The East of England
Priorities Advisory Committee
A function of PrescQIPP

GUIDANCE STATEMENT

Insulin degludec (Tresiba®)

Recommendations

1. Insulin degludec is **NOT** recommended for routine use in adults or children with either type 1 or type 2 diabetes.
2. Insulin degludec may be of benefit in certain patients with type 1 diabetes where other basal insulin options have been tried and failed, and who meet the following criteria:
    - Patients with significant nocturnal hypoglycaemia, despite optimal adjustments of lifestyle (eliminating any contributory factors), diet (undertaken structured education, e.g. DAFNE), and basal insulin/multiple daily injections and who fulfil the criteria for insulin pump therapy.
    - "Chaotic patients" who may be at significant risk of diabetic ketoacidosis (DKA) if daily basal insulin is missed, despite optimal adjustments of lifestyle, and diet and optimising basal insulin/multiple daily injections.
    - Patients with psychological problems (e.g. eating disorders or patients with intermittent compliance issues with insulin injections), who are not supervised by a daily carer and do not qualify to receive district nurse injections of daily insulin glargine, and who may be at significant risk of DKA if daily basal insulin is missed.
    - Patients with a diagnosed allergy to either insulin glargine or insulin detemir.
3. The use of the higher strength insulin degludec 200 units/ml is not routinely recommended.
4. Approval arrangements for treatment should be agreed locally. Following addition to local formularies, on-going assessment of treatment uptake should be monitored using ePACT data. It is also recommended that the commissioning decision is reviewed annually based on local audit and assessment of outcome data for patients started on insulin degludec to ensure that the treatment is continuing to meet the specific needs of the local population.
5. Insulin degludec should be initiated by a consultant-led specialist team and is NOT suitable for initiation by GPs or other prescribers in primary care unless under the supervision of a specialist. It is recommended that the initial dose titration and monitoring is closely supervised by a specialist team.
6. Ongoing provision of the insulin may be undertaken in primary care by agreement between the specialist and the patient's GP. All patients should be reviewed by the initiating specialist team at six months and returned to previous treatment if no improvement in overall disease control from baseline is demonstrated.

Key points

- Diabetes mellitus is a group of metabolic disorders in which persistent hyperglycaemia (high blood sugar) is caused by deficient insulin secretion or by resistance to the actions of insulin combined with relative insulin deficiency.
- Insulin degludec is an ultra-long-acting basal insulin for once-daily subcutaneous administration at any time of the day, preferably at the same time every day and should be dosed in accordance with the individual patient's needs.
- Insulin degludec has been shown to be non-inferior to insulin glargine 100units/ml for both type 1 and type 2 diabetes; with statistically significantly lower rates of hypoglycaemia, particularly nocturnal hypoglycaemia in some of the trials.
- There is limited comparative evidence with other insulins.
- There is limited evidence to confirm that insulin degludec use is associated with a reduction in hospital admissions for diabetes related complications.
- There is no comparative evidence with insulin pumps.
- There are no patient-oriented outcome data for the effects of insulin degludec on macrovascular or microvascular outcomes.
- There is limited long-term safety data.
- Insulin degludec is available in 100 units/ml strength and an additional higher strength 200 units/ml. The latter strength is classified as high strength insulin and may be associated with an increased risk of medication errors, due to the wrong product being supplied. A MHRA Drug Safety Update has been issued with advice for healthcare professionals to minimise risk of errors with the two strengths. The use of high strength insulins is not routinely supported.
- NICE Clinical Guideline on type 1 diabetes implies that insulin degludec can be used as an option in patients who have unsuccessfully tried other basal insulins. The NICE Clinical Guideline on type 2 diabetes recommends isophane insulin first line in patients who remain uncontrolled despite optimised oral hypoglycaemic therapy. Basal analogue insulins can be used where treatment with isophane insulin has failed. There is no specific recommendation regarding insulin degludec in the NICE Clinical Guideline on diabetes management in children.
- The Scottish Medicines Consortium has accepted the use of insulin degludec in adults only.
- Insulin degludec is recommended as an option for restricted use within NHS Wales for the treatment of diabetes mellitus in adult patients where treatment with a basal insulin analogue is considered appropriate. It is not recommended for use in adolescents and children from the age of one year.
- Insulin degludec is a higher cost than biphasic insulin or other long acting basal insulins. In clinical trials, insulin degludec was started at a dose of 10 units/day in insulin naïve patients. Patients on alternative insulins were transferred on a unit to unit basis. Current cost for biphasic insulin is approximately £30 per pack, or £0.40 for 20 units and £146 per year, based on 20 units per day, for insulin glargine (long acting basal insulin) is £0.56 for 20 units and £204 per year, versus £0.62 for 20 units or £226 per year for insulin degludec.
- Insulin degludec may offer few or no meaningful advantages for the majority of potential users but may be suitable for a small subgroup of patients, for whom glycaemic control cannot be achieved despite optimal adjustments of lifestyle (eliminating any contributory

factors), diet (undertaken structured education e.g. DAFNE), and basal insulin/multiple daily injections and who fulfil the criteria for insulin pump therapy or individuals for whom injecting at the same time every day may not always be possible.

Proposed sector of prescribing: Primary and secondary care

Introduction

Diabetes mellitus is a group of metabolic disorders, in which persistent hyperglycaemia is caused by deficient insulin secretion, or by resistance to the actions of insulin, often combined with relative insulin deficiency. Insulin deficiency and insulin resistance leads to the abnormalities of carbohydrate, fat, and protein metabolism that are characteristic of diabetes mellitus.[1,2]

Insulin degludec is an ultra-long-acting basal analogue 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. This leads to a flat and stable glucose-lowering effect.[3-5]

Insulin degludec has a cited duration of action between 36 and 42 hours[3-5] with a half-life of approximately 25 hours independent of dose.[4]

Type 1 diabetes

Two open-label, phase 3, non-inferiority trials have compared insulin degludec with insulin glargine once daily.[6,7] In the first trial,[6] 629 patients who had been treated with basal bolus insulin for at least a year and with a HbA1c level of 61-86mmol/mol (7.7%-10%), received either insulin glargine or insulin degludec once daily. Insulin aspart was used at mealtimes. The primary outcome measure was the mean decrease in HbA1c. Treatment was titrated to achieve plasma glucose control between 3.9-5.0mmol/L. After 52 weeks, mean decreases of 4.3-4.4mmol/mol (0.39% and 0.49%) were recorded in the insulin glargine and insulin degludec groups respectively ($p<0.0001$).[6]

In the second trial,[7] 493 patients received either insulin degludec administered at a variable interval of between eight to 40 hours or insulin glargine 100 units/ml given at a fixed time each day for 26 weeks. The mean HbA1c decreased by 4.4mmol/mol (0.4%) with the variable regime and 4.5mmol/mol (0.41% and 0.58%), for the insulin degludec and insulin glargine fixed time groups respectively. Nocturnal hypoglycaemia was assessed as a secondary endpoint in both trials and was reported as lower in patients being treated with insulin degludec vs insulin glargine in trial 1 but not in trial 2.[7] The overall clinical significance of this is unclear.

Children

In a 26 week, randomised open label, parallel group, non-inferiority trial, 350 children aged between one and 17 years with type 1 diabetes received either insulin degludec once daily (n=174) or insulin detemir (n=176) once or twice daily. Both groups received mealtime insulin aspart. After the initial 26 weeks 280 patients had entered a 26-week extension phase. The primary endpoint was change in baseline in Hb1Ac after 26 weeks' treatment.[8]

Non-inferiority was confirmed with respect to change in baseline for Hb1Ac; estimated treatment difference (ETD) 0.15% [0.03; 0.32]. At 52 weeks, HbA1c was 7.9% with insulin degludec vs 7.8% insulin detemir. The majority of insulin detemir treated patients required twice daily administration to achieve glycaemic targets [8]. Overall hypoglycaemia rates did not differ significantly between degludec and detemir, however nocturnal hypoglycaemic rates were lower in the degludec group, but serious hypoglycaemic episodes occurred more frequently. Rates of hyperglycaemia with ketosis were lower in those treated with insulin degludec vs insulin detemir.[8]

Type 2 diabetes

Two phase-3, open-label, trials, investigated the non-inferiority of insulin degludec compared to insulin glargine 100 units/ml in patients with type 2 diabetes previously treated with insulin.[9,10]

In the first trial,[9] 1,006 patients with inadequate HbA1c control despite treatment with insulin (with or without oral antidiabetic drugs) for at least three months were randomised to receive either insulin degludec or insulin glargine 100 units/ml. Metformin or pioglitazone were permitted during the trial. The primary end point was reduction in HbA1c at three months.

At three months the study reported that non-inferiority was proven by the reduction in HbA1c level of 12.1mmol/mol (1.1%) for insulin degludec versus 13mmol/mol (1.18%) for insulin glargine 100 units/ml. Rates of nocturnal hypoglycaemia were 40% vs. 47% resulting in 0.5 fewer episodes per year per patient for insulin degludec.[9]

In the second trial,[10] 687 patients with either type 1 or type 2 diabetes received either insulin glargine 100 units/ml or insulin degludec administered at a variable dose interval of 8-40 hours or a fixed time interval. Both insulin naïve and patients with prior insulin use were included. The primary outcome was the mean change in HbA1c. After 52 weeks, a decrease in HbA1c of 14mmol/mol (1.28%) was seen for insulin degludec (variable injection time), 11.8mmol/mol (1.07%) for insulin degludec (fixed time) and 13.9mmol/mol (1.26%) for the insulin glargine 100 units/ml group (fixed time), and the investigators concluded that non-inferiority had been demonstrated.[9] Rates of severe hypoglycaemia were similar between those treated with insulin degludec or insulin glargine 100 units/ml.[10]

Adverse events

The adverse events reported in the trials were generally similar between insulin glargine 100 units/ml and insulin degludec; however, concerns had been raised with respect to insulin degludec and cardiovascular safety.[4,11] The European Medicines Agency (EMA) approved degludec in September 2012, but the US FDA have only recently granted approval to insulin degludec and insulin degludec plus aspart. This was due to possible increased risk of cardiovascular events in patients being treated with insulin degludec and the FDA have therefore asked the manufacturer to conduct further cardiovascular safety studies. In support of their opinion, the FDA cited a meta-analysis of studies which calculated that degludec increased the risk of major adverse cardiovascular events (hazard ratio 1.67, 95% CI 1.01 to 2.75) as the reason for its decision at the time. Whilst the same data was available to the EMA in September 2012, the EMA used a different interpretation of events in the pre-specified analysis used during the product assessment process, which calculated the hazard ratio for major cardiovascular events was 1.097 (0.681 to 1.768).[12]

Other meta-analyses of publicly disclosed randomised controlled trials do not suggest an increased risk of major cardiovascular events between the different basal insulin analogues and no biological rationale for a possible difference in cardiovascular effect of basal insulins has been proposed so far. However, the number of available cardiovascular events in clinical trials is very small, preventing a clear-cut analysis and conclusion. As with other basal insulins, the risk of cardiovascular complications with insulin degludec remains unknown.[13]

A trial comparing the incidence of major cardiovascular events during therapy with insulin degludec versus insulin glargine in people with type 2 diabetes at high risk of cardiovascular events (DEVOTE; NCT01959529) is currently ongoing; and it is expected to report in 2018.[14]

Evidence strengths and limitations

- Insulin degludec has been shown to be non-inferior to insulin glargine 100 units/ml. There are no superiority trials.
- There is limited comparative evidence with other insulins. There are no trials comparing it to Neutral Protamine Hagedorn (NPH) insulin.
- There is no evidence to confirm that insulin degludec use is associated with a reduction in hospital admissions for diabetes related complications.

- There are no patient-oriented outcome data for the effects of insulin degludec on macrovascular or microvascular outcomes.
- There is limited long-term safety data.
- There is no evidence which directly compares insulin degludec with insulin pumps.
- There is limited evidence to confirm that using insulin degludec is associated with reduced admission rates and complications from diabetes.

National and local guidance and decisions

NICE Evidence Summaries are available for insulin degludec.[15,16] There are no technology appraisals (TAs) for insulin degludec. Insulin degludec is not in the NICE TA work programme. NICE Clinical Guideline for type 2 diabetes (NG28) recommends isophane (NPH) insulin including biphasics, as first line treatment for patients who remain uncontrolled despite optimised treatment with oral hypoglycaemics. Basal analogue insulins are only recommended second line to NPH insulins and there is no specific recommendation in relation to the use of insulin degludec in the type 2 clinical guideline. The full version of this guideline also states that the guideline development group, considered that, insulin degludec could not be recommended, as it was not cost effective; however, it should be noted that this guidance was produced before the recent price reduction of insulin degludec.[17]

The NICE Clinical Guideline on type1 diabetes in adults (NG17), does not specifically include insulin degludec, however it does suggest that basal insulin other than insulin glargine or insulin determir could be considered in patients where agreed targets are not being met. In addition, the clinical guidance for the management of diabetes in children does not include any discussion regarding insulin degludec.[18,19] The Scottish Medicines Consortium (SMC) have approved insulin degludec for use in adults but not in adolescents and children as it has not yet considered its use in these patient groups.[20]

Insulin degludec (Tresiba®) is recommended as an option for restricted use within NHS Wales for the treatment of diabetes mellitus in adult patients where treatment with a basal insulin analogue is considered appropriate. Insulin degludec (Tresiba®) is not recommended for use within NHS Wales for the treatment of diabetes mellitus in adolescents and children from the age of one year.[21]

Place in therapy

Insulin degludec may offer few or no meaningful advantages for the majority of potential users but may be suitable for a small subgroup of patients, for whom glycaemic control cannot be achieved despite optimal adjustments of lifestyle (eliminating any contributory factors), diet (undertaken structured education, e.g. DAFNE, and basal insulin/multiple daily injections and who fulfil the criteria for insulin pump therapy, or for individuals for whom injecting at the same time every day may not always be possible.

It has been suggested that insulin degludec may be an alternative to other insulins in patients with uncontrolled diabetes and experiencing multiple emergency admissions for hypoglycaemia and/or diabetic ketoacidosis, who would otherwise require treatment with an insulin pump or would continue to experience frequent hospital admissions. The number of likely patients with unstable diabetes who may benefit from a trial of insulin degludec is small and unstudied.

Comparative costs (eMIMs) and eBNF

Insulin degludec is the highest cost insulin available. Novo Nordisk announced a significant price reduction which came into effect on the 1st July 2016.[22] Insulin degludec is higher cost than biphasic insulin or other long acting basal insulins. Current cost for biphasic insulin is approx. £30 per pack, or £0.02 per unit, £0.40 for 20 units and £146 per year based on 20 units per day.[22-25] Costs of other long-acting basal insulins are shown below in Table 1.

Table 1. Comparative costs for long-acting basal analogue insulins

Product	Strength	Cost per pack	Cost per unit	Cost for 20 units	Cost per year
Insulin determir (Levemir®)	100 units/ml	£42.00	£0.028	£0.56	£204
Insulin glargine (Lantus®)	100 units/ml	£41.50	£0.028	£0.56	£204
Insulin degludec (Tresiba®)	100 units/ml	£46.60	£0.031	£0.62	£226
Insulin degludec (Tresiba®)	200 units/ml	£55.92	£0.031	£0.62	£226

Insulin degludec is included in the PbR tariff.[26]

The table shows cost per year based on 20 units/day. In clinical trials, degludec was started at a dose of 10 units/day in insulin naïve patients. Patients on alternative insulins were transferred on a unit to unit basis. With the average daily basal dosage for insulin degludec and insulin glargine reported as similar; 0.35-0.39units/kg/day for degludec and 0.40-0.42units/kg/day for glargine or 21 and 24 units per respectively. Until 1 July 2016, the list price of degludec was £72.00 and £88.52 for the 100 units/ml and 200 units/ml respectively, or £0.96 for 20 units or £350.60 per year, based on 20 units/day.[22-25]

Insulin degludec is available as cartridges (100units/ml) and as a pre-filled pen (Flex-Touch) which is available in two strengths (100 units/ml and the higher strength 200 units/ml). Both prefilled pens dial the dose in the number of units, which mitigates the risk of the incorrect number of doses being given.[3,22-25]

Estimated activity costs for an uncontrolled diabetic experiencing hypoglycaemic episodes resulting in hospital admissions once a month is approximately £18,000 per year.[26]

Implementation considerations

Insulin degludec (Tresiba®) is licensed for the treatment of diabetes mellitus in adults, adolescents and children from the age of one year.[3]

Concerns remain regarding the provision of adequate monitoring, support and overall management of high risk and/or complicated diabetic patients in primary care and all healthcare professionals are reminded of the need for extra vigilance when prescribing dispensing and using long-acting or high strength insulins. In 2011, following a review of 16,600 patient safety incidents involving all insulins, reported to the National Reporting and Learning System (NRLS) over a six-year period, between 1 November 2003 and 1 November 2009, the National Patient Safety Agency (NPSA) made several, recommendations to improve the safety of insulin use. Over the course of the review, six deaths and 12 incidents resulting in severe harm were reported. Of the 16,600 incidents, 26% were due to the wrong insulin dose, strength or frequency and 20% were due to omitted medicine. Patients being prescribed or dispensed the wrong insulin product accounted for 14% of incidents.[27-29] One of the measures initiated to mitigate this risk, was the introduction of the insulin passport to record the dose and brand on insulin, which is retained by the patient.

The EMA advise, that when switching patients from standard-strength insulin to another insulin formulation which is not bioequivalent, switching can be done on a unit to unit basis, but the dose may need to be adjusted to achieve target ranges for plasma glucose level. More detailed information on dose adjustment is provided in the product information.[29] However as with all insulin switches, there is great variability in the absorption and action of insulin in different patients and dose adjustment may be needed when patients are switched from Lantus or other basal insulins to insulin degludec® or vice versa.[27-29] All patients should be closely monitored, particularly at the start of treatment and when the dose or type of insulin changes.[29] Initial dose titration and monitoring should take place under the close supervision of a specialist team.

Community pharmacies and dispensing GP practices are reminded to check with the patient the brand and formulation, which they are expecting at the point of supply. Provider trusts and community trusts are advised to consider the practicalities of storage for the insulins to further minimise the potential for dispensing and medication supply errors.[27-29]

Insulin degludec is available as both standard strength (100 units/ml) and a higher strength (200 units/ml) formulations. The use of higher strength insulins is not routinely supported, due to a possible increased risk of medication errors.

The availability of higher strength insulin products has been associated with a possible increase risk of medication errors. The strength of the insulin formulation should always be included on the prescription. A Medicines and Healthcare Regulatory Agency (MHRA) Drug Safety Update has been issued with advice for healthcare professionals to minimise risk of errors with the two strengths, including risk assessment of clinical storage areas.[27-29]

The EMA has also published guidance to prevent medication errors with high strength insulins, including a series of recommendations for health care professionals.[27-29] Education and awareness of the risks of high strength and high dose insulin amongst healthcare professionals, patients and their carers is essential to ensure patient safety and to minimise the risk posed by these formulations. For the higher strength insulins, patients and carers should be advised to only administer the insulin via the pen device and to not tamper with the device to enable administration with needles and syringes, as this could lead to the wrong dosage being administered.[27-29]

Impact and quality assessment

Cost effectiveness (if available)	It is unknown if savings would be realised if patients with sub-optimally controlled type 1 diabetes who qualify for pump therapy received insulin degludec and subsequently did not require pump therapy or if the number of repeat admissions for diabetic ketoacidosis in patients treated with insulin degludec would be reduced as this has not been studied. There is limited data available on which to base an accurate assessment of likely patient numbers who would be eligible for treatment. It has been estimated from local data that approximately one patient per 100,000 populations could be eligible for treatment due to unstable or brittle diabetes resulting in multiple hospital readmissions and in line with the suggested start criteria. The average activity cost per year per patient is approximately £18,000 based on monthly admissions for 12 months of the year. There is no trial data to confirm the effect, if any on hospital admissions with either strength of insulin degludec. However, assuming that ten patients are admitted to hospital more than five times per year with an average spell cost of £1,500; the total cost of hospital treatment for one year will be £75,000. The cost of treating all ten patients with insulin degludec for one year, (40 units daily) would be £4,520. If one patient was successfully treated with insulin degludec (no hospital admissions) then the annual saving would be £1,000; if ten patients were successfully treated, then the annual potential cost saving would be £70,000.
Needs of the community	The needs of the community are considered moderate. The use of insulin degludec instead of alternatives would create a cost pressure which may have an impact on the local health economy which already has to identify savings. Any potential savings from the use of insulin degludec are unknown at this stage.

Needs of the population	The needs of the population appear to be low as there are available alternative treatment options recommended within local guidelines and by NICE However, specialists have highlighted a cohort of patients with sub-optimal control who may benefit from treatment with insulin degludec. For discussion regarding risks and benefits of high strength insulin products see safety section.
Equity	No issues with respect to equity have been identified.

*Consult Summary of Prescribing Characteristics for full prescribing details.

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

Author: Victoria Gibson on behalf of PAC

Document history

PAC approval date	10 July 2017
Version	2.1
History	Version 2 revised July 2017. Recommendations amended to remove reference to hyperosmolar hyperglycaemic state.
Consultation process	PAC members and East of England clinicians
QA process	Sue Smith, Senior Clinical Pharmacist, 18 April 2017

References

1. NICE Clinical Knowledge Summary Diabetes - type 1 Last revised in June 2015. Accessed 11/03/2016 via http://cks.nice.org.uk/diabetes-type-1#!annual_know_update
2. Diabetes UK (2014) Diabetes in the UK 2013 (revised 2014): key statistics on diabetes. Diabetes UK. Accessed 11/03/2016 via www.diabetes.org.uk
3. Anon. Insulin Degludec for Diabetes Mellitus. Drugs and Therapeutics Bulletin 2013; 51: 78-81.
4. Summary of Product Characteristics Tresiba® Novo Nordisk Ltd. Last updated April 2015. Accessed 03/05/2016 via http://www.medicines.org.uk/emc/medicine/27360#DOCREVISION
5. Ruszala V. Insulin Initiation in Diabetes. Clinical Pharmacist 2016;8, (1), online DOI: 10.1211/CP.2016.20200277
6. Heller S et al. Insulin degludec, ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN basal-bolus type 1): a phase 3 randomised open-label treat to target, non-inferiority trial. Lancet 2012; 379: 1489-97.
7. Mathieu C et al. Efficacy and safety of insulin degludec in a flexible dosing regime vs. insulin glargine in patients with type 1 diabetes (BEGIN: FLEX T1): A 26 week randomised treat to target trial with a 26-week extension. Journal of Clinical Endocrinology & Metabolism 2013; 98: 1154-62.

8. Thalange N, Deeb L et al. Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes. Pediatric Diabetes 2015; 16: 164-176.

9. Garber A et al. Insulin degludec, ultra-long acting basal insulin versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN basal bolus type 2): a phase 3, randomised, open-label, parallel-group, treat to target non-inferiority trial. Lancet 2012;379: 1498 -1507.

10. Meneghini L et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: A 26 week, randomized, open-label, parallel-group, treat-to-target trial in people with type 2 diabetes. Diabetes care 2013; 36: 858-864.

11. Euroean Product Assessment Report insulin degludec. European Mediicines Agency. 20/02/2013. Accesed 03/12/2016 via http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002498/human_med_001609.jsp&mid=WC0b01ac058001d124

12. US Food and Drug Administration. Briefing document for meeting of the FDA Endocrinologic and Metabolic Drug Advisory Committee meeting on 8 November 2012. Available online: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM327017.pdf or www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM327015.pdf

13. Anon Insulin degludec. Uncertainty over cardiovascular harms. Prescrire Int. 2014; 150: 149.

14. Clinical Trial Database. A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) US National institutes of Health. Last updated November 2016 Accessed 30/11/2016 via https://clinicaltrials.gov/ct2/show/NCT01959529

15. NICE. ESNM24 Type 1 diabetes: insulin degludec; September 2013. Accessed 04.07.2016 via http://publications.nice.org.uk/esnm24-type-1-diabetes-insulin-degludec-esnm24

16. NICE. ESNM25 Type 2 diabetes: insulin degludec; September 2013. Accessed 04/07/2016 via http://publications.nice.org.uk/esnm25-type-2-diabetes-insulin-degludec-esnm25

17. NICE. Type 2 Diabetes in adults management (NG28) December 2015.

18. NICE Type 1 diabetes in adults; management (NG17). August 2015.

19. NICE. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. (NG18). August 2015

20. Scottish Medicines Consortium. Advice for insulin degludec (Tresiba). No. 856/13, August 2016. Accessed via http://www.scottishmediocines.org.uk/home

21. All Wales medicines Strategy group Insulin Degludec (Tresiba) Reference no. 3158 http://www.awmsg.org/awmsgonline/app/appraisalinfo/3158

22. eMIMS, www.mims.co.uk. Accessed 03 July 2016

23. eBNF. Accessed via www.evidence.nhs.uk 03 July 2016

24. Personal Communication from P Du Plessis, Diabetes Outcome Director/ Novo Nordisk 3rd May 2016. Prescription Pricing Authority. Drug Tariff. May 2016. Accessed 03/05/2016 via http://www.nhsbsa.nhs.uk/PrescriptionServices/4940.aspx

25. Monitor and NHS England Statutory guidance. NHS National Tariff Payment System 2016/17 23rd March 2016 Accessed 04/07/2016 via https://www.gov.uk/government/publications/nhs-national-tariff-payment-system-201617

26. MHRA Drug Safety Update High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error April 2015. Accessed via https://www.gov.uk/drug-safety-update/high-strength-fixed-combination-and-biosimilar-insulin-products-minimising-the-risk-of-medication-error

27. MHRA Drug Safety Update Insulin degludec (Tresiba▼): available in additional higher strength April 2013 https://www.gov.uk/drug-safety-update/insulin-degludec-tresiba-available-in-additional-higher-strength

28. National Patient safety Agency. Passport to the safer use of Insulin. March 2011. Accessed 03/05/2016 via http://npsa.nhs.uk/corporate/news/passport-to-safer-use-of-insulin/

29. European Medicines Agency. Guidance on prevention of medication errors with high strength insulins November 2015. Accessed July 2016 via http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500197133.pdf