Clinical Considerations for Insulin Pharmacotherapy in Ambulatory Care, Part Two: Review of Primary Literature and an Evidence-Based Approach for Treatment

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■ **IN BRIEF** This article reinforces the dosing guidance from the package inserts of available insulin products and supplemental information provided by the manufacturers of insulin products. It reviews and evaluates pertinent primary literature detailing algorithms for the initiation and titration of insulin therapy that have helped to shape current clinical practice guidelines. The article discusses the clinical applicability of the evidence on insulin pharmacotherapy and offers recommendations for initiation and titration of various insulin products for insulin-requiring people with type 2 diabetes in the ambulatory care setting.

■ **EDITOR'S NOTE**: This is the second of a two-article series. The first, "Clinical Considerations for Insulin Pharmacotherapy in Ambulatory Care, Part One: Introduction and Review of Current Products and Guidelines," was published in an earlier issue (*Clinical Diabetes* 2014;32:66–75).

As discussed in part one of this series, the majority of current treatment guidelines for type 2 diabetes lack prescriptive recommendations for insulin titration beyond the weeks after insulin initiation; the exception is the 2013 American Association of Clinical Endocrinologists (AACE) algorithm and consensus statement (1–5). Furthermore, package inserts for available products offer little guidance with regard to insulin titration (6–21), and, although dosing information is available for some insulin preparations based on clinical trial data, it is not universally implemented in practice. However, a comprehensive review of insulin therapy published in the *Journal of the American Medical Association* in June 2014 reviewed the available literature and proposed an algorithm for insulin dosing (22).

Although an individualized, patient-centered approach is essential to ensure optimal outcomes and safety, this article will evaluate pertinent literature on ambulatory insulin dosing and discuss treatment strategies to aid clinicians in managing insulin therapy in patients with type 2 diabetes. Primary literature exists for the initiation of basal and bolus insulin analogs, as well as for regimens involving premixed products, and various titration algorithms have been published. However, clinical trial data for NPH and regular human insulin are lacking (J.A.G., personal communication). A thorough evaluation of the primary literature is required to fully understand and identify appropriate insulin titration techniques that may supplement available guidelines and be applied to individualized insulin regimens for ambulatory patients with type 2 diabetes.

Evidence-Based Recommendations: Basal Insulin

The manufacturers of the two currently available long-acting insulin products, insulin glargine and insulin detemir, provide statements in

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their package inserts regarding the initiation of therapy with a fixed or weight-based dose and offer recommendations for conversion from other types of basal insulin. However, neither manufacturer offers concrete recommendations for titrating their own insulin product. Instead, they suggest that dose adjustments should be individualized according to glucose measurements and made with caution under the supervision of a health care provider (6,7).

Fortunately, because these products are relatively new to the market, primary literature is available to assist providers in determining appropriate titration strategies for these agents after initiation. These data are described in Supplementary Table 1, which summarizes three key trials for each basal insulin product. The titration methods used in the trials are summarized in Supplementary Table 2 and also described in the following sections.

Insulin Glargine

The package insert for insulin glargine states that it should be dosed once daily at any time of the day and recommends that, although the starting dose should be individualized, patients with type 2 diabetes who are insulin naive may be initiated on 10 units daily (or 0.2 units/kg/day). Furthermore, the insert notes that the average initial dose for patients in clinical trials was 10 units daily.

However, the statement regarding dose adjustment is vague, stating that after initiation, the dose was ". . . subsequently adjusted according to the patient's need to a total daily dose ranging from 2 to 100 IU." The manufacturer supports dose adjustments by health care providers that meet a patient's need based on blood glucose measurements, but provides no elaboration on the frequency or magnitude of titration (6). Providers are encouraged to review the primary literature on insulin glargine titration

recommendations (23–25), which are also discussed below.

Riddle et al. (23) first evaluated an algorithm for insulin glargine titration in the Treat to Target Trial (4-T) published in 2003. Two additional trials involving titration methods for insulin glargine were published in 2005 and 2006 (24,25). The three trials had similar study designs, and each lasted for 6 months. Randomization of patients and a multicenter trial design were considered strengths of these trials. Although acceptable, a 6-month study period is sometimes insufficient to achieve disease state control in some people with type 2 diabetes, who may require a year or more to reach a target A1C.

The patient populations enrolled in these studies also shared commonalities, with the average patient being ~55 years of age and overweight, although Gerstein et al. (25) did not use BMI as an inclusion criterion. Additionally, patients had an average entry A1C of 8–9% (23–25), although the study by Davies et al. (24) allowed patients with an A1C up to 12% (representing significantly uncontrolled diabetes) to be enrolled. In general, these patients also had a longer history of diabetes, and 72% were pretreated with insulin. This trial was much larger than the other two, enrolling almost 5,000 patients.

Each of these three studies had unique objectives. Riddle et al. and Gerstein et al. sought to achieve a goal A1C (≤6.5 and ≤7%, respectively) with insulin glargine therapy, whereas Davies et al. compared a physician-managed versus a patient-managed titration algorithm. Riddle et al. compared insulin glargine to NPH insulin therapy, whereas the conventional therapy group in the study by Gerstein et al. was prescribed oral antidiabetic agents. Nevertheless, each trial offers crucial information concerning options for adjusting insulin therapy.

Riddle et al. required forced titrations of up to 8 units once weekly of either insulin glargine or

NPH. Titration was graded based on patients' fasting plasma glucose (FPG), and dose adjustments were provided in increments of 2 units, with a target FPG value ≤100 mg/dL (23). Although Gerstein et al. targeted the same FPG, insulin glargine titration was performed by patients in the amount of 1 unit/day until control was achieved (25). Finally, in the study by Davies et al., the physician-managed algorithm provided for weekly adjustments similar to those used in the study by Riddle et al., but titration was optional in patients with an FPG <120 mg/dL (24).

Results from these studies were generally favorable. The majority of patients (~60%) in 4-T achieved the goal A1C with systematic titration of both insulin types; however, it was noted that significantly more patients achieved this end point without nocturnal hypoglycemia in the insulin glargine group ($P <0.05$) (23). Davies et al. determined that there was no significant difference in the incidence of severe hypoglycemia between the two titration methods, but there were significant reductions in A1C, with a greater decrease ($P <0.001$) occurring with patient-managed titration (24). In the study by Gerstein et al., it was 1.68 times more likely for more patients receiving titrated insulin glargine to achieve two consecutive A1C levels ≤6.5% compared to those taking oral agents, with no differences in hypoglycemia noted (25).

The various strategies presented in these trials offer providers simple, widely applicable algorithms for systematic insulin glargine titration based on patients' FPG level. The 2013 AACE algorithm and consensus statement cite the 4-T study as an acceptable titration method for basal insulin (4,5).

Insulin Detemir

When initiating insulin detemir, the manufacturer suggests starting with a dose of 0.1–0.2 units/kg once daily in the evening or 10 units once or twice daily. The package insert states

that, after initiation, glycemic targets should be used to make dose adjustments. Further statements on dose determination made by the manufacturer focus on conversion from other types of basal insulin and report the mean dose of detemir required by patients in comparison to NPH at the end of a clinical trial. But, again, no specific titration schedule is provided with regard to the timing and magnitude of dose adjustments (7).

Three key clinical trials provide insight into potential titration algorithms for patients initiated on insulin detemir (26–28). The insulin detemir trials had study designs similar to those used in the trials of insulin glargine; they were randomized, multicenter, and open-label, with an average duration of ~6 months. All three trials were designed to prove noninferiority (26–28). Hermansen et al. published their insulin detemir treat-to-target trial in 2006 (26), and the other publications soon followed.

The trials by Hermansen et al. (26) and Philis-Tsimikas et al. (27) enrolled just over 450 and 500 patients, respectively, whereas Meneghini et al. had a significantly more robust sample of >5,600 patients in their PREDICTIVE 303 trial, which was published in 2007 (28). Patients in all three trials were generally overweight, in their late 50s to early 60s, and had been living with diabetes for at least 9 years. However, PREDICTIVE 303 tended to include more obese patients, with a longer history of diabetes and worse glycemic control. The average patient in that study had had type 2 diabetes for 11.4 years (28). Nevertheless, the average A1C for most subjects in the three studies ranged from 8 to 9% (26–28), consistent with the trials of insulin glargine (23–25).

Study objectives of the insulin detemir trials also shared commonalities with the insulin glargine trials. The studies by Hermansen et al. and Philis-Tsimikas et al. both compared titration of insulin detemir to NPH insulin, whereas the study

by Meneghini et al. compared a patient-adjusted algorithm to physician-managed standard-of-care titration (26–28). Forced titrations of insulin detemir occurred for patients in the detemir treat-to-target trial at intervals of every 1–2 weeks. Patients were categorized as responders or nonresponders, and dose increases were made in the amount of 2–10 units, with a provision to decrease the dose for hypoglycemia (26). Titrations in the amount of 2–8 units were made every 4 weeks in the trial by Philis-Tsimikas et al., which also had a provision for dose reduction in the event of hypoglycemia (27). However, the methodology of the PREDICTIVE 303 study was not as rigorous because there were no forced titrations, in an effort to mimic a real-world, observational setting (28). In that trial, one group of patients self-adjusted their evening insulin detemir dose by ± 3 units or kept it the same based on average FPG results every 3 days. The second group had their dose adjusted by the investigator "according to the standard-of-care practice," which was not defined in terms of frequency or magnitude. After the first 12 weeks, which focused on basal insulin doses, providers were encouraged to adjust the doses of other antidiabetic medications as needed, which may have confounded the results (28).

A subsequent study conducted by Blonde et al. (29) used the PREDICTIVE 303 titration method, but evaluated the efficacy and safety of two fasting glucose titration targets.

Favorable results were observed in the three insulin detemir trials discussed, fulfilling the criteria for noninferiority with regard to efficacy in A1C and tolerability. Details of these results are shown in Supplemental Table 1. These data offer providers practical algorithms for insulin detemir titration. The studies by Hermansen et al. and Meneghini et al. were also cited in the 2013 AACE algorithms and consen-

sus statement as acceptable titration methods for basal insulin (4,5).

Evidence-Based Recommendations: Bolus Insulin

Three rapid-acting insulin analogs—insulin glulisine, insulin aspart, and insulin lispro—are available for bolus, or prandial, insulin therapy. The package inserts for each of these products make general recommendations regarding their use as part of a regimen that includes intermediate- or long-acting insulin. The timing of administration differs slightly; glulisine should be used ≤15 minutes before a meal or within 20 minutes after starting a meal, aspart should be given 5–10 minutes before a meal, and lispro should be given ≤15 minutes before a meal or immediately after a meal. The package inserts do not provide specific initiation doses or titration guidance.

Clinical trial evidence is available for each of these products, supporting their addition to a basal regimen, either as single or multiple daily injection(s), with titration carried out in a variety of methods. In addition, some articles compare basal-bolus therapy to regimens involving premixed products and offer insight into the subsequent intensification of those regimens. Although not comprehensive, each of the key trials adds to the literature guiding clinicians in the optimal use of prandial insulin therapy. Select trials involving bolus insulin therapy are presented in Supplementary Table 3, and titration strategies are described in Supplementary Table 4.

Insulin Glulisine

Clinical trials involving glulisine have studied multiple dosing regimens, including the addition of a single injection at varying mealtimes, the addition of multiple daily injections, the comparison of premixed and basal-bolus regimens, and the effects of varying administration times (30–35).

The OPAL (Orals Plus Apidra and Lantus) study (30) demonstrated

that adding glulisine to basal therapy with glargine improved both A1C and postprandial glucose regardless of whether the glulisine injection was administered before breakfast or before the largest meal of the day. Both treatment groups experienced significantly improved glycemic control without a marked increase in hypoglycemia. Of note, the majority of patients in this trial had an A1C <8% at baseline. In another study, Owens et al. (31) demonstrated improved glycemic control with a basal-bolus regimen of glargine plus glulisine with or without oral antidiabetic medications in comparison to glargine with or without oral antidiabetic medications. Improvement was seen regardless of the titration method used; adjustments in bolus doses were made using pre- or postprandial blood glucose test results, depending on the study center. Significantly more patients reached their A1C goal in the basal-bolus group without substantial increases in hypoglycemia or weight gain.

Among the trials that compared a basal-bolus regimen with glulisine to a premixed insulin regimen was GINGER (Glulisine in Combination with Insulin Glargine in an Intensified Insulin Regimen) study (32) and a trial by Riddle et al. (33). Subjects in GINGER were on premixed therapy at baseline and then randomized to premixed NPH/regular insulin 70/30, NPH/aspart 70/30, or glargine plus mealtime glulisine. The results demonstrated superiority of the basal-bolus regimen, with a statistically significant decrease in A1C from baseline and a higher percentage of patients reaching their A1C goal (32). Although Riddle et al. were unable to confirm superiority of a basal-bolus regimen compared to a premixed regimen, glargine plus one injection of glulisine was as effective as a twice-daily premixed regimen, with less hypoglycemia (33). Additionally, the percentage of patients reaching their A1C goal was statistically higher for

glargine plus three injections of glulisine than for premixed insulin.

Although insulin dosing based on the carbohydrate content of a meal is frequently used in the management of those with type 1 diabetes, it can be difficult to implement for some patients with type 2 diabetes. Bergenstal et al. (34) sought to evaluate carbohydrate counting in patients with type 2 diabetes by comparing two regimens using glulisine as prandial therapy, either as a ratio based on the carbohydrate content of a meal or in an algorithm with fixed adjustments. Both regimens were adjusted based on the pattern of mealtime blood glucose values. Ultimately, use of an algorithm to adjust prandial insulin on a weekly basis was as effective as adjustments made based on insulin-to-carbohydrate ratios. Although the change in A1C from baseline was not significant, both patient groups saw a decrease in A1C of ~1.5 percentage points, and there were similar percentages of patients achieving their A1C goal in the two groups (34).

When the administration time of glulisine has been studied, similar glycemic control and noninferiority with regard to weight gain has been seen when comparing injection times of 0–15 minutes before a meal and 20 minutes after the start of a meal (35).

Insulin Aspart
Insulin aspart was studied by Meninghini et al., using three titration algorithms: SimpleSTEP, ExtraSTEP, and, most recently, FullSTEP (36,37). The original Step-Wise trial (36) included two titration methods. The first (SimpleSTEP) involved the addition of aspart at the largest meal, with titration based on premeal blood glucose values. The second (ExtraSTEP) consisted of adding aspart at the meal with the largest prandial glucose elevation based on postmeal blood glucose values. The Step-Wise trial illustrated that sequential addition of aspart bolus doses improved glycemic control,

with comparable efficacy between the two methods (36). In 2014, the FullSTEP study (37) incorporated a full basal-bolus regimen. Titration by the addition of an aspart dose at baseline, week 11, and week 22 was noninferior to full basal-bolus therapy and resulted in greater patient satisfaction (37).

Insulin Lispro
Two key trials involving insulin lispro have compared basal-bolus and premixed regimens (38,39). Although both of these studies were designed to evaluate noninferiority, neither was able to demonstrate this when comparing reduction in A1C from baseline. However, each study did provide a detailed initiation and titration algorithm that may be useful in practice. In addition, these studies addressed various clinically relevant conundrums: provider comfort with premixed insulins, the challenge of avoiding clinical inertia when making the decision to intensify insulin therapy, the relative efficacy of 50/50 premixed insulin products compared to 70/30 premixed products, and patient-specific considerations such as the number of daily injections.

Lispro administered three times daily has also been studied in comparison to once-daily glargine and thrice-daily lispro 50/50 premix (40,41). The APOLLO (A Parallel Design Comparing an Oral Antidiabetic Drug Combination Therapy With Either Lantus Once Daily or Lispro at Mealtime in Type 2 Diabetic Patients Failing Oral Treatment) study (40) was designed to determine whether insulin glargine administered once daily was noninferior to prandial insulin lispro administered three times daily when used in combination therapy with oral agents. Insulin glargine was initiated at 10 units/day, with dose titration based on two consecutive fasting blood glucose (FBG) test results. Insulin lispro was initiated at 4 units before every meal, with titration based on pre- and postprandial

glucose values. Results revealed that insulin glargine was noninferior to insulin lispro based on reduction in A1C, illustrating that basing titration on FBG or postprandial blood glucose is equally effective in improving overall glycemic control. However, rates of hypoglycemia were significantly higher in the insulin lispro group. Patient treatment satisfaction and perceived frequency of hypoglycemia were significantly improved in the insulin glargine group, which may illustrate that the addition of insulin glargine to oral agents may be preferred based on simplicity.

Yamashiro et al. (41) compared lispro 50/50 premix to insulin lispro as initial insulin therapy for type 2 diabetes, with each administered three times daily in combination with oral agents. Initial dosing for each regimen was 4 units before each meal for lispro 50/50 mix and 3 units before each meal for lispro. Dosage adjustments were made according to blood glucose levels before lunch, before dinner, and at bedtime. The addition of insulin glargine or NPH was allowed in the insulin lispro group if FBG levels remained >140 mg/dL despite targeted lispro titration. This trial had a smaller sample size than the other studies described. However, both regimens did significantly reduce A1C levels compared to baseline. In addition, there were significantly fewer hypoglycemia episodes with the prandial premixed regimen than with insulin lispro, supporting the use of a premixed product for initial insulin therapy.

U-500 Regular Insulin

Clinical trials providing dosing recommendations for U-500 insulin were published in the late 2000s. U-500 insulin is a type of regular insulin that it is five times more concentrated than U-100 (i.e., U-500 insulin has 500 units/mL of insulin). U-500 regular insulin has altered pharmacokinetic parameters compared to U-100 and thus requires a different dosing methodology; a

single dose of U-500 can last for up to 24 hours (21). Because of this discrepancy, studies have tried to develop algorithms for the use of U-500 in clinical practice (42,43).

Based on package insert recommendations, U-500 insulin should be administered two to three times daily 30 minutes before a meal. U-500 insulin is indicated for patients with severe insulin resistance, defined as requiring a total daily dose of insulin >200 units/day, based on the assumption that insulin-treated patients without severe insulin resistance require 0.5–1.0 units/kg/day. Despite the higher concentration, U-500 insulin is administered in U-100 insulin syringes. This requires proper education for patients. The package insert contains a dose conversion table to aid clinicians in dosing (21).

Lane et al. (42) developed a U-500 insulin dosing algorithm in 2009. Their article discussed the differences seen in a clinical case series of patients treated with U-500 insulin, provided conditions that identify potential candidates, and offered an implementation guide. The dosing algorithm provided by Lane et al. was initially developed by Cochran and Gorden in 2008 (43). Several other algorithms have been proposed that may be useful for clinicians using U-500 in their practice (44,45).

Of note, other concentrated insulin products (not of the regular insulin type) such as U-200 and U-300 are also in development. U-200, or insulin degludec, has been studied in a series of noninferiority trials in comparison to insulin glargine (46–50). Insulin glargine U-300 was also recently evaluated in comparison to insulin glargine (51,52). These products may offer future options for basal insulin.

NPH and Regular Insulin

Regular insulin was first used to treat patients with diabetes in 1922; Novo Nordisk did not begin to manufacture and market NPH insulin until 1950. These formulations are consid-

ered over-the-counter products that do not require a prescription. Overall, evidence-based recommendations for NPH and regular insulin are lacking (J.A.G., personal communication). This section describes dosing information found in package inserts and a subsequent clinical practice model for initiation and titration of NPH and regular insulin.

NPH insulin is an alternative for patients who are unable to tolerate or afford glargine or detemir; however, safety and efficacy should be given higher priority over cost considerations. Two types of NPH are currently available on the U.S. market: Humulin N and Novolin N, distinguished by the company that manufactures the product (Eli Lilly and Co. and Novo Nordisk, respectively.

The medications are biologics; therefore, a generic form is unable to be formulated for production. No specific information is found in either product's package insert or in the primary literature regarding initiation or titration of doses (8,9).

Similar to NPH insulin, two forms of regular insulin are commercially available, Humulin R and Novolin R, manufactured by Eli Lilly and Co. and Novo Nordisk, respectively. Unlike with NPH insulin, the package inserts of regular insulin products offer some guidance regarding initiation and titration of regular insulin, which states, "the dosage and timing [of regular insulin] must be individualized . . . . Total daily insulin requirements vary and are usually between 0.5 and 1.0 units/kg/day" (10,11). This information is vague and makes patient-specific recommendations difficult. Additionally, there is a paucity of primary literature available to provide clinicians with dosing or titration recommendations.

In the absence of guidance from either package inserts or primary literature and with limited concrete recommendations from disease-specific guidelines, tertiary resources were examined to provide insight

into the dosing of NPH and regular insulins. Again, specifics regarding these medications are vague; often, the references noted included limited external citations for the recommendations provided.

In clinical practice, clinicians often rely on a 2:1 ratio of NPH to regular insulin for initiation and titration in the treatment of type 2 diabetes. Practitioners first determine a patient's total daily dose, which may vary from 0.3 to 0.7 units/kg/day. NPH represents two-thirds of this total daily dose, which is further divided into another 2:1 ratio between morning and night. The remaining one-third of the total daily dose is regular insulin with the same ratio breakdown between morning and night. Subsequent titration is based on insulin sensitivity, as discussed below. This type of two-thirds/one-third split is what led to development of premixed products (53). However, in the 2013 AACE algorithm and consensus statement, the total daily dose is split 50/50 because of the recommended use of basal-bolus insulin regimens (4,5).

Titration of NPH and regular insulin is often based on determining a patient's specific insulin sensitivity, which is the expected reduction in blood glucose (in mg/dL) from the addition of 1 unit of insulin. Two determinants are used for insulin sensitivity (also known as "correction factor") calculations: the total daily dose and a mathematical constant. Historically, the constant was 1500 but has evolved to >2000, depending on the clinical scenario or the type of insulin used. In 2008, Davidson et al. (54) developed the "rule of 1700," in which the mathematically derived constant was 1700; therefore, the determination of the insulin sensitivity was made by dividing 1700 by the total daily dose of all insulins. It is important to note that the Davidson method was based on patients with type 1 diabetes only (54).

Over the years, clinicians have used many methods in practice to adjust insulin therapy. Although some strategies are better supported than others by available evidence, the general concept of personalized titration is appropriate.

Conclusion

Although there are clear recommendations for initiating insulin therapy in patients with type 2 diabetes, the manufacturers of insulin products provide limited guidance for titrating doses. Until the recent 2013 AACE algorithm and consensus statement (4,5), providers often had to rely on their clinical judgment and interpretation of the literature to determine appropriate titration strategies.

Generally, insulin therapy may be initiated with a basal product at a dose of ~10 units once daily, and then titrated by 1–2 units every 3 days until a fasting glucose target of 70–130 mg/dL is reached. Alternately, a tiered titration strategy may be used, with dose reductions for hypoglycemia. Follow-up care and A1C monitoring, often with escalation of therapy, are essential in ensuring that patients achieve glycemic control. When patients fail to achieve glycemic targets despite the use of basal insulin, clinicians should consider initiating a rapid-acting bolus insulin at a dose of 2–4 units before the largest meal of the day, with subsequent titration by 1–2 units every 3 days to achieve glycemic goals or the addition of another mealtime dose.

Although NPH and regular insulin are still commonly used in practice, their dosing is often based on clinical experience and not evidence from primary literature. The various titration algorithms available in the primary literature and presented in this article, as well as the guidance provided by AACE in 2013, offer strategies for clinicians to implement in practice, with the goal of improving outcomes for patients with type 2 diabetes.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. American Diabetes Association and European Association for the Study of Diabetes. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379

2. American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014;37(Suppl. 1):S14–S80

3. Handelsman Y, Mechanick JI, Blonde L, et al.; AACE Task Force for Developing Diabetes Comprehensive Care Plan: American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract 2011;17(Suppl. 2):1–53

4. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm 2013 consensus statement. Endocr Pract 2013;19:1–38

5. Garber A, Abrahamson M, Barzilay J, et al. AACE comprehensive diabetes management algorithm 2013. Endocr Pract 2013;19:327–336

6. Sanofi Diabetes. Lantus (insulin glargine injection) [product information]. Bridgewater, N.J., Sanofi-Aventis U.S., March 2007

7. Novo Nordisk. Levemir (insulin detemir injection) [product information]. Princeton, N.J., Novo Nordisk, July 2009

8. Eli Lilly and Co. Humulin N (NPH, human insulin, rDNA origin) isophane suspension [patient information]. Indianapolis, Ind., Eli Lilly and Co., 2009

9. Novo Nordisk. Novolin N (NPH, human insulin isophane suspension injection) [patient information]. Princeton, N.J., Novo Nordisk, May 2010

10. Novo Nordisk. Novolin R (regular, human insulin injection) [product information]. Princeton, N.J., Novo Nordisk, May 2012

11. Eli Lilly and Co. Humulin R (regular, human insulin, rDNA origin) [product information]. Indianapolis, Ind., Eli Lilly and Co., 2011

12. Novo Nordisk. NovoLog (insulin aspart injection) [product information]. Princeton, N.J., Novo Nordisk, June 2011

13. Eli Lilly and Co. Humalog (insulin lispro injection) [product information].

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Indianapolis, Ind., Eli Lilly and Co., May 2011

14. Sanofi Diabetes. Apidra (insulin glulisine injection) [product information]. Bridgewater, N.J., Sanofi-Aventis U.S., February 2009

15. Eli Lilly and Co. Humulin 70/30 (70% human insulin isophane suspension and 30% human insulin injection, rDNA origin) [patient information]. Indianapolis, Ind., Eli Lilly and Co., 2011

16. Eli Lilly and Co. Humulin 70/30 pen (70% human insulin isophane suspension and 30% human insulin injection, rDNA origin) [patient information]. Indianapolis, Ind., Eli Lilly and Co., 2009

17. Eli Lilly and Co. Humalog Mix 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro injection, rDNA origin) [product information]. Indianapolis, Ind., Eli Lilly and Co., 2009

18. Eli Lilly and Co. Humalog Mix 50/50 (50% insulin lispro protamine suspension and 50% insulin lispro injection, rDNA origin) [product information]. Indianapolis, Ind., Eli Lilly and Co., 2009

19. Novo Nordisk. Novolin 70/30 (70% NPH, human insulin isophane suspension, 30% regular, human insulin injection, rDNA origin) [patient information]. Princeton, N.J., Novo Nordisk, 2010

20. Novo Nordisk. NovoLog Mix 70/30 (70% insulin aspart protamine suspension, 30% insulin aspart injection, rDNA origin) [product information]. Princeton, N.J., Novo Nordisk, September 2011

21. Eli Lilly and Co. Humulin R U-500 (concentrated) insulin human injection, USP, rDNA origin [product information]. Indianapolis, Ind., Eli Lilly and Co., 2011

22. Wallia A, Molitch ME. Insulin therapy for type 2 diabetes mellitus. JAMA 2014;311:2315–2325

23. Riddle MC, Rosenstock J, Gerich J. The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080–3086

24. Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. Diabetes Care 2005;28:1282–1288

25. Gerstein HC, Yale J-F, Harris SB, Issa M, Stewart JA, Dempsey E. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas: the Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) study. Diabet Med 2006;23:736–742

26. Hermansen K, Davies M, Derezinski T, Ravn GM, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006;29:1269–1274

27. Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006;28:1569–1581

28. Meneghini L, Koenen C, Weng W, Selam J-L. The usage of a simplified self-titration dosing guideline (303 algorithm) for insulin detemir in patients with type 2 diabetes: results of the randomized, controlled PREDICTIVE 303 study. Diabetes Obes Metab 2007;9:902–913

29. Blonde L, Merilainen M, Karwe V, Raskin P; TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets: the TITRATE study. Diabetes Obes Metab 2009;11:623–631

30. Lankisch MR, Ferlinz KC, Leahy JL, Scherbaum WA; Orals Plus Apidra and Lantus (OPAL) Study Group. Introducing a simplified approach to insulin therapy in type 2 diabetes: a comparison of two single-dose regimens of insulin glulisine plus insulin glargine and oral antidiabetic drugs. Diabetes Obes Metab 2008;10:1178–1185

31. Owens DR, Luzio SD, Sert-Langeron C, Riddle MC. Effects of initiation and titration of a single pre-prandial dose of insulin glulisine while continuing titrated insulin glargine in type 2 diabetes: a 6-month "proof-of-concept" study. Diabetes Obes Metab 2011;13:1020–1027

32. Fritsche A, Larbig M, Owens D, Häring H-U, on behalf of the GINGER Study Group. Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes: results of the GINGER study. Diabetes Obes Metab 2010;12:115–123

33. Riddle MC, Rosenstock J, Vlajnic A, Gao L. Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. Diabetes Obes Metab 2014;16:396–402

34. Bergenstal RM, Johnson M, Powers MA, et al. Adjust to Target in Type 2 Diabetes: comparison of a simple algorithm with carbohydrate counting for adjustment of mealtime insulin glulisine. Diabetes Care 2008;31:1305–1310

35. Ratner R, Wynne A, Nakhle S, Brusco O, Vlajnic A, Rendell M. Influence of preprandial vs. postprandial insulin glulisine on weight and glycaemic control in patients initiating basal-bolus regimen for type 2 diabetes: a multicenter, randomized, parallel, open-label study (NCT00135096). Diabetes Obes Metab 2011;13:1142–1148

36. Meneghini L, Mersebach H, Kumar S, Svendsen A, Hermansen K. Comparison of 2 intensification regimens with rapid-acting insulin aspart in type 2 diabetes mellitus inadequately controlled by once-daily insulin detemir and oral antidiabetes drugs: the Step-Wise randomized study. Endocr Pract 2011;17:727–736

37. Rodbard HW, Visco VE, Andersen H, Hiort LC, Shu DH. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP study): a randomised, treat-to-target clinical trial. Lancet Diabetes Endocrinol 2014;2:30–37

38. Jain SM, Mao X, Escalante-Pulido M, Vorokhobina N, Lopez I, Ilag LL. Prandial-basal insulin regimens plus oral antihyperglycaemic agents to improve mealtime glycaemia: initiate and progressively advance insulin therapy in type 2 diabetes. Diabetes Obes Metab 2010;12:967–975

39. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. Diabetes Care 2008;31:20–25

40. Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, Linn T. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet 2008;371:1073–1084

41. Yamashiro K, Ikeda F, Fujitani Y, Watada H, Kawamori R, Hirose T. Comparison of thrice-daily lispro 50/50 vs thrice-daily lispro in combination with sulfonylurea as initial insulin therapy for type 2 diabetes. J Diabetes Investig 2010;1:149–153

42. Lane W, Cochran E, Jackson J, et al. High-dose insulin therapy: is it time for U-500 insulin? Endocr Pract 2009;15:71–79

43. Cochran E, Phillip G. Use of U-500 insulin in the treatment of severe insulin resistance. Insulin 2008;3:211–218

44. Ballani P, Tran MT, Navar MD, Davidson MB. Clinical experience with U-500 regular insulin in obese, markedly insulin-resistant type 2 diabetic patients. Diabetes Care 2006;29:2504–2505

45. Cochran EK, Valentine V, Samaan KH, Corey IB, Jackson JA. Practice tips and tools for the successful use of U-500 regular human insulin: the diabetes educator is key. Diabetes Educ 2014;40:153–165

46. Heller S, Buse J, Fisher M, et al. Insulin degludec, an 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;379:1489–1497

47. Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an 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, treat-to-target non-inferiority trial. Lancet 2012;379:1498–1507

48. Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 2012;35:2464–2471

49. Zinman B, DeVries JH, Bode B, et al. Efficacy and safety of insulin degludec three times a week versus insulin glargine once a day in insulin-naïve patients with type 2 diabetes: results of two phase 3, 26 week, randomised, open-label, treat-to-target, non-inferiority trials. Lancet Diabetes Endocrinol 2013;1:123–131

50. Meneghini L, Atkin SL, Gough SC, 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 individuals with type 2 diabetes. Diabetes Care 2013;36:858–864

51. Riddle MC, Bolli GB, Ziemen M, Muehlen-Bartmer I, Bizet F, Home PD. 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;37:2755–2762

52. Yki-Jarvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/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 Epub ahead of print (DOI:10.2337/dc14-0990)

53. Texas Diabetes Council. Diabetes tool kit: a practitioner's reference. 2013. http://www.tdctoolkit.org/algorithms-guidelines. Accessed 1 July 2014

54. Davidson P, Hebblewhite H, Steed R, Bode B. Analysis of guidelines for basal-bolus insulin dosing: basal insulin, correction factor, and carbohydrate-to-insulin ratio. Endocr Pract 2008;14:1095–1101