Human regular U-500 insulin (U-500), a fivefold concentrated form of U-100 regular human insulin, was introduced to address the insulin needs of patients with severe insulin resistance (1). Severe insulin resistance has historically been characterized by patients with total daily insulin dose (TDD) requirements exceeding 200 units/day (1). With the increasing prevalence of diabetes and obesity in the United States, severe insulin resistance has become more common, increasing the need for U-500.

The safe and effective use of U-500 requires careful monitoring to optimize glycemic control while minimizing the risk of hypoglycemia. The elevated risk of medication errors associated with U-500 therapy and a lack of clear guidelines for its use may have been responsible for its underutilization by both patients and health care providers (HCPs). In a survey administered to internal medicine physicians and ward nurses evaluating the inpatient use of U-500, 47% of respondents said they were “very uncomfortable” with the use of U-500 (2). A 2013 article published by the Institute for Safe Medication Practices (ISMP) reported on an increasing number of medication error reports and complaints from HCPs related to the use of U-500 (3). To address these medication errors, innovations (i.e., a dedicated U-500 syringe and a U-500 pen delivery device) have been developed to help solve dosing confusion issues and potentially enhance HCP and patient comfort with U-500 therapy. Here, we review the available evidence for U-500 and the innovations for its delivery.

Pharmacokinetics and Pharmacodynamics
When considering the use of U-500, patients and HCPs must be aware of the unique pharmacokinetic/pharmacodynamic (PK/PD) profile that distinguishes it from both basal insulins and prandial insulins. Unlike other insulins, U-500 covers both the basal and prandial insulin needs of patients. This unique PK/PD profile allows for its use as monotherapy, and patients can inject smaller volumes with fewer injections compared to therapy with U-100 insulin.

The PK/PD profile of U-500 shows similar overall insulin exposure when compared to human regular insulin U-100. However, it has significantly lower peak serum insulin concentrations (C_{max}) (~32% in C_{max} with a 50-unit dose and ~27% in C_{max} with a 100-unit dose) and maximum glucose infusion rates (GIR_{max}) and a longer duration of action of 21 hours (4). The GIR_{max} describes the mean maximal amount of glucose that must be infused or injected to maintain a target blood glucose concentration, providing a quantitative measure of the metabolic activity of an insulin formulation (5). Investigators attribute the extended duration of action to the continued absorption of insulin from the subcutaneous depot and
to measure doses of U-500 with the assistance of a dose conversion chart (3). They also recommended that doses be communicated in both units and volume to avoid the confusion associated with the U-100 scale “syringe units” terminology (3).

After the U-500 insulin syringe and the U-500 pen device were introduced to the market, HCPs and patients were discouraged from using the U-100 insulin or tuberculin syringes to administer U-500, and the dose conversion charts for these syringes were removed from the package insert of U-500 (1).

**U-500 Pen Device**

In 2016, a dedicated U-500 prefilled disposable insulin pen device (Humulin R U-500 KwikPen; Eli Lilly, Indianapolis, Ind.) was introduced to the market, allowing patients to prepare doses based on the number of units prescribed (8). Each pen device delivers insulin in 5-unit increments and allows for a maximum of 300 units to be delivered in a single injection. Each pen holds 1,500 units of insulin (3 mL U-500 regular human insulin per pen).

The pen device must be primed 5 units before each use to ensure that it is functional and that there is no blockage in the needle and to remove any air from the cartridge and needle to help ensure that the full dose is delivered (8). It is also important to instruct patients using the pen device to use a new pen needle with each injection and to practice proper injection site rotation to reduce the risk of dermal complications such as lipohypertrophy, which can alter the absorption of insulin (8–11).

Unused pens should be stored in the refrigerator and may be used until the expiration date printed on the label (8). Pens that are in use should be stored at room temperature away from light and heat for up to 28 days. After 28 days of use, the pen device must be replaced with a new pen, even if there is insulin remaining in it.

Patients can turn the dial on the pen to their prescribed number of units and administer the dose without having to perform any dose conversion calculations such as were previously required with the vial and a U-100 insulin or tuberculin syringe (8). With the pen device, HCPs and patients need to communicate the prescribed dose in actual units rather than as a volume (as with a tuberculin syringe) or “syringe units” (as with a U-100 syringe) to mitigate potential medication errors that can result in detrimental overdoses. The direct 1:1 dose conversion from the pen to a vial may help reduce the over- or under-dosing that patients taking U-500 are at risk of when undergoing a transition of care and during hospitalizations (12).

**Dedicated U-500 Insulin Syringe**

The U-500 scale syringe is designed to help reduce the risk of medication errors associated with U-500 therapy. Despite the rise in popularity of insulin pen devices in the hospital setting (13), the use of a vial and syringe may still be preferable in some inpatient settings where protocols have not been established to reduce the risk of blood-borne pathogen transmission among patients when an insulin pen device is used for more than one patient.

Introduced to the market in 2016, the U-500 insulin syringe is designed to be used only with vials of U-500 regular human insulin (14). Now that the U-500 scale syringe is available, to avoid errors, patients who use vials of U-500 should be prescribed the U-500 insulin syringe. The U-100 insulin syringes and tuberculin syringes should no longer be used (1). Patients who were previously using U-100 or tuberculin syringes to administer U-500 doses should consult their HCP to obtain a prescription for the U-500 syringe with a corresponding U-500 dose indicated by their prescriber. The
labeling for U-500 has been updated with this requirement, and the dose conversion tables needed for use with tuberculin and U-100 syringes have been removed from package inserts.

Similar to the pen device, the U-500 syringe allows patients and HCPs to draw up a dose of U-500 without having to perform a dose conversion calculation. The U-500 syringe features bold scale markings in 5-unit increments and allows for a maximum of 250 units to be delivered in a single injection. The U-500 syringe features a 6-mm, 31-gauge needle, which is a sufficient needle length to deliver insulin into the subcutaneous layer regardless of a patient’s BMI and to reduce the risk of an intramuscular injection that can lead to variable insulin absorption (11,15,16). U-500 syringes are also visually distinct from U-100 syringes to reduce medication errors. They feature green needle shields instead of the orange needle shields found on U-100 syringes.

Unopened vials of U-500 should be stored in the refrigerator and can be used until the printed expiration date (1). If unopened vials are stored at room temperature, vials must be discarded after 40 days. Vials that have been opened can be stored in the refrigerator or at room temperature but must be discarded after 40 days, even if there is insulin remaining in the vial (1).

**Continuous Subcutaneous Insulin Infusion of U-500**

Continuous subcutaneous insulin infusion (CSI), or insulin pump therapy, in patients with type 2 diabetes is an area of active research. In the randomized, controlled OpT2mise trial (17), investigators observed that patients with type 2 diabetes treated with a multiple daily injection (MDI) regimen who switched to CSII were able to achieve clinically significant reductions in A1C and spent less time in hyperglycemia (17). These clinically significant benefits of insulin pump therapy were maintained for at least 1 year (18). However, in patients with severe insulin resistance, the use of U-100 insulin analogs with CSII would require very high basal rates and very large prandial boluses, rapidly depleting insulin pump cartridges and requiring frequent and costly insulin cartridge changes.

The use of concentrated insulins in insulin pump devices is not currently approved by the U.S. Food and Drug Administration (FDA) but may serve as a potential solution for CSII use in patients with high-dose insulin requirements. Studies evaluating the efficacy and safety of U-500 administered by CSII are limited to case studies, retrospective studies, and small, prospective studies (19–26). Table 1 provides an overview of studies that have evaluated the use of U-500 in CSII. A meta-analysis of studies in which U-500 was administered via CSII determined a mean reduction in A1C of 1.64%, a nonsignificant increase in weight (2.99 kg), and a decrease in TDD (13.6 units) (27). The meta-analysis determined that hypoglycemia was not common with U-500 administered via CSII. The lack of statistical significance of some of these findings may have been a result of the small number of patients (n = 55) or short follow-up periods in the studies included in the meta-analysis (27).

A randomized, open-label, parallel study of U-500 administration via a dedicated U-500 CSII system compared to MDI (VIVID; TABLE 1. Summary of Studies of U-500 Delivered via CSII

| Study                 | Subjects (n) | Mean Duration (months) | Mean Baseline A1C (%) | Mean A1C Reduction (%) | Mean Baseline TDD (units) | Mean TDD Change (units) | Mean Weight Change (kg) |
|-----------------------|--------------|------------------------|-----------------------|------------------------|--------------------------|-------------------------|-------------------------|
| Knee et al., 2003     | 4            | 6                      | 10.8                  | 3.5                    | 334                      | –120                    | N/A                     |
| Schwartz, 2004        | 5            | N/A                    | 10.24                 | 2.49                   | 410                      | N/A                     | 4.5                     |
| Lane, 2006            | 9            | 3                      | 8.8                   | 1.13                   | 172                      | –5.3                    | 1.9                     |
| Bulchandani et al., 2007 (19) | 6            | 6                      | 9.1                   | 2.2                    | 391                      | –95                     | –2.8                    |
| Lane et al., 2010     | 21           | 12                     | 8.6                   | 1.23                   | 197                      | 12                      | 5.4                     |
| Reutrakul et al., 2011 (25) | 10           | 30                     | 9.0                   | 1.6                    | 234                      | 1.7                     | 8.9                     |
| Lane et al., 2013     | 59           | 49                     | 8.3                   | 1.0                    | 175                      | N/A                     | N/A                     |
| Meade et al., 2017    | 30           | 12                     | 8.1                   | 0.63                   | 175                      | 22                      | 3.1                     |

N/A, not applicable.
NCT02561078) was recently completed in adult patients with type 2 diabetes. The results of the primary population (n = 340), excluding patients taking glucagon-like peptide 1 (GLP-1) receptor agonists or sodium–glucose cotransporter 2 (SGLT2) inhibitors, were presented in a poster during the ADA 78th Scientific Sessions in June 2018 (28). Patients were treated with either CSII or MDI three times daily for 26 weeks. U-500 administered via a dedicated U-500 CSII system resulted in a greater mean A1C reduction from baseline (1.30 vs. 0.86% for CSII and MDI, respectively) and used less insulin after 26 weeks. Compared to those treated with an MDI regimen, patients randomized to the CSII arm had higher rates of nocturnal hypoglycemia (19.07 and 12.43 events/patient/year for CSII and MDI, respectively) and severe hypoglycemia (0.15 and 0.04 events/patient/year for CSII and MDI, respectively) (28). A subgroup of patients concurrently taking GLP-1 receptor agonists or SGLT2 inhibitors were also enrolled in this study, but the results of the entire patient population were reported separately as an oral presentation (29). When the entire patient population (n = 420) was evaluated, including this subgroup, similar A1C reductions (1.27 vs. 0.85% for CSII and MDI, respectively) were observed with lower insulin doses in the CSII group. Nocturnal hypoglycemia was higher with CSII administration compared to MDI (18.22 vs. 11.17 events/patient/year for CSII and MDI, respectively) (29).

**Clinical Evidence for the Use of U-500**

Clinical evidence providing guidance on the use of U-500 is relatively limited compared to other insulin products. Before completion of the U-500R titration-to-target study (30), evidence supporting the use of U-500 was limited to retrospective reviews, case studies, and expert opinions. In the aforementioned meta-analysis of PubMed-indexed studies reporting the use of U-500 (27), in which 310 patients had administered U-500 by MDI, a significant reduction in A1C of 1.59% was observed. The meta-analysis also revealed that U-500 via MDI was associated with increases in weight (4.37 kg) and TDD (51.9 units). The incidence of severe hypoglycemia was either not reported or no different from rates reported with U-100 insulin (27).

The U-500R titration-to-target study (30) was the largest study evaluating the clinical efficacy and safety of U-500. It was a 24-week, open-label, parallel, randomized, controlled trial (RCT) comparing the safety and efficacy of BID to TID dosing of U-500 in 325 overweight patients with diabetes.

Patients met the inclusion criteria if they were previously treated with 201–600 units/day of insulin for a minimum of 3 months before study initiation. Subjects were randomized in a 1:1 allocation to either the TID (40% breakfast, 30% lunch, 30% dinner) or the BID (60% breakfast, 40% dinner) treatment arm.

The titration-to-target algorithms specified adjustments of +5, +10, or +15% per dose as needed to achieve a premeal target of 71–130 mg/dL or −10% for hypoglycemia (≤70 mg/dL) based on the median of the three most recent self-monitoring blood glucose (SMBG) readings. The maximum dose increase was 15% per dose (30% maximum TDD increase), and the maximum dose reduction was 10% per dose (20% maximum TDD reduction). Both BID doses, but only two of the three TID doses were titrated depending on which doses most needed adjustment and prioritizing dose reductions for hypoglycemia over dose increases.

Mean A1C reductions were similar between the BID and TID regimens (1.2 vs. 1.1% for the BID and TID regimens, respectively). There was an increase in mean TDD for both treatment arms. The incidences of severe hypoglycemia and modest weight gain were also similar between the two treatment regimens. A higher incidence of nonsevere hypoglycemia was observed in the BID arm (30). Rates of both severe and mild hypoglycemia were observed to be higher in patients taking >300 units of insulin per day at baseline (31).

The U-500R titration-to-target study determined that both the BID and TID regimens of U-500 therapy are safe and effective for severely insulin-resistant patients with type 2 diabetes (30). However, an analysis of patient-reported outcomes demonstrated that patients preferred the BID regimen over the TID regimen, with the BID regimen scoring higher in the treatment burden, daily life, compliance, and overall treatment domains of the Treatment-Related Impact Measure–Diabetes questionnaire (32). Given the clinical equivalency for efficacy and safety of the BID regimen compared to the TID regimen and considering the reported patient preference for the BID dosing schedule, BID dosing may be the preferred regimen in clinical practice when initiating therapy with U-500.

**Adjunctive Strategies With U-500 Therapy**

Although U-500 monotherapy is an appropriate treatment strategy, in practice, patients with type 2 diabetes will likely be treated with other agents in addition to insulin. However, formal studies evaluating the safety and efficacy of adjunctive therapies in conjunction with U-500 therapy are limited. In a retrospective review evaluating patients (n = 12) treated with U-500 either as monotherapy (n = 2) or as a component of a basal/bolus insulin regimen (n = 7 with a long-acting insulin and n = 3 with a rapid-acting insulin), a 1.8% reduction in A1C after 6–9 months was observed, suggesting that U-500 therapy resulted in improved glycemic control whether used alone or as a part of combination therapy (33). However, patients using U-500 also
experienced weight gain and an increase in TDD (33).

GLP-1 receptor agonists are an attractive class of medications for patients with type 2 diabetes who are severely insulin resistant. These agents improve glycemic control by reducing glucagon secretion, increasing insulin secretion when glucose levels are elevated, slowing gastric emptying, increasing satiety, and delaying carbohydrate absorption. Recently, the FDA has approved combination products containing a GLP-1 receptor agonist and a basal insulin. A limited number of studies have evaluated U-500 therapy in combination with a GLP-1 receptor agonist.

In an observational case series of 15 patients with a mean baseline A1C of 8.48% who were treated with a combination of U-500 (administered via either MDI or CSII) and liraglutide for at least 12 weeks, A1C was reduced by 1.4% (34). A mean weight reduction of 5.1 kg and a TDD reduction of 28% were also observed. Hypoglycemia (<70 mg/dL) was seen soon after liraglutide was added to U-500 in 53% of the patients, but no severe episodes (requiring assistance) occurred. In this study, baseline U-500 doses were reduced by up to 30% before starting liraglutide, depending on patients’ baseline A1C and SMBG readings and based on the managing physicians’ judgment. Subjects with higher baseline A1Cs had minimal reductions in their baseline U-500 dose before starting liraglutide (34).

In a separate 24-week RCT, the effect of adding liraglutide to high-dose intensive insulin therapy was compared to standard insulin up-titration in obese patients with type 2 diabetes (35). Subjects who received liraglutide had a mean A1C reduction of 0.65% (from a mean baseline A1C of 7.8%), whereas those in the control group experienced a 0.39% reduction in A1C (from a mean baseline A1C of 7.79%). Those treated with liraglutide also experienced a mean weight loss of 5.27 kg and a mean 34% reduction in TDD after 24 weeks, whereas the control group had a mean weight gain of 0.37 kg and a mean 4% increase in TDD. In this study, 17 of the 37 patients (46%) included in the study were treated with U-500 at enrollment; 10 of those 17 patients were randomized to receive liraglutide. These U-500 subjects reportedly experienced overall results (reductions in A1C, TDD, and weight) similar to those who were treated with intensive U-100 insulin regimens, but the detailed results of the U-500 subgroup were not published (35).

In a 24-week, prospective, randomized, open-label, treat-to-target pilot study, the safety and efficacy of U-500 therapy with metformin was compared to U-500 therapy with metformin and BID dosing of exenatide, a short-acting GLP-1 receptor agonist (36). Similar statistically significant reductions in A1C were observed in the treatment arms, but patients in the exenatide arm generally did not experience significant weight change, whereas those in the U-500 and metformin arm did experience a nonsignificant weight increase (36).

In a retrospective chart review of 18 patients with type 2 diabetes treated with U-500 and adjunctive extended-release, once-weekly exenatide, no significant changes in A1C from baseline were observed, but patients did achieve nonsignificant modest weight loss and a significant reduction in insulin TDD. There was an increase in hypoglycemic episodes 3 months after the addition of exenatide (37).

Given such small study populations, the efficacy of U-500 combination therapy with a GLP-1 receptor agonist cannot be conclusively determined at this time.

**Conclusion**

Human regular U-500 insulin has clinical utility in that it can cover both the basal and prandial insulin needs of patients with severe insulin resistance. Its unique PK/PD characteristics allow it to be used as monotherapy administered either TID or BID. Compared to U-100 insulin, U-500 has a lower maximum glucose-lowering response and a longer duration of action. With the rising prevalence of obesity, the prevalence of patients with high insulin dose requirements will also increase, potentially increasing the clinical utility of U-500 in practice.

With the completion of the U-500R titration-to-target RCT (30), there is now better guidance for HCPs on how to initiate and titrate therapy with U-500. Additionally, the introduction of new insulin delivery technologies, including a U-500 pen device and dedicated U-500 insulin syringe, may help to mitigate the risk of medication errors historically associated with the use of U-500, thus enhancing HCP and patient confidence in and comfort with initiating U-500 therapy.

U-500 administered via CSII may be another useful treatment modality to reduce the burden of multiple injections faced by patients with severe insulin resistance and improve their glycemic control. Adjunctive therapy with newer classes of medications such as GLP-1 receptor agonists may help to limit the weight gain and reduce the insulin TDDs of patients using U-500.

Based on the available evidence, U-500 insulin serves as a useful therapeutic option for patients with severe insulin resistance.

**Duality of Interest**

D.S. is an employee of Becton Dickinson and Company. J.G. serves on the speakers bureau for Novo Nordisk and Sanofi and is a consultant for Becton Dickinson and Company. No other potential conflicts of interest relevant to this article were reported.

**References**

1. Eli Lilly and Company. Humulin R U-500 (insulin human injection) product information. Indianapolis, Ind., Lilly USA, 2016.

2. Colburn JA, True MW. Knowledge gaps in the inpatient use of U-500 regular insulin [SAT-0961]. Poster presented at the
Endocrine Society’s 96th annual meeting and Expo. Chicago, Ill., 21–24 June 2014

3. Institute for Safe Medication Practices. As U-500 insulin safety concerns mount, it’s time to rethink safe use of strengths above U-100. Available from www.ismp.org/newsletters/acutehealth/showarticle.aspx?id=62. Accessed 7 October 2017

4. de la Pena A, Riddle M, Morrow LA, et al. Pharmacokinetics and pharmacodynamics of high-dose human regular U-500 insulin versus human regular U-100 insulin in healthy obese subjects. Diabetes Care 2011;34:2496–2501

5. Heinemann L, Anderson JH Jr. Measurement of insulin absorption and insulin action. Diabetes Technol Ther 2004;6:698–718

6. de la Pena A, Ma X, Reddy S, Ovalle F, Bergenstal RM, Jackson JA. Application of PK/PD modeling and simulation to dosing regimen optimization of high-dose human regular U-500 insulin. J Diabetes Sci Technol 2014;8:821–829

7. Cohen MR, Smetzer JL. Pen device for U-500 insulin; tamper-resistant seals; dispelling myths about ISMP. Hosp Pharm 2016;51:279–283

8. Eti Lilly and Company. Humulin R U-500 KwikPen instructions for use. Indianapolis, Ind., Lilly USA, 2015

9. Hambridge K. The management of lipohypertrophy in diabetes care. Br J Nurs 2007;16:520–524

10. Famulla S, Hovelmann U, Fischer A, et al. Insulin injection into lipohypertrophic tissue: bluntied and more variable insulin absorption and action and impaired postprandial glucose control. Diabetes Care 2016;39:1486–1492

11. Frid AH, Kreugel G, Grassi G, et al. New insulin delivery recommendations. Mayo Clin Proc 2016;91:1231–1255

12. Palladino CE, Eberly ME, Emmons JT, Tannock LR. Management of U-500 insulin users during inpatient admissions within a Veterans Affairs medical center. Diabetes Res Clin Pract 2016;114:32–36

13. Reinke T. Though costly, insulin pens facilitate better adherence. Manag Care 2013;22:20–21

14. U.S. Food and Drug Administration. FDA approves a dedicated syringe to be used with Humulin R U-500 insulin. Available from www.fda.gov/drugs/drug-safety/ucm310318. Accessed 7 October 2017

15. Frid A, Gunnarsson R, Guntner P, Linde B. Effects of accidental intramuscular injection on insulin absorption in IDDM. Diabetes Care 1988;11:41–45

16. Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Curr Med Res Opin 2010;26:1519–1530

17. Reznik Y, Cohen O, Aronson R, et al. OpTm2ise Study Group. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpTm2ise): a randomised open-label controlled trial. Lancet 2014;384:1265–1272

18. Aronson R, Reznik Y, Conget I, et al. OpTm2ise Study Group. Sustained efficacy of insulin pump therapy compared with multiple daily injections in type 2 diabetes: 12-month data from the OpTm2ise randomized trial. Diabetes Obes Metab 2016;18:500–507

19. Bulchandani DG, Konradty T, Hamburg MS. Clinical efficacy and patient satisfaction with U-500 insulin pump therapy in patients with type 2 diabetes. Endocr Prac 2013;17:721–725

20. Knee TS, Seidensticker DF, Walton JL, Solberg LM, Lassetter DH. A novel use of U-500 insulin for continuous subcutaneous insulin infusion in patients with insulin resistance: a case series. Endocr Prac 2003;9:181–186

21. Lane WS. Use of U-500 regular insulin by continuous subcutaneous insulin infusion in patients with type 2 diabetes and severe insulin resistance. Endocr Prac 2006;12:251–256

22. Lane WS, Weinrib SL, Rappaport JM, Hale CB, Farmer LK, Lane RS. 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 type 2 diabetes. Endocr Prac 2013;19:196–201

23. Lane WS, Weinrib S, 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 Prac 2010;16:778–784

24. Meade LT, Tart RC, Nuzum D. Clinical experience with U-500 regular insulin by multiple daily injections and continuous subcutaneous insulin infusion. Diabetes Technol Ther 2017;19:220–225

25. Reutrakul S, Brown RL, Koh CK, Hor TK, Baldwin D. Use of U-500 regular insulin via continuous subcutaneous insulin infusion: clinical practice experience. J Diabetes Sci Technol 2011;5:1025–1026

26. Schwartz FL. A caution regarding U-500 insulin versus human regular U-100 insulin for continuous subcutaneous insulin infusion in patients with type 2 diabetes—primary population. Poster presented at the American Diabetes Association 78th Scientific Sessions, Orlando, Fla., 22–26 June 2018

27. Grunberger G, Bharagava A, Ly T, et al. Human regular U-500 insulin via continuous subcutaneous insulin infusion vs. multiple daily injections in adults with T2D—the VIVID study— all randomized population. Oral presentation at the American Diabetes Association 78th Scientific Sessions. Orlando, Fla., 22–26 June 2018

28. Hood RC, Arakaki RF, Wysham C, Li YG, Settles JA, Jackson JA. Two treatment approaches for human regular U-500 insulin in patients with type 2 diabetes not achieving adequate glycemic control on high-dose U-100 insulin therapy with or without oral agents: a randomized, titration-to-target clinical trial. Endocr Prac 2015;21:782–793

29. Wysham C, Hood RC, Warren ML, Wang T, Morwick TM, Jackson JA. Effect of total daily dose on efficacy, dosing, and safety of 2 dose titration regimens of human regular U500 insulin in severely insulin-resistant patients with type 2 diabetes. Endocr Prac 2016;22:653–665

30. Kabul S, Hood RC, Duan R, DeLozier AM, Settles J. Patient-reported outcomes in transition from high-dose U-100 insulin to human regular U-500 insulin in severely insulin-resistant patients with type 2 diabetes: analysis of a randomized clinical trial. Health Qual Life Outcomes 2016;14:139

31. Lowery JB, Donihi AC, Korytkowski MT, U-500 insulin as a component of basal bolus insulin therapy in type 2 diabetes. Diabetes Technol Ther 2012;14:505–507

32. Lane W, Weinrib S, Rappaport J. The effect of lixisudge added to U-500 insulin in patients with type 2 diabetes and high insulin requirements. Diabetes Technol Ther 2011;13:592–595

33. Lane W, Weinrib S, Rappaport J, Hale C. The effect of addition of liraglutide to high-dose intensive insulin therapy: a randomized prospective trial. Diabetes Obes Metab 2014;16:827–832

34. Distiller LA, Nortje H, Wellmann H, Amod A, Lombard L. A 24-week, prospective, randomized, open-label, treat-to-target pilot study of obese type 2 diabetes patients with severe insulin resistance to assess the addition of exenatide on the efficacy of u-500 regular insulin plus metformin. Endocr Pract 2014;20:1143–1150

35. Farwig PA, Zielinski AJ, Accursi ML, Burant CJ. The impact of extended release exenatide as adjuvant therapy on hemoglobin A1C, weight, and total daily dose of insulin in patients with type 2 diabetes mellitus using U-500 insulin. Diabetes Res Clin Pract 2017;134:38–43