Attachment 1: Product information for AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Final 22 May 2018. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

TRESIBA® Penfill®

TRESIBA® FlexTouch®

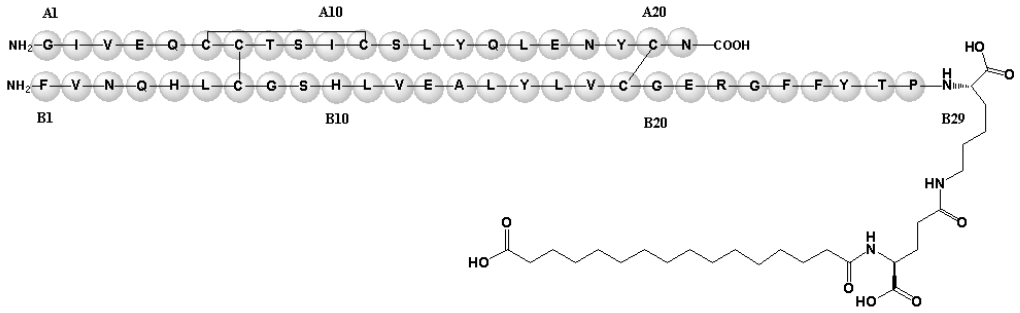
NAME OF THE MEDICINE

Australian Approved Biological Name (ABN)

Insulin degludec

Schematic structure of the molecule

Insulin degludec has the molecular formula $C_{274}H_{411}N_{65}O_{81}S_6$ and a molecular weight of 6103.97 daltons.



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

The CAS no. is 844439-96-9.

DESCRIPTION

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

TRESIBA is an ultra-long acting basal insulin analogue, for once-daily (OD) subcutaneous administration at any time of the day

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.

TRESIBA has a slow consistent rate of absorption which provides a flat and stable glucose-lowering-effect with a low variability. When needed the patient has the option of changing the once daily injection time from day-to-day.

TRESIBA 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 or cartridge contains 3 mL equivalent to 300 U. The prefilled pen can provide a maximum dose of 80 U in a single injection in dose increments of 1 U.

TRESIBA 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 pen can provide a maximum dose of 160 U in a single injection in dose increments of 2 U.

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.

Attachment 1: Product information for AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Final 22 May 2018. This Product Information was approved at the time this AusPAR was published.

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 also contains the following inactive ingredients: glycerol, phenol, metacresol, zinc acetate, hydrochloric acid and sodium hydroxide for pH adjustment, and water for injections.

PHARMACOLOGY

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.

Pharmacodynamics

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 OD 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).

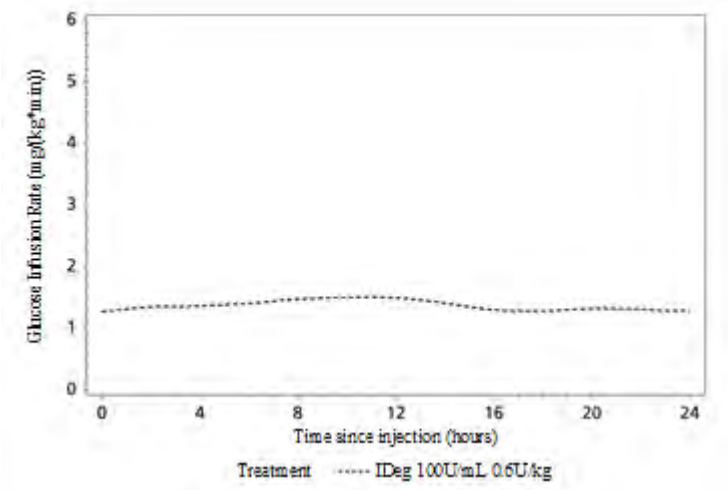


Figure 1: Mean glucose infusion rate (GIR) profile of TRESIBA (steady state) in type 2 diabetes mellitus

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 1).

Attachment 1: Product information for AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Final 22 May 2018. This Product Information was approved at the time this AusPAR was published.

Table 1: 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 (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

Total glucose lowering effect of TRESIBA increases linearly with increasing doses.

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.

Pharmacokinetics

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 OD 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 AUCIDeg,τ,SS and Cmax, IDeg,SS).

Attachment 1: Product information for AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Final 22 May 2018. This Product Information was approved at the time this AusPAR was published.

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 were investigated in children (6–11 years) and adolescents (12–18 years) and compared to 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 is higher in children/adolescents than in adults with type 1 diabetes mellitus.

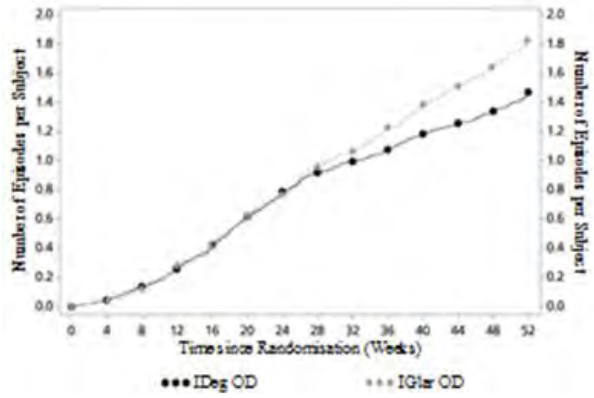
CLINICAL TRIALS

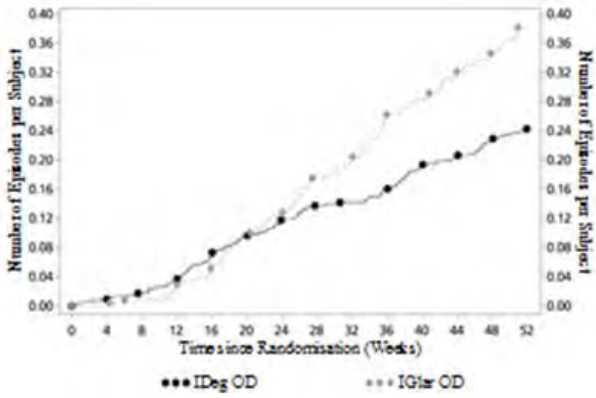
11 multi-national clinical trials of 26 or 52 weeks' duration were conducted as controlled open label randomised, parallel, treat-to-target trials exposing 4275 patients to TRESIBA (1102 in type 1 diabetes mellitus and 3173 in type 2 diabetes mellitus). Efficacy and safety of OD dosing, including flexible 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 trials 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 OD 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.





Attachment 1: Product information for AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Final 22 May 2018. This Product Information was approved at the time this AusPAR was published.

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 OD compared to insulin glargine OD (Table 2).

Table 2: Hypoglycaemia meta-analysis outcomes

Estimated treatment ratio (TRESIBA/Insulin glargine)	Confirmed hypoglycemia 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

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 OD 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 3).

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 OD 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 3).

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

Attachment 1: Product information for AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Final 22 May 2018. This Product Information was approved at the time this AusPAR was published.

Table 3: Results of clinical trials in type 1 diabetes mellitus (trials 3583 and 3585)

	Trial 3583 (52 weeks)		Trial 3585 (26 weeks)	
	TRESIBA OD + Insulin aspart	**Insulin glargine OD + Insulin aspart**	**TRESIBA OD + Insulin aspart**	**Insulin detemir OD + 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 OD – insulin glargine OD	-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 OD – insulin glargine OD	-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 OD/ insulin glargine OD	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 OD/ insulin glargine OD	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 OD as part of a regimen of combination therapy with one or two of the following OAD's: 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 4)

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 OD as part of a regimen of combination therapy with one or more of the following OAD's: 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 4).

Table 4: Results of clinical trials in type 2 diabetes mellitus (trials 3579 and 3672)

Attachment 1: Product information for AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Final 22 May 2018. This Product Information was approved at the time this AusPAR was published.

	Trial 3579 (52 weeks)		**Trial 3672 (26 weeks)**	
	TRESIBA OD + OAD(s) (+ met ± DPP-IV)	**Insulin glargine OD + OAD(s)** (+ met ± DPP-IV)	**TRESIBA OD** + met ± DPP-IV	**Insulin glargine OD** + 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 OD 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 OAD's: 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 5).

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 OD as part of a regimen of combination therapy with one or more of the following OAD's: 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 5)

Attachment 1: Product information for AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Final 22 May 2018. This Product Information was approved at the time this AusPAR was published.

Table 5: Results of clinical trials in type 2 diabetes mellitus (trials 3582 and 3580)

	Trial 3582 (52 weeks)		**Trial 3580 (26 weeks)**	
	TRESIBA OD + insulin aspart ± OAD(s) (+ IAsp TID ± met ± PIO)	**Insulin glargine OD + insulin aspart ± OAD(s)** (+ IAsp TID ± met ± PIO)	**TRESIBA OD + OAD(s)** (± met ± SU/glinide ± PIO)	**Sitagliptin OD + 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)

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 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 OD (dosed according to the approved Product Information) in a basal-bolus regimen with insulin aspart administered at each meal. TRESIBA OD and flexible dosing regimens and insulin glargine had similar HbA_{1c} reductions and overall rates of confirmed hypoglycaemia. Treatment with TRESIBA OD 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 OD (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 OD (dosed according to the approved Product Information) as part of a regimen of combination therapy with one or two of the following OAD's: metformin, SU/glinides, pioglitazone. TRESIBA OD 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 OD in the flexible dosing regimen resulted in reduction in FPG compared to insulin glargine (Table 6).

Table 6: TRESIBA (fixed or flexible dosing schedule) compared with insulin glargine, with or without combination with OAD treatment in patients with type 2 diabetes mellitus (trial 3668)

	TRESIBA OD	**TRESIBA OD (Flex)**	**Insulin glargine OD**
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 OD FF (Fixed flexible) - Insulin degludec OD) [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 OD FF - Insulin degludec OD) [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)		1.03 [0.75;1.40]	

Attachment 1: Product information for AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Final 22 May 2018. This Product Information was approved at the time this AusPAR was published.

[95%CI]			
Estimated treatment ratio (TRESIBA OD FF/Insulin degludec OD) [95%CI]	1.10 [0.79;1.52]		
Nocturnal confirmed hypoglycaemia	0.56	0.63	0.75
Treatment ratio (TRESIBA / Comparator) [95%CI]		0.77 [0.44;1.35]	
Estimated treatment ratio (TRESIBA OD FF/Insulin degludec OD) [95%CI]	1.18 [0.66;2.12]		

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

Cardiovascular evaluation

In the phase 3a development programme of insulin degludec and insulin degludec/insulin aspart, a prespecified meta-analysis showed a comparable risk for major adverse cardiovascular events (MACE) for insulin degludec versus comparators. However, additional analyses including non-randomised extension trials and phase 3b trials could not exclude a possible small increased risk of MACE.

To confirm the cardiovascular safety of insulin degludec a dedicated cardiovascular outcomes trial (DEVOTE) was conducted. DEVOTE was a randomised, double-blind, and event-driven clinical trial comparing the cardiovascular safety of insulin degludec versus insulin glargine (100 units/mL) in 7,638 patients with type 2 diabetes mellitus at high risk of cardiovascular events. The primary endpoint was time from randomisation to first occurrence of a 3-component major adverse cardiovascular event (MACE) comprising cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

A pre-planned interim analysis was performed when 150 first MACEs were accrued (average duration of treatment 6 months), providing 95% power to rule out hazard ratios (HRs) exceeding 1.8, assuming a true HR of 1.0. The interim analysis supported the cardiovascular safety of insulin degludec compared to insulin glargine (HR 0.92 $[0.67; 1.27]_{95\% CI}$). Confirmation of these preliminary results will be available when the study concludes.

INDICATIONS

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

CONTRAINDICATIONS

Hypersensitivity to insulin degludec or any of the excipients.

PRECAUTIONS

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.

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.

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.

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.

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.

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: B3

There is no clinical experience with TRESIBA in pregnant women.

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 trimester. After delivery, insulin requirements normally return rapidly to pre-pregnancy values.

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.

Paediatric use

Safety and efficacy of TRESIBA in children and adolescents have not yet been established.

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.

Renal and hepatic impairment

TRESIBA can be used in patients with renal and/or hepatic impairment. As with all insulin products, glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis.

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 tumors 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.

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.

INTERACTIONS WITH OTHER MEDICINES

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 sulphonamides.

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.

Attachment 1: Product information for AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Final 22 May 2018. This Product Information was approved at the time this AusPAR was published.

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.

ADVERSE EFFECTS

A. 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.

B. Tabulated list of adverse reactions

Table 7: 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 8: 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 9: 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 10: 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

Adverse Event Term	TRESIBA, % (n=753)	IGlar, % (n=251)
Back Pain	5.4	7.2
Pain in extremity	5.0	5.6
Arthralgia	4.2	8.0

Table 11: 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

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

C. 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.

Lipodystrophy

As with any insulin therapy, lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

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 (please see 'Pharmacokinetics'). Safety and efficacy have not been investigated in children and adolescents.

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.

DOSAGE AND ADMINISTRATION

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.

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.

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

Safety and efficacy of TRESIBA in children and adolescents have not yet been established.

Initiation of TRESIBA

For patients with type 1 diabetes mellitus, TRESIBA is to be used once daily with meal time 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 patients 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, changing the basal insulin to TRESIBA can be done unit-to-unit based on the previous basal insulin dose with subsequent individual dosage adjustments. For patients

with type 1 diabetes mellitus transferring from twice-daily basal insulin or having HbA1c <8.0% at the time of transfer, the dose of TRESIBA needs to be determined on an individual basis. Dose reduction needs to be considered based on the glycaemic response.

For patients with type 2 diabetes mellitus taking 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.

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

Based on the needs of the patient, and unlike other basal insulins, TRESIBA allows for some flexibility in the timing of insulin administration. Patients who forget a dose are advised to take it upon discovery and then resume their usual OD dosing schedule. Ensure a minimum of 8 hours between injections.

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.

TRESIBA 200 U/mL

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

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 be rotated within the same region in order to reduce the risk of lipodystrophy.

Instructions for use and handling

TRESIBA Penfill and TRESIBA FlexTouch must not be used if the solution does not appear clear and colourless. TRESIBA which has been frozen must not be used.

TRESIBA Penfill and TRESIBA FlexTouch are for use by one person only.

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.

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.

Attachment 1: Product information for AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Final 22 May 2018. This Product Information was approved at the time this AusPAR was published.

OVERDOSAGE

A specific overdose can not 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 Poison Information Centre on 131126 (Australia).

PRESENTATIONS AND STORAGE CONDITIONS

Presentations

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 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: 3mL solution in cartridge (type 1 glass), with a plunger (halobutyl) and a stopper (halobutyl/isoprene) in a carton.

TRESIBA FlexTouch100 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 stopper (halobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene.

Storage conditions

Unopened Penfill cartridges or FlexTouch prefilled pens

Store at 2°C to 8°C. Refrigerate. Do not freeze. Store TRESIBA away from the freezing element in the refrigerator.

FlexTouch 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. They 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. They should not be exposed to excessive heat or light.

TRESIBA FlexTouch: 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.

The shelf life for TRESIBA is 30 months.

NAME AND ADDRESS OF SPONSOR

Novo Nordisk Pharmaceuticals Pty Limited
Level 3, 21 Solent Circuit,
Baulkham Hills,
NSW 2153,
Australia.

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

Date of first inclusion in the Australian Register of Therapeutic Goods:

29 November 2017