

# Insulin U100, 200, 300 or 500?

UMESH DASHORA, ERWIN CASTRO

## Abstract

**This article reviews the currently available information about insulin preparations in a concentration higher than 100 units/mL. These might be particularly useful in people with significant insulin resistance and high insulin requirement. U-200 insulin has low variability and lower (nocturnal) or similar risk of hypoglycaemia compared with U-100 insulin but is currently more expensive. U-300 glargine insulin has low variability, less weight gain and lower nocturnal hypoglycaemia in some studies in comparison to U-100 glargine. It is priced lower than U-100 glargine. U-500R insulin has been in use for some time worldwide but is not licensed in the UK. It also has low variability and lower cost per unit of insulin compared with U-100R. There is no specific delivery device and it has a higher risk of hypoglycaemia and weight gain. More insulins are in development (U-500 short-acting analogue [Fluorolog] and U-400 pre-mix like insulin BIOD-531, amongst others).**

*Br J Diabetes* 2016;16:10-15

**Key words:** U200, U300, U500, insulin, type 2 diabetes, weight, hypoglycaemia

## Introduction

A high percentage of adults with type 2 diabetes in the UK (90%) are overweight or obese and hence require relatively larger doses of insulin.<sup>1,2</sup> Globally, approximately 30% of patients with type 2 diabetes are using more than 60 units of basal insulin per day.<sup>2,3</sup>

In patients requiring high doses of insulin, active efforts should be made to restrict diet and increase exercise to reduce weight. Medications that reduce insulin resistance like metformin and glitazones should be utilised. GLP-1 analogues and SGLT 2 inhibitors may also act as insulin-sparing agents. However, if these attempts fail, then the insulin dose may need to be increased to control hyperglycaemia and reduce complications. A 1% reduction in HbA<sub>1c</sub> can reduce the risk of any end point/death related to diabetes by 21%, myocardial infarction

by 14% and microvascular complications by 37%.<sup>4-6</sup>

Historically, when insulin was first used in the 1920s it was available in at least eight different concentrations. Insulin strengths of 40, 80 and later 100 units/mL were produced. Insulin syringes were initially available as 20 marks per mL. Hence, insulin available as 40 and 80 units/mL administered by a U20 syringe would deliver 2 and 4 units of insulin per mark. Not surprisingly, there were many instances of errors in insulin dosing (64% in a survey in the UK). As a result, the British Diabetes Association recommended standardising all available insulins to 100 units/mL with a specifically designed graduated insulin syringe.<sup>7</sup>

However, with the currently available insulin concentrations in common use (i.e. 100 units/mL), it is not always possible to satisfy the dose requirement without injecting a large volume of insulin in very insulin-resistant patients. As the pens can only inject a certain amount of insulin in one injection (i.e. 60 or 80 units), these patients have to resort to multiple shots (i.e. up to 9 injections a day or more).<sup>8</sup> When large volumes of insulin are injected at one site, the absorption is likely to be erratic and the effect unpredictable.<sup>9</sup> Moreover, about 64% of the UK adults with diabetes do not meet their composite recommended treatment goals for diabetes care.<sup>10</sup> For all these reasons, there is scope for high strength insulins in diabetes practice.

## Types of high strength insulins

There are three basic types: those with extended period of action, those with short duration of action and those with mixed action (see Table 1).<sup>2</sup>

## Insulin degludec

Insulin degludec is a novel basal insulin used in once daily therapies and has a distinct absorption mechanism. After subcutaneous injection, insulin degludec forms long chains of multimers resulting in a soluble depot in subcutaneous tissue from which insulin degludec monomers gradually separate. This mechanism allows for a slow and sustained release of insulin into the circulation with a relatively flatter and stable pharmacokinetic and pharmacodynamic profile.<sup>11,12</sup> Insulin degludec has four times less within-subject variability of glucose-lowering effect than insulin glargine in patients with type 1 diabetes.<sup>13</sup>

Insulin degludec in 200 U/mL clamp studies of individuals with type 1 diabetes has demonstrated almost equivalent activity during the first and second 12 h of a 26-h study with maximum concentration at 9 h and a decline slowly thereafter. Glucose infusion rates were horizontal but increased proportionately with increasing doses.<sup>12-14</sup> There was no clinically relevant difference

Diabetes and Endocrine Centre, Conquest Hospital, Hastings, UK

**Address for correspondence:** Dr Umesh Dashora  
Diabetes and Endocrine Centre, Conquest Hospital, The Ridge,  
St Leonards on Sea, TN37 7RD, UK  
Tel: +44 (0)1424755255  
E-mail: u.dashora@nhs.net

<http://dx.doi.org/10.15277/bjd.2016.056>

**Table 1** Insulin preparations in higher concentration

Insulin	Concentration (units/mL)	Duration of action (h)	Company	Stage of development/ use
<b>Extended action</b>				
Degludec (Tresiba™)	200	42	Novo Nordisk	Available in the EU and the UK
Glargine (Tougeio™)	300	36	Sanofi	Available in the UK and the EU
<b>Short action</b>				
Lispro	200	6	Lilly	Available in the EU and the UK
<b>Mixed action</b>				
Regular (humulin R™)	500	12	Lilly	Available world wide, not licensed for use in the UK

in the handling of insulin degludec by younger people compared with an older group.<sup>15</sup> The duration of action of insulin degludec was reported to be >42 h.<sup>11</sup>

#### IDegU200 vs. IDegU100

The efficacy and safety of insulin degludec was studied by Bode *et al* in 373 patients with type 2 diabetes who were randomised to receive IDegU200 or IDegU100.<sup>16</sup> HbA<sub>1c</sub> reduction with IDegU200 was non-inferior to IDegU100. The proportion of patients with confirmed hypoglycaemic episodes as well as the overall confirmed hypoglycaemia rate was low and similar for both formulations (55% vs. 52% patients with 5.17 vs. 5.66 events per patient year of exposure: estimate RR 0.96 [95% CI 0.67 to 1.36, NS]). On a similar note, the rate of nocturnal confirmed hypoglycaemia was low (1.27 vs. 1.70 events per patient years for IDegU200 and IDegU100; RR 0.93 [95% CI 0.56 to 1.55, NS]).

#### IDegU200 vs. IGLarU100

In a comparative study of IDegU200 and IGLarU100 in insulin-naïve subjects with type 2 diabetes inadequately controlled with oral antidiabetic agents, HbA<sub>1c</sub> reduction (by 1.3%) with IDegU200 was not inferior to IGLarU100. Mean observed fasting plasma glucose reductions were greater with insulin degludec (-3.7 vs. -3.4 mmol/L; estimated treatment difference [ETD] -0.42 [95% CI -0.78 to -0.06; p=0.02]). There were no differences in hypoglycaemia rate between the two, although a non-significant lower rate of confirmed (<3.1 mmol/L) nocturnal hypoglycaemia was noted with IDegU200 (RR 0.86, p=0.46). The daily basal dose was significantly lower (by 11%) with IDegU200 compared with IGLarU100. Quality of life assessment using Short Form 36 identified two of eight domains in the health-related quality of life questionnaire which significantly favoured IDegU200: less bodily pain (ETD 1.6 [95% CI 0.1 to 3.2, p=0.04]) and improved vitality (ETD 1.5 [95% CI 0.1 to -3.0, p=0.04]).<sup>17</sup>

A recent meta-analysis comparing hypoglycaemic rates of insulin degludec with insulin glargine in elderly subjects with a pooled population of type 1 and type 2 diabetes has shown a

**Table 2** What can high strength insulin preparations offer?

Insulin	Strengths	Limitations
<b>Extended action</b>		
Degludec (Tresiba™)	<ul style="list-style-type: none"> <li>Lower variability</li> <li>Similar level of HbA<sub>1c</sub> reduction with similar doses and hypoglycaemic events (vs. IDegU100)</li> <li>Similar risk of hypoglycaemia in type 2 diabetes (vs. IGLarU100) with lower fasting glucose, lower doses and better quality of life in some domains (see text)</li> <li>Lower risk of nocturnal hypoglycaemia (vs. IGLarU100) in pooled patients with type 1 and 2 diabetes (prospective planned meta-analysis)</li> <li>U-200 pen shows the actual dose being delivered</li> </ul>	<ul style="list-style-type: none"> <li>More expensive than available U-100 basal insulin analogue preparations and U-500</li> <li>Currently not recommended by NICE as a standard therapy</li> </ul>
Glargine (Toujeo™)	<ul style="list-style-type: none"> <li>Lower variability (vs. IGLarU100)</li> <li>Higher or similar doses (vs. IGLarU100) for the same effect</li> <li>Less weight gain in some studies and low rate of hypo (21%)</li> <li>Lower nocturnal hypos (vs. IGLarU100)</li> </ul>	<ul style="list-style-type: none"> <li>Priced lower than IGLarU100</li> <li>SoloSTAR pen device allows only 80 units in one dose.</li> <li>Likely to be for specialist use only</li> </ul>
<b>Mixed action</b>		
Regular (Humulin R™)	<ul style="list-style-type: none"> <li>Lower cost per unit of insulin</li> <li>Low variability</li> <li>Lower volume allows fewer injections</li> </ul>	<ul style="list-style-type: none"> <li>Potential for overdosing by mistake</li> <li>Only available in vials not pens</li> <li>Needs injection by either a tuberculin syringe or by an insulin syringe</li> <li>Insulin peaks and longer duration increases risks of hypoglycaemia</li> <li>Discrepant funding sources depending on local agreement</li> <li>Weight gain in some studies</li> </ul>
<b>Short-acting insulins</b>		
Fluorolog™ (U-500)	In development	In development
Lispro 200	<ul style="list-style-type: none"> <li>Mainly exhibits bolus action</li> <li>Cost same as lispro U-100</li> </ul>	<ul style="list-style-type: none"> <li>The pen device can only go up to 60 units which will result in dose splitting for patients requiring more than 60 units of prandial insulin</li> </ul>

numerically lower (by 20%) rate of overall confirmed hypoglycaemia with insulin degludec during the maintenance period and a reduced confirmed nocturnal hypoglycaemia (by 35%) with insulin degludec.<sup>18</sup>

### Studies on U300 insulin

IGlarU300 forms a smaller concentrated depo matrix allowing for slower and prolonged absorption similar to insulin Humulin R U500. Euglycaemic clamp studies comparing IGLarU300 with IGLarU100 in patients with type 1 diabetes demonstrated slower peak-to-trough ratio with the increase in concentration occurring by 2 h and continuing through 12 h followed by a gradual decline through the 36 h duration of the studies. Duration of activity was longer for the dose of 0.4 and 0.6 units/kg at 32 and 34 h for IGLarU300 compared with 29 h for 0.4 units/kg IGLarU100.<sup>19,20</sup> Within-subject variability was lower with IGLarU300 than previously reported with IGLarU100.<sup>21,22</sup>

Data from phase III clinical trials (EDITION) have shown that IGLarU300 results in a distinct pharmacokinetic and pharmacodynamic profile. It also has a longer duration of action and variability is much less than for IGLarU100. The studies have shown that both insulin formulations exhibit similar efficacy and safety profile but U300 is associated with less weight gain and lower incidents of hypoglycaemic events compared with IGLarU100 in some studies.<sup>2,23</sup>

IGlarU300 was compared with IGLarU100 glargine in a series of clinical trials called EDITION trials. Patients with type 2 diabetes were studied in EDITION 1, 2, 3 and JP (Japanese) 2 trials whereas participants with type 1 diabetes were studied in EDITION 4 and JP1 trials. High doses of U-300 were necessary to attain similar efficacy to IGLarU100 in all the EDITION studies except for JP1 where the dose requirements were comparable. The efficacy study showed that HbA<sub>1c</sub> reduction was similar with glargine IGLarU300 and IGLarU100.

In the EDITION 1 trial, glycaemic control was maintained for a 6-month open label extension period with similar prandial insulin requirement for both groups. The percentage of people suffering severe or night time (nocturnal) hypoglycaemia was less, with 21% fewer patients suffering hypoglycaemia between week 9 and month 6 of the study.<sup>24,25</sup>

In the EDITION 2 trial, improved control was maintained for 12 months with a similar decline in fasting plasma glucose for both glargine formulations in addition to oral agents.<sup>26</sup> The percentage of patients experiencing one severe or confirmed hypoglycaemia was similar, but the percentage of nocturnal events was lower with IGLarU300 from week 9 to month 6 (RR 0.77 [95% CI 0.61 to 0.99],  $p=0.038$ ).<sup>26</sup>

Insulin-naive subjects studied in the EDITION 3 trial also showed similar HbA<sub>1c</sub> reduction in both treatment groups. The risk of any confirmed or severe hypoglycaemia was lower with IGLarU300 over the 6-month treatment period (RR 0.76 [95% CI 0.59 to 0.99]).<sup>27</sup>

EDITION JP2, focusing on Japanese subjects, showed a similar decline in HbA<sub>1c</sub> over 6 months with no differences observed in changes from baseline and fasting plasma glucose or in the percentage of patients reaching the HbA<sub>1c</sub> target of less than 7%. Hypoglycaemia was lower, particularly in the first 8 weeks of the study.<sup>28</sup>

A similar reduction in HbA<sub>1c</sub> was noted in the EDITION 4 and EDITION JP1 trials in patients with type 1 diabetes. EDITION 4 trials showed there was no difference in any time hypoglycaemia rates, but the rate of night time hypoglycaemias was lower with

**Table 3** Comparison of IGLarU300 with IGLarU100 in controlled settings with non-inferior outcome

Trial	Hypoglycaemia measure	Insulin dose	Weight change	Comparator
EDITION 1	Lower severe or confirmed nocturnal hypo between 3 and 6 months (36% vs. 46% with Gla-100; relative risk 0.79 [95% CI 0.67 to 0.93]; $p<0.005$ )	Higher	Similar	IGlarU100
EDITION 2	Lower nocturnal severe or confirmed hypos (RR 0.77 [95% CI 0.61 to 0.99]; $p=0.04$ )	Higher	Less weight gain ( $p=0.015$ )	IGlarU100
EDITION 3	Lower any confirmed hypos or severe hypo at any time (RR 0.76 [95% CI 0.59 to 0.99])	Higher	Similar	IGlarU100
EDITION JP2	Lower percentage of people with >1 confirmed or severe event and significantly lower % of people with more than one event during first 8 weeks	Higher	Weight loss	IGlarU100
EDITION 4	Lower nocturnal hypos between 3 and 6 months in the first 8 weeks	Higher	Less weight gain ( $p=0.037$ )	IGlarU100
EDITION JP1	Lower (34% reduction) nocturnal hypos; lower (20% reduction) hypo event rate; lower or comparable proportion of patients experiencing one confirmed severe hypo; lower percentage of people affected by severe hypoglycaemia (5.7% vs. 9.9%)	Comparable	Weight loss	IGlarU100

IGlarU300 in the first 8 weeks (RR 0.69 [95% CI 0.53 to 0.91]).<sup>29</sup> The EDITION JP1 study also showed that approximately 13.5% in both groups reached target without any hypoglycaemic events in Japanese subjects.<sup>30</sup> JP1 showed lower severe or confirmed hypoglycaemia with IGLarU300 over the 6-month period of the study (RR 0.87 [95% CI 0.78 to 0.96]) with the greatest difference during the first 8 weeks (RR 0.74 [95% CI 0.62 to 0.87]) (see Table 3).

In summary, all the EDITION trials showed a lower hypoglycaemia risk with IGLarU300 than with IGLarU100 in one or other aspect in which hypoglycaemia was measured. Although IGLarU300 tended to require a higher dose, the weight changes were either comparable or favoured IGLarU300.<sup>25,27</sup> Patients in

the JP1 and JP2 trials saw their weight decline while patients in EDITION 2 and 4 trials gained less weight compared with IGLarU100.<sup>26,28-30</sup>

### U-500R

The activity profile for U-500R is shorter in onset with a delayed but prolonged peak and extended duration compared with U-100R.<sup>31,32</sup> Efficacy studies of U-500R have already been published.<sup>33,34</sup> In a retrospective database analysis, U-500R was found to be more economical in pharmacy and overall cost and compliance but with a slightly higher rate of hypoglycaemia compared with U-100R.<sup>35</sup> Variability in absorption from day to day and from different parts of the body appears to be less.<sup>36</sup> The onset, peak action and duration is similar to neutral protamine hagedorn rather than human soluble insulin and the effect can last up to 24 h or more.<sup>37</sup> The recommended doses are therefore twice daily unless the requirement is very high when a third dose or an insulin pump may be considered.<sup>38-40</sup> U-500R can reduce mean HbA<sub>1c</sub> with fewer injections but the body weight, insulin dose and hypoglycaemic episodes increase.<sup>41,42</sup> There is an added risk of error with U-500R as there is no dedicated device for administration and calculation has to be made to decide how much volume would deliver the right units of insulin. As this insulin remains unlicensed in the UK, there are additional problems of funding and responsibility of treatment within the NHS structure.

### Lispro U200

Lispro 200 units/mL pharmacokinetics and dynamic profiles are similar to lispro 100 units/mL.<sup>43</sup> It is delivered by Humalog U-200 KwikPen which can hold 600 units compared with the U-100 pen which contains 300 units. It is of the same size as the U-100 pen. In a single dose, however, both pens can only go up to 60 units.

### Concentrated insulin for insulin pumps

Concentrated insulins for continuous subcutaneous insulin infusion (CSII) have not been adequately studied. None of the pumps are calibrated for dosing concentrated insulin and the chances of errors can be high. Humulin U-500R dose rates and ratios may be converted by either dividing or multiplying by 5 for CSII.<sup>44-46</sup>

Newer products may not be available in vials to avoid the dose conversion necessity. BIOD-531, which demonstrates similar activity with the exception of faster onset of action compared with Humulin U-500R, is also a potential insulin which may be useful in pumps.

U-500R in insulin pumps has been evaluated in small retrospective studies and one prospective study as well as a few case reports.<sup>44-47</sup>

### Challenges of high strength insulin and the potential solutions

The use of high strength insulin is associated with the potential for error. While using the U-500R insulin syringe, the mark on the insulin syringe actually reflects five times the units. There is therefore a potential for confusion in relation to doses or a chance of misunderstanding the dose by the patient or health



### Key messages

- Significant insulin resistance is common in some patients treated with insulin therapy, especially those with a high body mass index
- When the total daily dose of insulin nears, for example, 200 units per day, it is important to consider the use of more concentrated forms of insulin preparation such as U500
- Safety will remain a concern due to potential confusion over dose adjustments, mathematical conversions and the delivery devices used

professional leading to overdosing. This is mitigated by a structured system of patient education, alert triggers on hospital systems identifying these patients and clear understanding amongst health professionals and patients about the insulin concentration being used.

With regard to tuberculin syringe use, these syringes are only available with larger needles and are not covered by most insurers and are rarely available in pharmacies. These difficulties may delay initiation and appropriate use of this medication. Administration of U-500R dose by volume using tuberculin syringe is the technique that has been recommended by the Institute for Safe Medication Practices.<sup>48</sup>

IDegU200 is available with a pen, but with the same brand name as IDegU100. The problem of misunderstanding units is mitigated to a large extent by the dose counter window for IDegU200 displaying doses in actual units. Each click is equivalent to a 2-unit increment in dose. The dose delivered is therefore what you see on the dial.

IGlarU300 has a different brand name (i.e. Toujeo™ rather than Lantus™), which would also mitigate the chances of confusion and error.<sup>49</sup> The pen for IGLarU300 is SoloSTAR which can only go up to 80 units in one dose, adding another layer of safety.

Another way to avoid confusion could be to use tables for conversion and wallet cards.<sup>50,51</sup> The European Medicine Agency is consulting on guidance to minimise the risk of error with the use of insulin in high concentration alone (U200, U300 and others) or in combination with other medicines.<sup>52</sup>

Ultimately, multiple new types of insulin preparations are going to become available with which we will need to become familiar and experienced. This is good news for patients who may not be winning with their current insulin regimes and help to overcome some of the traditional problems associated with insulin therapy.

**Conflict of interest** None.

**Funding** None.

## References

- Public Health England. Adult obesity and type 2 diabetes 2014. [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/338934/Adult\\_obesity\\_and\\_type\\_2\\_diabetes\\_.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/338934/Adult_obesity_and_type_2_diabetes_.pdf) (accessed May 2015)
- Segal AR, El Sayed N. Are you ready for more insulin concentrations? *J Diabetes Sci Technol* 2015;**9**:331-8. <http://dx.doi.org/10.1177/1932296814557860>
- Rodbard H, Handelsman Y, Gough S, et al. Reduced risk of hypoglycemia with insulin degludec vs. insulin glargine in patients with type 2 diabetes requiring high doses of basal insulin: meta-analysis of five randomized trials (abstract 241). AACE 21st Annual Scientific and Clinical Congress, 23-27 May 2012, Philadelphia, Pennsylvania.
- Turner RC. The UK Prospective Diabetes Study: a review. *Diabetes Care* 1998;**21**:C35-C38. <http://dx.doi.org/10.2337/diacare.21.3.C35>
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837-53. [http://dx.doi.org/10.1016/S0140-6736\(98\)07019-6](http://dx.doi.org/10.1016/S0140-6736(98)07019-6)
- Stratton IM, Adler AI, Neil HA, Matthews DR. Association of glycaemia with macrovascular and microvascular complications in type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ* 2000;**321**:405-12. <http://dx.doi.org/10.1136/bmj.321.7258.405>
- Bloom A, Keen H. A change to 100-unit insulin dosage will reduce insulin errors. *BMJ* 1981;**283**:33-4. Watkins JD et al. *American journal of public health* 1967;**57**:452. <http://dx.doi.org/10.2105/AJPH.57.3.452>
- Dashora UK, Collins A, Castro E. U 500 for patients with insulin resistance. Poster presentation at ABCD Autumn Meeting, 7-8 November 2013, London. <http://www.diabetologists-abcd.org.uk/Posters/Autumn2013/Dashora.pdf>
- Megarbane B, Deye N, Bloch V, et al. Intentional overdose with insulin: prognostic factors and toxicokinetic/toxicodynamic profiles. *Critical Care* 2007;**11**:R115. <http://dx.doi.org/10.1186/cc6168>
- Health and Social Care Information Centre. National Diabetes Audit 2012-2013. <http://www.hscic.gov.uk/catalogue/PUB14970/nati-diab-audi-12-13-care-proc-rep.pdf> (accessed May 2015)
- Kurtzhals P, Heise T, Strauss HM, et al. Multi-hexamer formulation is the underlying mechanism behind the ultra-long glucose-lowering effect of insulin degludec. *Diabetes* 2011;**60**:42-LB.
- Heise T, Haermanski L, Nosek L, et al. Ultra long acting insulin degludec has a flat glucose lowering effect in type 2 diabetes. *Diabetes Obes Metab* 2012;**14**:944-50. <http://dx.doi.org/10.1111/j.1463-1326.2012.01638.x>
- Heise T, Haermanski L, Nosek L, et al. Insulin degludec: four times less pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes Obes Metab* 2012;**14**:859-64. <http://dx.doi.org/10.1111/j.1463-1326.2012.01627.x>
- Korsatko S, Deller S, Koehler G, et al. Comparison of the steady-state pharmacokinetic and pharmacodynamic profiles of 100 and 200 u/ml formulations of ultra-long-acting insulin degludec. *Clin Drug Investig* 2013;**33**:515-21. <http://dx.doi.org/10.1007/s40261-013-0096-7>
- Korsatko S, Deller S, Mader JK, et al. Ultra-long pharmacokinetic properties of insulin degludec are comparable subjects and younger adults with type 1 diabetes mellitus. *Drugs Aging* 2014;**31**:47-53. <http://dx.doi.org/10.1007/s40266-013-0138-0>
- Bode BW, Chaykin LB, Sussman AM, et al. Efficacy and safety of insulin degludec 200 U/ml and insulin degludec 100 U/ml in patients with Type 2 diabetes (Begin: Compare). *Endocrine Practice* 2014;**20**:785-91. <http://dx.doi.org/10.4158/EP13411.OR>
- Gough SC, Bhargava A, Jain R, et al. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to target trial: the BEGIN LOW VOLUME trial. *Diabetes Care* 2013;**36**:2536-42. <http://dx.doi.org/10.2337/dc12-2329>
- Sorli C, Warren M, Oyer D, et al. Elderly patients with diabetes experience a lower rate of nocturnal hypoglycaemia with insulin degludec than with insulin glargine: a meta-analysis of phase IIIa trials. *Drugs Aging* 2013;**30**:1009-18. <http://dx.doi.org/10.1007/s40266-013-0128-2>
- Jax T, Heise T, Dahmen R, et al. New insulin glargine formulation has a flat and prolonged steady state profile in subjects with type 1 diabetes [abstract]. *Diabetologia* 2013;**56**(Suppl):A1029.
- Tillner JA, Bergmann K, Telchert I, et al. Euglycaemic clamp profile of new insulin glargine U300 formulation in patients with type 1 diabetes (T1DM) is different from glargine U100. *Diabetes* 2013;**62**:A234.
- Becker RH, Nowotny I, Teichert L, et al. Low within and between-day variability in exposure to new insulin glargine 300 u.nL-1 [abstract]. *Diabetes* 2014;**63**(Suppl 1):A228.
- Heise T, Nosek L, Ronn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with Type 1 diabetes. *Diabetes* 2004;**53**:1614-20. <http://dx.doi.org/10.2337/diabetes.53.6.1614>
- Sutton G, Minguet J, Ferrero C, Bramlage P. U300, a novel long-acting insulin formulation. *Expert Opin Biol Ther* 2014;**14**:1849-60. <http://dx.doi.org/10.1517/14712598.2014.970633>
- Riddle MC, Bolli GB, Yki-Jarvinen H, et al. Sustained glycemic control and less hypoglycemia with new insulin glargine 300 U/mL compared with 100 U/mL: 1-year results in people with T2DM using basal + meal-time insulin (EDITION 1) [abstract]. *Diabetes* 2014;**63**(Suppl 1):LB20.
- Riddle MC, Bolli GB, Ziemer M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care* 2014;**37**:2755-62. <http://dx.doi.org/10.2337/dc14-0991>
- Yki-Jarvinen H, Bergenstal R, Ziemer M, et al. New insulin glargine 300 U/mL versus glargine 100 U/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care* 2014;**37**:3235-43. <http://dx.doi.org/10.2337/dc14-0990>
- Bolli GB, Riddle MC, Bergenstal R, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab* 2015;**17**:386-94. <http://dx.doi.org/10.1111/dom.12438>
- Terauchi Y, Koyama M, Cheng X, et al. EDITION JP 2 Study Group. Glycemic control and hypoglycaemia in Japanese people with T2DM receiving new insulin glargine 300 U/mL in combination with OADs (EDITION JP 2) [abstract]. *Diabetes* 2014;**63**(Suppl 1):LB24.
- Home PD, Bergenstal RM, Riddle MC, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300U/mL in people with Type1DM (EDITION 4) [abstract]. *Diabetes* 2014;**63**(Suppl 1):LB19-20.
- Matsuhisa M, Koyama M, Cheng X, et al. New insulin glargine 300 u/mL: glycemic control and hypoglycemia in Japanese people with T1DM (EDITION JP 1) [abstract]. *Diabetes* 2014;**63**(Suppl 1):LB22.
- de la Pena A, Riddle M, Morrow LA, Jiang HH. Pharmacokinetic and pharmacodynamics of high-dose human regular U-500 insulin versus human regular U-100 insulin in healthy obese subjects. *Diabetes Care* 2011;**34**:2496-501. <http://dx.doi.org/10.2337/dc11-0721>
- De la Pena A, Ma X, Reddy S, et al. Application of PK/PD modelling and simulation to dosing regimen optimisation of high-dose human regular U-500 insulin. *J Diabetes Sci Technol* 2014;**8**:821-9. <http://dx.doi.org/10.1177/1932296814532326>
- Jones P, Idris I. The use of U-500 regular insulin in the management of patients with obesity and insulin resistance. *Diabetes Obes Metab* 2013;**15**:882-7. <http://dx.doi.org/10.1111/dom.12094>
- Reutrakul S, Wroblewski K, Brown RL. Clinical use of U-500 regular insulin: review and meta-analysis. *J Diabetes Sci Technol* 2012;**6**:412-20. <http://dx.doi.org/10.1177/193229681200600229>
- Eby EL, Wang P, Curtis BH, et al. Cost, healthcare resource utilization, and adherence of individuals with diabetes using U-500 or U-100 insulin: a retrospective database analysis. *J Med Econ* 2013;**16**:529-38. <http://dx.doi.org/10.3111/13696998.2013.772059>
- Binder C, Brange J. Insulin chemistry and pharmacokinetics. In: Ellenberg's and Rifkin's Diabetes Mellitus. 5th ed. Porte D Jr, Sherwin RS, eds. Stamford, CT: Appleton & Lange, 1997, p. 689
- Distiller LA. The use of highly concentrated U-500 regular insulin for the severely insulin resistant patient with type 2 diabetes. *Endocr Pract*. Published Online First 4 Nov 2014.
- Knee TS, Seidensticker DF, Walton JL, et al. A novel use of U-500 insulin for continuous subcutaneous insulin infusion in patients with insulin re-

- sistance: a case series. *Endocr Pract* 2003;**9**:181-6. <http://dx.doi.org/10.4158/EP.9.3.181>
39. Lalej-Bennis D, Selam JL, Fluteau-Nadler S, et al. Extreme insulin resistance: clinical management by external subcutaneous insulin infusion. *Diabetes Metab* 1997;**23**:533-6.
  40. Nathan DM, Axelrod L, Flier JS, Carr DB. U-500 insulin in the treatment of antibody-mediated insulin resistance. *Ann Intern Med* 1981;**94**:653-6. <http://dx.doi.org/10.7326/0003-4819-94-5-653>
  41. Boldo A, Comi RJ. Clinical experience with U500 insulin: risks and benefits. *Endocr Pract* 2012;**18**:56-61. <http://dx.doi.org/10.4158/EP11163.OR>
  42. Eby EL, Curtis BH, Gelwicks SC, et al. Initiation of human regular U-500 insulin use is associated with improved glycemic control: a real-world US cohort study. *BMJ Open Diabetes Res Care* 2015;**3**:e000074. <http://dx.doi.org/10.1136/bmjdr-2014-000074>
  43. Eli Lilly. Humalog 200 units/ml KwikPen. Summary of Product Characteristics 2014. <https://www.medicines.org.uk/emc/medicine/30005> (accessed June 2015)
  44. Lane WS. Use of U-500 regular insulin by continuous subcutaneous insulin infusion in patients with type 2 diabetes and severe insulin resistance. *Endocr Pract* 2006;**12**:251-6. <http://dx.doi.org/10.4158/EP.12.3.251>
  45. Bulchandani DG, Konrady T, Hamburg MS. Clinical efficacy and patient satisfaction with U-500 insulin pump therapy in patients with type 2 diabetes. *Endocr Pract* 2007;**13**:721-5. <http://dx.doi.org/10.4158/EP.13.7.721>
  46. Lane WS, Weinrib SL, Rappaport JM, Przestrzelski T. A prospective trial of U500 insulin delivered by Omnipod in patients with type 2 diabetes mellitus and severe insulin resistance. *Endocr Pract* 2010;**16**:778-84. <http://dx.doi.org/10.4158/EP10014.OR>
  47. Lane WS, Weinrib SL, Rappaport JM, et al. The effect of long-term use of U-500 insulin via continuous subcutaneous infusion on durability of glycemic control and weight in obese, insulin-resistant patients with type2 diabetes. *Endocr Pract* 2013;**19**:196-201. <http://dx.doi.org/10.4158/EP12226.OR>
  48. Institute for Safe Medication Practices. As U-500 insulin safety concerns mount, it's time to rethink safe use of strengths above U-100. 31 October 2013 [cited 3 July 2014]. In: Acute Care ISMP Medication Safety Alert. Horsham, PA: Institute for Safe Downloaded from [dst.sagepub.com](http://dst.sagepub.com) by guest on 13 November 2014.
  49. Masangkay EG. Sanofi's NDA for basal insulin Toujeo™ accepted by FDA. 11 July 2014 [cited 13 July 2014]. <http://www.bioresearchonline.com/doc/sanofi-s-nda-for-basal-insulin-toujeo-accepted-byfda-0001?atc~c=771+s=773+r=001+l=a>.
  50. Cochran E. U-500 insulin: when more with less yields success. *Diabetes Spectrum* 2009;**22**:116-22. <http://dx.doi.org/10.2337/diaspect.22.2.116>
  51. Segal AR, Brunner JE, Burch FT, Jackson JA. Use of concentrated insulin human regular (U-500) for patients with diabetes. *Am J Health Syst Pharm* 2010;**67**:1526-35. <http://dx.doi.org/10.2146/ajhp090554>
  52. Medicines and Healthcare Products Regulatory Agency. Drug Safety Update. High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error. <https://www.gov.uk/drug-safety-update/high-strength-fixed-combination-and-biosimilar-insulin-products-minimising-the-risk-of-medication-error>