose following the binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

Tresiba is an ultra-long acting basal insulin that forms soluble multi-hexamers upon subcutaneous injection, resulting in a depot from which insulin degludec is continuously and slowly absorbed into the circulation leading to a flat and stable glucose lowering effect (Figure 1). During a period of 24 hours with once daily treatment the glucose-lowering effect of Tresiba, in contrast to insulin glargine, was evenly distributed between the first and second 12 hours ($AUC_{GIR,0\text{-}12h,SS}$ / $AUC_{GIR,total,SS}$ = 0.5 compared with 0.6 for insulin glargine).

Figure 1: Mean glucose infusion rate (GIR) profile of Tresiba (steady state) in type 2 diabetes mellitus



The duration of action of Tresiba is beyond 42 hours within the therapeutic dose range. In a steady state, glucose clamp trial lasting for 42 hours, subjects receiving 0.6 U/kg of Tresiba (n=21) did not have blood glucose elevations requiring supplemental insulin during the clamp period. For these subjects the duration of action was greater than 42 hours.

Steady state will occur after 2–3 days of dose administrations.

The glucose lowering action of Tresiba at steady state shows four times' lower day to day variability in terms of Coefficients of Variation (CV) for the glucose lowering effect during one dosing interval ($AUC_{GIR,\tau,SS}$) and 2-24 hours ($AUC_{GIR,2\text{-}24h,SS}$) as compared to insulin glargine (Table 6).

Table 6: Day to day variability in glucose lowering effect of Tresiba and insulin glargine at steady state in subjects with type 1 diabetes mellitus (trial 1991)

	Tresiba (n=26) (CV%)	Insulin glargine (100 units/mL) (n=27) (CV%)	p value
Day to day variability in glucose lowering effect during one dosing interval ($AUC_{GIR,\tau,SS}$)	20	82	p<0.0001
Day to day variability in glucose lowering effect from 2-24 hours ($AUC_{GIR,2\text{-}24h,SS}$)	22	92	p<0.0001

CV: within-subject coefficient of variation in %
SS: Steady State
$AUC_{GIR,2\text{-}24h}$: metabolic effect in last 22 hours of dosing interval (i.e., not influenced by i.v. insulin during the clamp run-in period)
n: number of subjects randomised

The total glucose lowering effect of Tresiba increases linearly with increasing doses.

The total glucose lowering effect is comparable for Tresiba 100 U/mL and 200 U/mL after administration of the same doses of the two products.

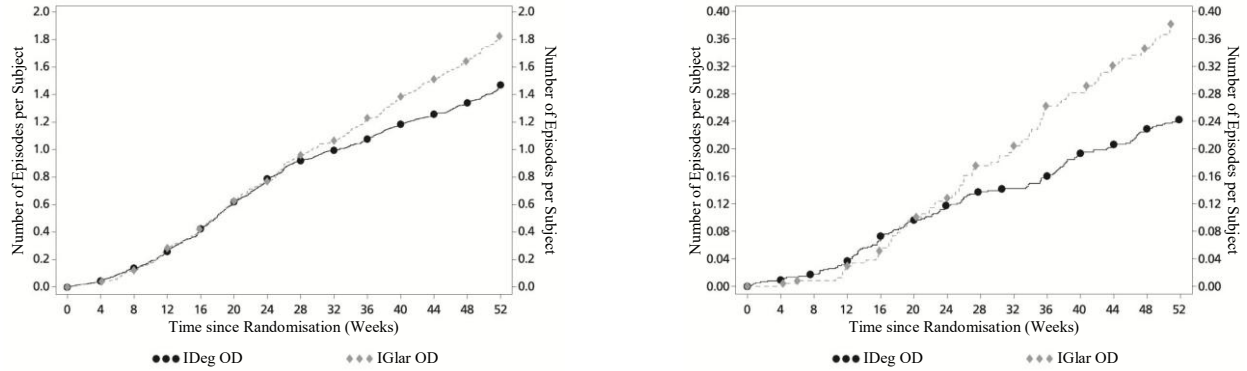
There is no clinically relevant difference in the pharmacodynamics of Tresiba between elderly and younger adult subjects.

Clinical trials
Eleven (11) multinational clinical trials of 26 or 52 weeks' duration were conducted as controlled open-label randomised, parallel, treat-to-target trials exposing 4275 patients to Tresiba (1102 in type 1 diabetes mellitus and 3173 in type 2 diabetes mellitus). Efficacy and safety of once daily dosing, including flexible dosing, of Tresiba (from 8-40 hours between doses), either for insulin initiation or insulin intensification, was confirmed.

Tresiba effectively improves glycaemic control as measured by HbA_{1c}. All trials comparing insulin products were carried out using a treat-to-target design, where titration of basal insulin was based on pre-breakfast glucose values in order to achieve similar degrees of glycaemic control allowing for objective comparison of overall safety profile of the tested insulins, including risk of hypoglycaemia. Non-inferiority for HbA_{1c} change from baseline to end of trial was confirmed in all trials against all comparators, except against sitagliptin, where insulin degludec was statistically significantly superior. Non-inferiority of change in HbA_{1c} was also confirmed for both dosing at the same time of the day and flexible dosing regimens in type 1 and in type 2 diabetes mellitus.

Hypoglycaemia
In type 2 diabetes mellitus, a treat-to-target clinical trial for insulin initiation showed a 36% lower rate of nocturnal confirmed hypoglycaemia (defined as episodes between midnight and 6 a.m. confirmed by plasma glucose < 3.1 mmol/L or by the patient needing third party assistance) with once daily Tresiba compared to insulin glargine, both in combination with oral anti-diabetic drugs (OADs). In a treat-to-target clinical trial (Trial 3579, n=1030), assessing basal bolus regimen in patients with type 2 diabetes mellitus, Tresiba showed a reduced overall risk of hypoglycaemia as well as nocturnal hypoglycaemia compared to insulin glargine.

Figure 2: Confirmed (left) and nocturnal confirmed (right) hypoglycaemic episodes – treatment emergent - mean cumulative function. Trial 3579: A 52 week basal OAD trial in type 2 diabetes mellitus.



In type 1 diabetes mellitus, treat-to-target clinical trials in patients of Tresiba vs. insulin detemir and vs. insulin glargine, showed 34% and 25% lower rates, respectively, of nocturnal confirmed hypoglycaemia for Tresiba.

In a prospectively planned meta-analysis across seven treat-to-target confirmatory trials in patients with type 1 and type 2 diabetes mellitus, Tresiba was superior in terms of a lower number of treatment emergent confirmed hypoglycaemic episodes and nocturnal confirmed hypoglycaemic episodes compared to insulin glargine. The results demonstrate that the lower FPG level with Tresiba is achieved with a lower risk of hypoglycaemia. In the maintenance period, the observed benefits become more pronounced, reflecting a sustained or even greater reduction in risk of hypoglycaemia over time with Tresiba once daily compared to insulin glargine once daily (Table 7).

Table 7: Hypoglycaemia meta-analysis outcomes

Estimated treatment ratio (Tresiba/Insulin glargine)	Confirmed hypoglycaemia Estimate [95% CI] Total	Nocturnal
Type 1 + type 2 diabetes mellitus (pooled)	0.91[0.83; 0.99]*	0.74 [0.65; 0.85]*
Maintenance period **	0.84 [0.75; 0.93]*	0.68 [0.58; 0.80]*
Geriatric subjects ≥ 65 years	0.82 [0.66; 1.00]	0.65 [0.46; 0.93]*
Type 1 diabetes mellitus	1.10 [0.96; 1.26]	0.83 [0.69; 1.00]
Maintenance period **	1.02 [0.88; 1.19]	0.75 [0.60; 0.94]*
Type 2 diabetes mellitus	0.83 [0.74; 0.94]*	0.68 [0.57; 0.82]*

Maintenance period **	0.75 [0.66; 0.87]*	0.62 [0.49; 0.78]*
Basal only therapy in previously insulin-naïve	0.83 [0.70; 0.98]*	0.64 [0.48; 0.86]*

*Statistically significant ** Episodes from week 16

Furthermore, two 64-week controlled, double-blind, randomised, cross-over, treat-to-target (SWITCH) trials were conducted in patients with type 1 diabetes mellitus (501 patients) and type 2 diabetes mellitus (721 patients), respectively. Patients with type 2 diabetes who had prior or concomitant treatment with sulfonylureas, glinides or bolus insulin were excluded from the SWITCH trial.

The double-blind, cross-over trials (Table 8) were conducted in patients with at least one risk factor* for hypoglycaemia. Patients were randomised to one of the two treatment sequences: Tresiba/insulin glargine (100 units/mL) or insulin glargine (100 units/mL)/Tresiba once daily and patients were also randomised to morning or evening dosing. In both trials, the reduction in HbA_{1c} from baseline to end of trial was confirmed to be non-inferior against insulin glargine (100 units/mL). For patients with type 1 diabetes mellitus, Tresiba significantly reduced the rates of severe hypoglycaemic events and of severe or blood glucose confirmed symptomatic events (overall and nocturnal), both in the maintenance and in the full treatment period, compared to insulin glargine (100 units/mL). For patients with type 2 diabetes mellitus, Tresiba significantly reduced the rates of severe or blood glucose confirmed symptomatic hypoglycaemic events (overall and nocturnal), both in the maintenance and in the full treatment period, and reduced the rate of severe hypoglycaemic events in the full treatment period compared to insulin glargine (100 units/mL).

* Subjects fulfilling at least one of the below criteria:
a) experienced at least one severe hypoglycaemic episode within the last year (ADA definition, April 2013)
b) moderate chronic renal failure, defined as glomerular filtration rate 30 – 59 mL/min/1.73m^2
c) hypoglycaemic symptom unawareness
d) diabetes mellitus duration for more than 15 years (T1D) or insulin use for at least 5 years (T2D) recent episode of hypoglycaemia 9defined by symptoms of hypoglycaemia and/or episode with low glucose measurement (≤70 mg/dL [≤3.9 mmol/L]) within the last 12 weeks prior to visit 1 (screening).

Table 8: Results from the double-blind, cross-over clinical trials in type 1 and type 2 diabetes mellitus

	Type 1 diabetes mellitus		**Type 2 diabetes mellitus[6]**	
	Tresiba[1]	**Insulin glargine (100 units/mL)[1]**	**Tresiba[2]**	**Insulin glargine (100 units/mL)[2]**
N	501		721	
HbA_{1c} (%)				
Baseline	7.6		7.6	
End of treatment	6.9	6.9	7.1	7.0
FPG (mmol/L)				

Baseline	9.4		7.6	
End of treatment	7.5	8.4	6.0	6.1
Rate of severe hypoglycaemia[3]				
Maintenance period[4]	0.69	0.92	0.05	0.09
	Ratio: 0.65 [0.48; 0.89]		*Ratio: 0.54 [0.21; 1.42]*	
Rate of severe or BG confirmed symptomatic hypoglycaemia[3,5]				
Maintenance period[4]	22.01	24.63	1.86	2.65
	Ratio: 0.89 [0.85; 0.94]		*Ratio: 0.70 [0.61; 0.80]*	
Rate of severe or BG confirmed nocturnal hypoglycaemia[3,5]				
Maintenance period[4]	2.77	4.29	0.55	0.94
	Ratio: 0.64 [0.56; 0.73]		*Ratio: 0.58 [0.46; 0.74]*	

[1] In a once-daily regimen + insulin aspart to cover mealtime insulin requirements
[2] In a once-daily regimen ± OADs (any combination of metformin, dipeptidyl peptidase-4 inhibitor, alpha-glucosidase inhibitor, thiazolidinediones, and sodium glucose cotransporter-2 inhibitor)
[3] Per patient year of exposure
[4] Episodes from week 16 in each treatment period
[5] Blood glucose (BG) confirmed symptomatic hypoglycaemia was defined as episodes confirmed by a plasma glucose value of less than 3.1 mmol/L, with symptoms consistent with hypoglycaemia. Nocturnal confirmed hypoglycaemia was defined as episodes between midnight and 6 a.m.
[6] Patients on prior or concomitant sulfonylureas/glinides and bolus insulin excluded

Clinical trials in type 1 diabetes mellitus
A total of 1578 subjects were randomised to treatment in the 3 therapeutic confirmatory trials in type 1 diabetes mellitus. The mean age at baseline was 42.8 years: 107 subjects (7%) were >65 years and 14 subjects (0.9%) were >75 years of age. All trials were similarly designed to allow for a pre-defined meta-analysis of hypoglycaemic endpoints.

In an open-label, treat to target clinical trial (trial 3583, n=629), adult patients with type 1 diabetes mellitus were randomised to 52 weeks of treatment with either Tresiba or insulin glargine once daily in a basal-bolus regimen with insulin aspart administered at each meal. Tresiba and insulin glargine had similar HbA_{1c} and fasting plasma glucose (FPG) reductions with a similar overall rate of confirmed hypoglycaemia. Treatment with Tresiba resulted in a statistically significant reduction in nocturnal hypoglycaemia (Table 9).

In an open label, treat to target clinical trial (trial 3585, n=455), adult patients with type 1 diabetes mellitus were randomised to 26 weeks of treatment with either Tresiba once daily or insulin detemir once or twice daily in a basal-bolus regimen with insulin aspart administered at each meal. Tresiba and insulin detemir had similar HbA_{1c} reductions with a similar overall rate of confirmed hypoglycaemia. Treatment with Tresiba resulted in a reduction in FPG and statistically significant reduction in nocturnal hypoglycaemia (Table 9).

See also trial 3770 in type 1 diabetes mellitus under "*Clinical trials investigating flexibility in time of dosing of Tresiba"* below.

Table 9: Results of clinical trials in type 1 diabetes mellitus (trials 3583 and 3585)

	Trial 3583 (52 weeks)		**Trial 3585 (26 weeks)**	
	Tresiba once daily + Insulin aspart	**Insulin glargine once daily +**	**Tresiba once daily + Insulin aspart**	**Insulin detemir once daily + Insulin aspart**

		Insulin aspart		
n	472	157	302	153
HbA_{1c}				
End of trial	7.3	7.3	7.3	7.3
Mean change from baseline	-0.40	-0.39	-0.73	-0.65
Estimated treatment difference [95%CI] Tresiba once daily – insulin glargine once daily	-0.01 [-0.14; 0.11]		-0.09 [-0.23; 0.05]	
FPG (mmol/L)				
End of trial	7.8	8.3	7.3	8.9
Mean change from baseline	-1.27	-1.39	-2.60	-0.62
Estimated treatment difference [95%CI] Tresiba once daily – insulin glargine once daily	-0.33 [-1.03; 0.36]		-1.66 [-2.37; -0.95]	
Rate of hypoglycaemia per patient year of exposure				
Severe hypoglycaemia	0.21	0.16	0.31	0.39
Confirmed hypoglycaemia	42.54	40.18	45.83	45.69
Treatment ratio [95%Cl] Tresiba once daily/ insulin glargine once daily	1.07 [0.89;1.28]		0.98 [0.80;1.20]	
Nocturnal confirmed hypoglycaemia	4.41	5.86	4.14	5.93
Treatment ratio [95%Cl] Tresiba once daily/ insulin glargine once daily	0.75 [0.59;0.96]		0.66 [0.49;0.88]	

n = number of subjects in the full analysis set (FAS)

Clinical trials in type 2 diabetes mellitus: Combination therapy with oral antidiabetic drugs (OADs) (trials 3579, 3672, 3582, 3580, 3668) or as monotherapy (trial 3582)
The 6 trials with Tresiba once daily dosing (at the same time each day) in type 2 diabetes mellitus included 4076 randomised subjects. The mean age at baseline was 58.0 years: 969 subjects (24%) were >65 years and 123 subjects (3%) were >75 years of age.

In an open label, treat to target clinical trial (Trial 3579, n=1030), adult patients with type 2 diabetes mellitus were randomised to 52 weeks of treatment with either Tresiba or insulin glargine once daily as part of a regimen of combination therapy with one or two of the following OADs: metformin or DPP-4 inhibitor. Tresiba and insulin glargine produced

similar HbA_{1c} reductions and treatment with Tresiba resulted in a reduction in FPG and a reduction in nocturnal hypoglycaemia. The overall rate of the confirmed hypoglycaemia was lower but not statistically significant with Tresiba compared to insulin glargine (Table 10)

In an open label, treat to target clinical trial (Trial 3672, n=457), adult patients with type 2 diabetes mellitus were randomised to 26 weeks of treatment with either Tresiba or insulin glargine once daily as part of a regimen of combination therapy with one or more of the following OADs: metformin or DPP-4 inhibitor. Tresiba and insulin glargine produced similar HbA_{1c} reductions. The overall rates of confirmed hypoglycaemia and nocturnal hypoglycaemia were lower but not statistically significant with Tresiba compared to insulin glargine. Treatment with Tresiba resulted in a reduction in FPG (Table 10).

Table 10: Results of clinical trials in type 2 diabetes mellitus (trials 3579 and 3672)

	Trial 3579 (52 weeks)		**Trial 3672 (26 weeks)**	
	Tresiba once daily + OAD(s) (+ met ± DPP-IV)	**Insulin glargine once daily + OAD(s)** (+ met ± DPP-IV)	**Tresiba once daily** + met ± DPP-IV	**Insulin glargine once daily** + met ± DPP-IV
n	773	257	228	229
HbA_{1c} (%)				
End of trial	7.1	7.0	7.0	6.9
Mean change from baseline	-1.06	-1.19	-1.30	-1.32
Estimated treatment difference (Tresiba - comparator) [95%CI]	0.09 [-0.04; 0.22]		0.04 [-0.11; 0.19]	
FPG (mmol/L)				
End of trial	5.9	6.4	5.9	6.3
Mean change from baseline	-3.76	-3.30	-3.70	-3.38
Estimated treatment difference (Tresiba-comparator) [95%CI]	-0.43 [-0.74; -0.13]		-0.42 [-0.78; -0.06]	
Rate of hypoglycaemia per Patient year of exposure				
Severe hypoglycaemia	0	0.02	0	0
Confirmed hypoglycaemia	1.52	1.85	1.22	1.42
Treatment ratio (Tresiba/ comparator) [95%Cl]	0.82 [0.64;1.04]		0.86 [0.58;1.28]	
Nocturnal confirmed hypoglycaemia	0.25	0.39	0.18	0.28
Treatment ratio (Tresiba/ comparator) [95%Cl]	0.64 [0.42;0.98]		0.64 [0.30;1.37]	

n = number of subjects in the full analysis set (FAS)

In an open label, treat to target clinical trial (Trial 3582, n=992), adult patients with type 2 diabetes mellitus were randomised to 52 weeks of treatment with either Tresiba or insulin glargine once daily in a basal-bolus regimen with insulin aspart administered at each meal as part of regimen of combination therapy with one or two of the following OADs: metformin or pioglitazone (PIO). Tresiba and insulin glargine resulted in similar $HbA_{1c.}$ FPG was lower but not statistically significant with Tresiba compared to insulin glargine. Treatment with Tresiba resulted in a statistically significant reduction in the overall rate of hypoglycaemia and a reduction in nocturnal hypoglycaemia (Table 11).

In an open label, treat to target clinical trial (Trial 3580, n=447), adult patients with type 2 diabetes mellitus were randomised to 26 weeks of treatment with either Tresiba or sitagliptin once daily as part of a regimen of combination therapy with one or more of the following OADs: metformin, sulfonylurea (SU), or PIO. Treatment with Tresiba resulted in a statistically significant reduction in mean HbA_{1c} and FPG compared to sitagliptin with a higher overall rate of confirmed hypoglycaemia. The overall rate of nocturnal hypoglycaemia was higher but not statistically significant with Tresiba compared to sitagliptin (Table 11).

Table 11: Results of clinical trials in type 2 diabetes mellitus (trials 3582 and 3580)

	Trial 3582 (52 weeks)		**Trial 3580 (26 weeks)**	
	Tresiba once daily + insulin aspart ± OAD(s) (+ IAsp TID ± met ± PIO)	**Insulin glargine once daily + insulin aspart ± OAD(s)** (+ IAsp TID ± met ± PIO)	**Tresiba once daily + OAD(s)** (± met ± SU/glinide ± PIO)	**Sitagliptin once daily + OAD(s)** (± met ± SU/glinide ± PIO)
n	744	248	225	222
HbA_{1c} (%)				
End of trial	7.1	7.1	7.2	7.7
Mean change from baseline	-1.17	-1.29	-1.56	-1.22
Estimated treatment difference (Tresiba-comparator) [95%CI]	0.08 [-0.05; 0.21]		-0.43 [-0.61; -0.24]	
FPG (mmol/L)				
End of trial	6.8	7.1	6.2	8.5
Mean change from baseline	-2.44	-2.14	-3.22	-1.39
Estimated treatment difference (Tresiba - comparator) [95%CI]	-0.29 [-0.65; 0.06]		-2.17 [-2.59; -1.74]	
Rate of hypoglycaemia per Patient year of exposure				
Severe hypoglycaemia	0.06	0.05	0.01	0
Confirmed hypoglycaemia	11.09	13.63	3.07	1.26

Treatment ratio (Tresiba / comparator) [95%Cl]	0.82 [0.69; 0.99]		3.81 [2.40; 6.05]	
Nocturnal confirmed hypoglycaemia	1.39	1.84	0.52	0.30
Treatment ratio (Tresiba / comparator) [95%Cl]	0.75 [0.58; 0.99]		1.93 [0.90; 4.10]	

n = number of subjects in the full analysis set (FAS)

Paediatric population
The efficacy and safety of Tresiba have been studied in a 1:1 randomised controlled clinical trial in children and adolescents with type 1 diabetes mellitus for a period of 26 weeks (n=350), followed by a 26-week extension period (n=280). Patients in the Tresiba arm included 43 children aged 1– 5 years, 70 children aged 6–11 years and 61 adolescents aged 12–17 years.

At week 26, the difference in HbA_{1c} reduction from baseline between Tresiba and insulin detemir was 0.15% with a 95% confidence interval of [-0.03%; 0.33%] and met the pre-specified non-inferiority margin (0.4%) (Table 12).

Table 12: Results at week 26 in a trial comparing Tresiba to insulin detemir in paediatric patients 1 year of age and older with type 1 diabetes mellitus receiving insulin aspart at mealtimes

	Tresiba once daily + insulin aspart	**Insulin detemir once or twice daily + insulin aspart**
n	174	176
HbA_{1c} (%)		
Baseline	8.2	8.0
End of 26 weeks	8.0	7.7
Estimated treatment difference (Tresiba-insulin detemir) [95%CI]*	0.15 [-0.03; 0.33]	
FPG (mmol/L)		
Baseline	9.0	8.4
End of 26 weeks	8.4	8.9
Adjusted mean change from baseline after 26 weeks	2.9	3.3
Daily basal insulin dose		
Baseline mean	15 U (0.37 U/kg)	16 U (0.41 U/kg)
Mean dose after 26 weeks	16 U (0.37 U/kg)	22 U (0.51 U/kg)
Daily bolus insulin dose		
Baseline mean	20 U (0.50 U/kg)	20 U (0.52 U/kg)
Mean dose after 26 weeks	23 U (0.56 U/kg)	22 U (0.57 U/kg)

*The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with missing data imputed by multiple imputation carrying forward the baseline value and adding the error term, with treatment, region, sex, and age group as fixed factors, and baseline HbA_{1c} as covariate.
In this trial, there were 2.9% of subjects in Tresiba and 6.3% Insulin detemir arms for whom data was missing at the 26-week HbA_{1c} measurement.

Tresiba dosed once daily showed similar reduction in HbA_{1c} at week 52 and greater reduction in FPG from baseline vs. the comparator insulin detemir dosed once or twice daily. These results show that the efficacy seen at 26 weeks was maintained throughout the full extension period of the trial. This was achieved with 30% lower daily doses of Tresiba compared to insulin detemir. The rates (events per patient-year of exposure) of severe hypoglycaemia (ISPAD definition; 0.51 vs. 0.33), confirmed hypoglycaemia (57.71 vs. 54.05) and nocturnal confirmed hypoglycaemia (6.03 vs. 7.60) were comparable with Tresiba vs. insulin detemir. In both treatment arms, children aged 6–11 years had a numerically higher rate of confirmed hypoglycaemia than in the other age groups. A numerically higher rate of severe hypoglycaemia in children aged 6–11 years in the Tresiba arm was observed. The rate of hyperglycaemic episodes with ketosis was significantly lower for Tresiba vs. insulin detemir, 0.68 and 1.09, respectively.

The frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population. Antibody development was sparse and had no clinical impact.

Clinical trials investigating flexibility in time of dosing of Tresiba
Tresiba provides the same level of glucose control while maintaining an overall reduced risk of hypoglycaemia, when injection time is changed from day to day compared to dosing at the same time every day, in treat-to target trials in both type 1 and type 2 diabetes mellitus adult subjects.

In an open label, treat to target clinical trial (trial 3770, n=493), adult patients with type 1 diabetes were randomised to 26 weeks of treatment with Tresiba either in a once-daily (with main evening meal) or flexible dosing regimen (intervals of approximately 8-40 hours between doses) with dosing in the morning on Monday, Wednesday and Friday and dosing in the evening on Tuesday, Thursday, Saturday and Sunday, or insulin glargine once daily (dosed according to the approved Product Information) in a basal-bolus regimen with insulin aspart administered at each meal. Tresiba once daily and flexible dosing regimens and insulin glargine had similar HbA_{1c} reductions and overall rates of confirmed hypoglycaemia. Treatment with Tresiba once daily with the main evening meal resulted in a reduction in FPG compared to insulin glargine, while treatment with Tresiba in the flexible dosing regimen resulted in a reduction in nocturnal hypoglycaemia.

In an open label, treat to target clinical trial (trial 3668, n=687), adult patients with type 2 diabetes were randomised to 26 weeks of treatment with either Tresiba in a once daily (with the main evening meal) or flexible dosing regimen [FF] (intervals of approximately 8-40 hours between doses) with dosing in the morning on Monday, Wednesday and Friday and dosing in the evening on Tuesday, Thursday, Saturday and Sunday, or insulin glargine once daily (dosed according to the approved Product Information) as part of a regimen of combination therapy with one or two of the following OADs: metformin, SU/glinides, pioglitazone. Tresiba once daily and flexible dosing regimens and insulin glargine had similar HbA_{1c} reductions and overall rate of confirmed hypoglycaemia. The overall rate of nocturnal hypoglycaemia was lower but not statistically significant with Tresiba compared to insulin glargine. Treatment with Tresiba once daily in the flexible dosing regimen resulted in reduction in FPG compared to insulin glargine (Table 13).

Table 13: Tresiba (fixed or flexible dosing schedule) compared with insulin glargine, with or without combination with OAD treatment in adult patients with type 2 diabetes mellitus (trial 3668)

	Tresiba once daily	**Tresiba once daily (Flex)**	**Insulin glargine once daily**
n	228	229	230
HbA_{1c} (%)			
End of trial	7.3	7.2	7.1
Mean change from baseline	-1.07	-1.28	-1.26
Estimated treatment difference (Tresiba - Comparator) [95%CI]		0.04 [-0.12; 0.20]	
Estimated treatment difference (Tresiba once daily FF (Fixed flexible) - Insulin degludec once daily) [95%CI]	-0.13 [-0.29; 0.03]		
FPG (mmol/L)			
End of trial	5.8	5.8	6.2
Mean change from baseline	-2.91	-3.15	-2.78
Estimated treatment difference (Tresiba - Comparator)[95%CI]		-0.42 [-0.82; -0.02]	
Estimated treatment difference (Tresiba once daily FF - Insulin degludec once daily) [95%Cl]	0.05 [-0.45; -0.35]		
Rate of hypoglycaemia per Patient year of exposure			
Severe hypoglycaemia	0.02	0.02	0.02
Confirmed hypoglycaemia	3.63	3.64	3.48
Treatment ratio (Tresiba /Comparator) [95%Cl]		1.03 [0.75;1.40]	
Estimated treatment ratio (Tresiba once daily FF/Insulin degludec once daily) [95%Cl]	1.10 [0.79;1.52]		
Nocturnal confirmed hypoglycaemia	0.56	0.63	0.75
Treatment ratio (Tresiba / Comparator) [95%Cl]		0.77 [0.44;1.35]	
Estimated treatment ratio (Tresiba once daily FF/Insulin degludec once daily) [95%Cl]	1.18 [0.66;2.12]		

n = number of subjects in the full analysis set (FAS)

Combination with GLP-1 Receptor Agonists

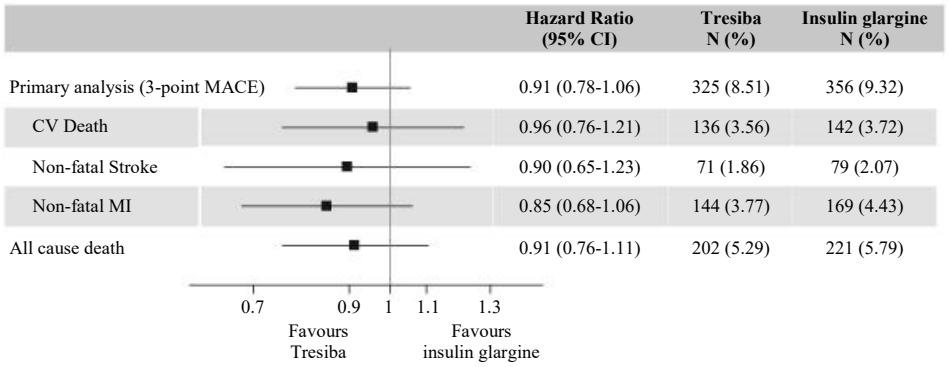
In a 104-week clinical trial, 57% of patients with type 2 diabetes treated with Tresiba (insulin degludec) in combination with metformin achieved a target $HbA_{1c} < 7.0\%$, and the remaining patients continued in a 26-week open-label trial and were randomised to add liraglutide or a single dose of insulin aspart (with the largest meal). In the insulin degludec plus liraglutide arm, the insulin dose was reduced by 20% in order to minimise the risk of hypoglycaemia. Addition of liraglutide resulted in a statistically significantly greater reduction of HbA_{1c} (-0.73% for liraglutide vs. -0.40% for comparator, estimated means) and body weight (-3.03 vs.

0.72 kg, estimated means). The rate of hypoglycaemic episodes (per patient year of exposure) was statistically significantly lower when adding liraglutide compared to adding a single dose of insulin aspart (1.0 versus 8.15; ratio: 0.13; 95% CI: 0.08 to 0.21).

Cardiovascular evaluation
DEVOTE was a randomised, double-blind, active-controlled, treat-to-target and event-driven clinical trial with a median duration of 2 years comparing the cardiovascular safety of Tresiba versus insulin glargine (100 units/mL) in 7,637 patients with type 2 diabetes mellitus at high risk of cardiovascular events. Patients eligible to enter the trial were 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure (85% of the enrolled population) or were 60 years of age or older and had other specified risk factors for cardiovascular disease (15% of the enrolled population).

The primary analysis was time from randomisation to first occurrence of a 3-component major adverse cardiovascular event (MACE) defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The trial was designed as a non-inferiority trial to exclude a pre-specified risk margin of 1.3 for the hazard ratio of MACE comparing Tresiba to insulin glargine. The cardiovascular safety of Tresiba as compared to insulin glargine was confirmed (Figure 3). Further, the analysis of the composite 3-point MACE in subgroups was aligned with the primary analysis.

Figure 3: Forest plot of analysis of the composite 3-point MACE and individual cardiovascular endpoints in DEVOTE



N: Number of subjects with a first EAC confirmed event during trial. %: Percentage of subjects with a first EAC confirmed event relative to the number of randomised subjects. EAC: Event adjudication committee. CV: Cardiovascular. MI: Myocardial infarction. CI: 95% confidence interval

The cardiovascular safety of Tresiba as compared to insulin glargine (100 units(mL) was confirmed (HR: 0.91; 95% CI [0.78;1.06], p = 0.209). Similar improvements in HbA_{1c} were achieved with Tresiba and insulin glargine, and a greater reduction in FPG was achieved with Tresiba.

Tresiba was superior compared to insulin glargine in terms of a lower rate of severe hypoglycaemic events and a lower proportion of subjects experiencing severe hypoglycaemia. The rate of nocturnal severe hypoglycaemia was significantly lower for Tresiba compared to insulin glargine.

Pregnancy

Tresiba has been studied in an open-label, randomised, active controlled clinical trial, in which pregnant women with type 1 diabetes mellitus were treated within a basal-bolus treatment regimen with Tresiba (92 women) or insulin detemir (96 women) as basal insulin, both in combination with insulin aspart as mealtime insulin (trial 4300, EXPECT).

Tresiba was non-inferior to insulin detemir as measured by HbA_{1c} at last planned HbA_{1c} visit prior to delivery after gestational week 16. Moreover, no difference between treatment groups was observed for glycaemic control (change in HbA_{1c}, FPG and post prandial glucose [PPG]) during pregnancy.

No clinically relevant differences were observed between Tresiba and insulin detemir for the maternal safety endpoints: hypoglycaemia, pre-term delivery and adverse events during the pregnancy. Pre-eclampsia was reported in 12 subjects treated with Tresiba (13.2%) and in 7 subjects (7.4%) who were treated with insulin detemir. Non-planned caesarean section was reported in 23 subjects (25.3%) treated with Tresiba and in 15 subjects (16.0%) treated with insulin detemir. The majority of adverse events reported in both groups were non-serious, mild in severity, unlikely related to the trial product and had the outcome "recovered/resolved". No deaths were reported in the subjects who were randomised in the trial.

No perinatal or neonatal death was reported. No clinically relevant differences were observed between Tresiba and insulin detemir for the pregnancy endpoints (early fetal death, presence of major abnormalities, neonatal hypoglycaemia, perinatal mortality, neonatal mortality, fetal macrosomia, large for gestational age and adverse events in the infant during the 30 days after birth).

5.2 Pharmacokinetic Properties

Absorption
The ultra-long action of insulin degludec derives from molecular modifications that alter the rate of absorption. After subcutaneous injection, soluble and stable multi-hexamers are formed creating a depot of insulin in the subcutaneous tissue. Insulin degludec monomers gradually separate from the multi-hexamers resulting in a slow and continuous delivery of insulin degludec into the circulation. Due to these properties, insulin degludec has a long half-life resulting in a flat and stable pharmacokinetic profile at steady state. Furthermore, during a period of 24 hours with once daily treatment, the exposure of insulin degludec was evenly distributed between the first and second 12 hours.

The ratio between $AUC_{Ins,0\text{-}12h,SS}$ and $AUC_{Ins,total,SS}$ was 0.53 for insulin degludec compared with 0.6 for insulin glargine.

Steady state serum concentrations are reached after 2–3 days of OD dose administrations.

Distribution
The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma.

Metabolism
Degradation of insulin degludec is similar to that of human insulin.

Excretion
The half-life after subcutaneous administration is determined by the rate of absorption from the subcutaneous tissue. The half-life of insulin degludec is approximately 25 hours independent of dose.

Linearity
Dose proportionality in total exposure is observed after subcutaneous administration within the therapeutic dose range. In direct comparison, requirements for bioequivalence are met for Tresiba 100 U/mL and Tresiba 200 U/mL (based on $AUC_{IDeg,\tau,SS}$ and $C_{max, IDeg,SS}$).

Special populations

Elderly, renal and hepatic impairment
There are no differences in the pharmacokinetics of Tresiba between elderly and younger adult patients at steady-state, or between healthy subjects and subjects with renal or hepatic impairment following a single dose.

Gender
There are no gender differences in the pharmacokinetic properties of Tresiba.

Paediatrics
The pharmacokinetic properties of Tresiba in children (1–11 years) and adolescents (12–18 years) were at steady state comparable to those in adults with type 1 diabetes mellitus. The ultra-long acting properties of Tresiba seen in adults are preserved in children and adolescents. Total exposure after a single fixed dose was higher in children/adolescents than in adults with type 1 diabetes mellitus.

5.3 Preclinical Safety Data

Genotoxicity
Genotoxicity studies have not been carried out with insulin degludec.

Carcinogenicity
Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of insulin degludec. In a 52-week study, rats received subcutaneous doses of insulin degludec up to 10 U/kg/day (resulting in 5 times the AUC in humans at a dose of 0.8 U/kg/day). No treatment-related increases in incidences of hyperplasia, benign or malignant tumours were recorded, and no treatment related changes in the female mammary gland cell proliferation were found using BrdU incorporation. *In vitro* studies showed the ratio of mitogenic relative to metabolic potency for insulin degludec is unchanged compared to human insulin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Glycerol, phenol, metacresol, zinc, hydrochloric acid and sodium hydroxide for pH adjustment, and water for injections.

6.2 Incompatibilities
Incompatibilities were either not assessed or not identified as part of the registration of this medicine. See Section 4.5 Interactions with Other Medicines and Other Forms of Interactions – Incompatibilities.

6.3 Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Unopened FlexTouch prefilled pens, FlexPen prefilled pens or Penfill cartridges
Store at 2°C to 8°C. Refrigerate. Do not freeze. Store Tresiba away from the freezing element in the refrigerator.

FlexTouch or FlexPen in use or carried as a spare
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. Pens should not be exposed to excessive heat or light.

Penfill cartridges in use or carried as a spare
Store below 30°C for up to 28 days. Do not refrigerate. Any remainder must then be discarded. Cartridges should not be exposed to excessive heat or light.

Tresiba FlexTouch and Tresiba FlexPen: Keep the pen cap on when Tresiba is not in use in order to protect from light.

Tresiba Penfill: Keep cartridges in the outer carton in order to protect from light.

6.5 Nature and Contents of Container

Tresiba contains insulin degludec 100 U/mL or insulin degludec 200 U/mL, in the following presentations:

Tresiba Strength	**Total insulin (units)**	**Total Volume**	**Pack sizes***	**Maximum dose per injection**	**Dose increment**	**Dose range**
100 U/mL FlexTouch	300	3 mL	1x3mL 5x3mL	80 U	1 U	1- 80 U
200 U/mL FlexTouch	600	3 mL	1x3mL 3x3mL	160 U	2 U	2 - 160 U
100 U/mL FlexPen	300	3 mL	1x3mL 5x3mL	60 U	1 U	1- 60 U
100 U/mL Penfill	300	3 mL	5x3mL	This will be dependent on the Penfill cartridge delivery device used.		

*Not all pack sizes may be marketed.

Tresiba Penfill 100 U/mL, solution for injection in cartridge
Tresiba Penfill: 3 mL solution in cartridge (type 1 glass), with a plunger (halobutyl) and a laminate rubber sheet (halobutyl/polyisoprene) in a carton.

Tresiba FlexTouch 100 U/mL, solution for injection in prefilled pen
Tresiba FlexTouch 200 U/mL, solution for injection in prefilled pen
Tresiba FlexTouch 3 mL solution in cartridge (type 1 glass) with a plunger (halobutyl) and a laminate rubber sheet (halobutyl/polyisoprene) contained in a prefilled multidose disposable pen made of polypropylene.

Tresiba FlexPen 100 U/mL, solution for injection in prefilled pen
Tresiba FlexPen 3 mL solution in cartridge (type 1 glass) with a plunger (halobutyl) and a laminate rubber sheet (halobutyl/polyisoprene) contained in a prefilled multidose disposable pen made of polypropylene.

6.6 Special Precautions for Disposal
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

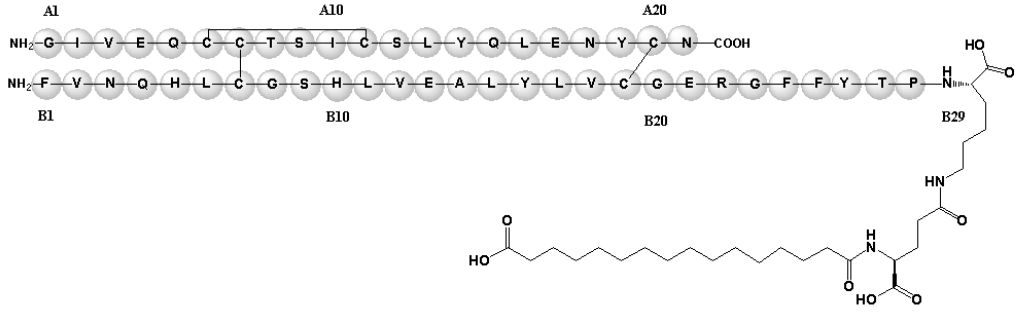
6.7 Physicochemical Properties
Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side chain consisting of glutamic acid and a C16 fatty acid has been attached.

Chemical name: LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin.

Molecular formula: $C_{274}H_{411}N_{65}O_{81}S_6$.

Molecular weight: 6103.97 daltons.

Chemical structure



CAS number
844439-96-9.

7. MEDICINE SCHEDULE (POISONS STANDARD)
S4

8. SPONSOR
Novo Nordisk Pharmaceuticals Pty Ltd
Level 10, 118 Mount Street,
North Sydney NSW 2060
Australia

www.novonordisk.com.au

9. DATE OF FIRST APPROVAL
29 November 2017

10. DATE OF REVISION
29 August 2025

Summary table of changes

Section changed	Summary of new information
4.6 & 5.1	Change to Pregnancy Category A and inclusion of results from study in pregnant women with type 1 diabetes mellitus (EXPECT)