



DRUG PROFILE

Dulaglutide, a long-acting GLP-1 analog fused with an Fc antibody fragment for the potential treatment of type 2 diabetes

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Dulaglutide (LY-2189265) is a novel, long-acting glucagon-like peptide 1 (GLP-1) analog being developed by Eli Lilly for the treatment of type 2 diabetes mellitus (T2DM). Dulaglutide consists of GLP-1(7-37) covalently linked to an Fc fragment of human IgG4, thereby protecting the GLP-1 moiety from inactivation by dipeptidyl peptidase 4. In vitro and in vivo studies on T2DM models demonstrated glucose-dependent insulin secretion stimulation. Pharmacokinetic studies demonstrated a $t_{1/2}$ in humans of up to 90 h, making dulaglutide an ideal candidate for once-weekly dosing. Clinical trials suggest that dulaglutide reduces plasma glucose, and has an insulinotropic effect increasing insulin and C-peptide levels. Two phase II clinical trials demonstrated a dose-dependent reduction in glycated hemoglobin (HbA1c) of up to 1.52% compared with placebo. Side effects associated with dulaglutide administration were mainly gastrointestinal. To date, there have been no reports on the formation of antibodies against dulaglutide, but, clearly, long-term data will be needed to assess this and other possible side effects. The results of several phase III clinical trials are awaited for clarification of the expected effects on HbA1c and body weight. If dulaglutide possesses similar efficacy to other GLP-1 analogs, the once-weekly treatment will most likely be welcomed by patients with T2DM.

Introduction

In 2000, an estimated 171 million people worldwide had diabetes (all types). This figure is expected to increase by 144% to 366 million by 2030, as a result of increasing longevity, obesity and sedentary lifestyle [880516]. The most common form of diabetes is type 2 diabetes mellitus (T2DM), which is characterized by two main physiological defects: β -cell dysfunction and insulin resistance [995537], [995560]. Additionally, T2DM is characterized by fasting and postprandial hyperglucagonemia contributing to the hyperglycemic state of the patients via glucagon-induced hepatic glucose production. It is evident that T2DM is a progressive disease with an almost linear decline in β -cell function over time [995565]. Consequently, the current treatment paradigm aims to counteract the progressive deterioration in blood glucose homeostasis.

The classical oral antidiabetic drugs (OADs) include insulin sensitizers, such as biguanides (eg, metformin) and thiazolidinediones (TZDs; eg, pioglitazone), insulin secretagogues, such as sulfonylureas (SUs; eg, glibenclamide) and meglitinides (eg, repaglinide), or drugs that delay

Therapeutic Dulaglutide

Originator Eli Lilly

Status Phase III Clinical

Indication Type 2 diabetes mellitus

Actions Glucagon-like peptide-1 analog, Glucose-lowering agent

Technologies Antibody fragment, Biological therapeutic, Protein fusion, Subcutaneous formulation

Synonym LY-2189265

such as acarbose. These medications enable modest reductions of glycated hemoglobin (HbA1c), usually between 0.5 and 1.5%, but are not able to correct either the impairment or the progressive decline of β -cell function [995569]. Therefore, regardless of optimal treatment, the endogenous insulin response becomes attenuated, and, in later stages of disease, lost, necessitating exogenous insulin replacement [931356]. It is currently believed that treatments that preserve or improve β -cell function

delaying or even preventing the need for insulin therapy [995571]. Medications that are able to address cardiovascular risk factors, as well as provide glycemic control and preserve or improve β -cell function, thereby possibly halting or delaying disease progression, are highly anticipated [995571].

The scientific knowledge regarding optimal HbA1c levels has been recently complicated by the publication of mega trials demonstrating limitations to the paradigm of an overzealous glucose lowering strategy [1048568], [1147074], [1147078]. However, because of the long-standing evidence for an association between poor glycemic control and long-term diabetes-related complications, the overall scientific consensus and major guidelines still advocate intensification of treatment to maintain a HbA1c level of $< 7.0\%$ [996028]. The majority of patients fail to achieve this target, as exemplified in a recent trial in the US, which demonstrated that more than half of patients with diabetes did not meet a target HbA1c level of $< 7.0\%$ [996031]. This may, in part, be a result of reluctance on the part of physicians to prescribe therapies with unwanted side effects; hypoglycemia, a common side effect of insulin and also frequently associated with SUs, may be of particular concern. Diabetes is a complex disease to manage and primary care physicians rate diabetes as harder to treat than other common diseases [996035]. Another limiting factor to treatment may be the patient's own acceptance of a prescribed regimen. Common barriers to patient adherence include concern about unwanted weight gain [996037], fear of hypoglycemia and perceived inconvenience [996040], [996603], which may all indirectly undermine glycemic control if the prescribed therapy is not followed.

Under physiological conditions, insulin secretion is controlled by several factors including the incretin hormone glucagon-like peptide-1 (GLP-1). This hormone, secreted by endocrine cells in the intestine, stimulates glucose-dependent insulin secretion and accounts for a considerable part of the insulin response to glucose [827063], [996043], [1147079]. The physiological effects of GLP-1 are mediated by a G-protein-coupled receptor [996045], which is widely distributed across different tissues. As a result, the peripheral and central nervous systems, heart, stomach, lungs, intestines, pituitary, endothelium, kidneys and pancreas are all affected by GLP-1 [827063], [996047]. In addition to its incretin effect, GLP-1 exerts several effects that are also potentially beneficial in the treatment of T2DM. These include preservation of β -cell mass [439499], [475556], [996049], potentiation of glucose-induced suppression of glucagon secretion from pancreatic α -cell, a protective effect on the cardiovascular system [580626], [996071], delayed gastric emptying and an increase in the feeling of satiety [996074]; the latter two factors can contribute to a decreased energy intake.

The early established role of GLP-1 in glucose homeostasis prompted research into its potential for therapeutic use

patients with T2DM, despite a frequently impaired secretion of GLP-1 [875837], [996163], [996169], the insulinotropic effect is preserved [931364]. This established GLP-1 as a therapeutic candidate for the treatment of T2DM, and subsequent trials have demonstrated that exogenous native GLP-1 normalizes the insulin response in individuals with impaired glucose tolerance [996079] and decreases blood glucose levels in patients with T2DM [475562], [760698].

While native GLP-1 offers significant benefits for patients with T2DM, its rapid breakdown by the enzyme dipeptidyl peptidase 4 (DPP-4) incurs the critical disadvantage of a short half-life (1 to 2 min) following intravenous administration [996173]; thus, native GLP-1 would need to be continually infused for effective therapy. To circumvent this physiological degradation, DPP-4-resistant GLP-1 analogs have been developed. Two such compounds are currently on the market: exenatide, a synthetic version of exendin-4(1-39), which is a hormone isolated from the saliva of the Gila monster lizard [996232], and liraglutide, an acylated GLP-1 analog with 97% amino acid sequence homology to endogenous human GLP-1(7-37) [1070808]. However, many more agents are in phase II or III clinical development [1147081].

The focus of this review is dulaglutide (LY-2189265), a novel, long-acting GLP-1 analog, being developed by Eli Lilly for the treatment of T2DM. Dulaglutide consists of a DPP-4-protected GLP-1 analog covalently linked to an Fc fragment of human IgG4, thereby increasing its duration of pharmacological activity. The first phase III clinical trials of dulaglutide were initiated in early 2008 [970293].

Synthesis and SAR

Dulaglutide comprises a DPP-4-protected GLP-1(7-37) analog fused to a modified IgG4 Fc fragment [1100363]. Initial studies using DPP-4-protected GLP-1 fused to IgG1 demonstrated significantly reduced *in vitro* activity compared with free DPP-4-protected GLP-1. Linker sequences between the C-terminus of the GLP-1 analog and the N-terminus of the Ig molecule were assessed in an attempt to improve activity, and IgG1 was replaced with a modified IgG4 (Phe²³⁴Ala and Leu²³⁵Ala to reduce interaction with high-affinity Fc receptors, and Ser²²⁸Pro to eliminate half-antibody formation) to reduce the potential of complement- and/or antibody-dependent cell-mediated cytotoxicity. An Arg³⁶Gly mutation in GLP-1 was introduced to de-immunize the fusion protein and the C-terminal lysine of the IgG4-Fc was removed. Dulaglutide exhibited 4-fold greater *in vitro* activity than the free DPP-4-protected GLP-1. The GLP-1-Fc fusion proteins used in these studies were expressed from HEK293-EBNA cells [1100363].

Preclinical development

In vitro

Isolated rat islets were used to measure the effect of dulaglutide on glucose-induced insulin secretion

secretion was enhanced 2.5- to 3-fold by the addition of 3 or 30 nM dulaglutide to the extracellular medium. No enhancement was observed at low glucose levels (2.8 mM). In comparison, human GLP-1 (3 nM) caused a 4-fold increase in insulin secretion at 16.8 mM glucose. At 2.7 nM dulaglutide, half-maximal stimulation of insulin secretion was observed, and the maximal 4-fold stimulation was observed with 300 nM dulaglutide. The addition of the GLP-1 receptor antagonist exendin(9-39) (1 μ M) to the medium reversed the effects of dulaglutide on insulin secretion. In islets isolated from cynomolgus monkeys, dulaglutide increased insulin secretion in a concentration-dependent manner at high concentrations of glucose [1100363].

In vivo

Dose-dependent increases in glucose-dependent insulin secretion were demonstrated 24 h after a single dose of dulaglutide (0.3, 1, 3 or 30 nmol/kg sc) in conscious rats receiving a graded glucose infusion. However, only the 3- and 30-nmol/kg doses achieved statistically significant ($p < 0.05$) increases in insulin secretion (up to 4-fold) compared with vehicle [1100363].

Insulin secretion in response to graded glucose infusion was evaluated 1, 5 and 7 days after a single dose of dulaglutide (1.7 nmol/kg sc) to cynomolgus monkeys [1100363]. Plasma concentrations of dulaglutide remained detectable throughout the 7 days. Insulin (2-fold versus vehicle; $p < 0.0001$) and C-peptide levels were significantly enhanced during the 7-day period, whereas glucose, GLP-1 and glucagon levels were unaffected. Multiple dosing of dulaglutide (1.7 nmol/kg sc, qw for 4 weeks) before graded glucose infusion (4 days after the last dose) was also assessed in cynomolgus monkeys. Progressively increasing glucose-stimulated insulin release (2-fold versus vehicle; $p < 0.0002$) and C-peptide levels were observed following the glucose infusion. Triglyceride levels were reduced, but glucose and glucagon levels remained unaltered [1100363].

In 5-week-old diabetic (*db/db*) mice treated with dulaglutide (10 nmol/kg sc, biw for 4 weeks), plasma glucose levels were consistently decreased throughout the study period ($p < 0.001$ versus vehicle); treated mice also exhibited a small, but significant, reduction in body mass versus vehicle (body mass = 35.5 versus 38.5 g; $p < 0.02$) [1100363].

Toxicity

At the time of publication, toxicity data were not available.

Metabolism and pharmacokinetics

The pharmacokinetic profile of single-dose dulaglutide (0.1 mg/kg sc) was assessed in rats and cynomolgus monkeys. In rats and monkeys respectively, C_{max} values were 179.7 and 292.2 ng/ml, T_{max} values were 24.0 and 16.7 h, $AUC_{0-\infty}$ values were 10,537 and 15,207 ng/ml·h,

7.3 ml/h/kg, and the volume of distribution was 525.0 and 557.5 ml/kg [1100363].

The pharmacokinetics of dulaglutide (0.1 to 12 mg sc; administered ≥ 3 weeks apart) were analyzed in healthy volunteers ($n = 20$). The $t_{1/2}$ value of dulaglutide was ~ 90 h and the T_{max} value was between 24 and 48 h. When the dose was doubled, C_{max} and $AUC_{0-\infty}$ of plasma dulaglutide increased by 1.84- and 1.88-fold, respectively, suggesting linear kinetics [1013502], [1087432]. In patients ($n = 43$) with T2DM, dulaglutide (0.05 to 8 mg sc, qw) had a $t_{1/2}$ value of ~ 95 h [1087431], [1087438].

Clinical development

Phase I

In a randomized, double-blind, placebo-controlled, three-period, crossover, single-center clinical trial, the safety, tolerability, pharmacokinetics and insulinotropic activity of escalating single doses of dulaglutide (0.1 to 12 mg sc; administered ≥ 3 weeks apart) were analyzed in healthy volunteers ($n = 20$). Compared with placebo, there was a glucose-dependent increase in insulin secretion after graded glucose infusion, and a suppression of plasma glucose after an oral glucose tolerance test at all doses [1013502], [1087432].

In an open-label, parallel clinical trial, the effects of dulaglutide (1 or 3 mg sc, qw for 4 weeks) on gastric emptying were assessed in healthy volunteers ($n = 30$) using paracetamol (1 g po) pharmacokinetics as a probe. Both the 1- and 3-mg doses of dulaglutide caused a reduction in paracetamol C_{max} (36 and 50%, respectively) and a delay in T_{max} (1 and 2 h, respectively), indicating a delay in gastric emptying; this was only observed after the first dose of dulaglutide and not at steady-state. The body mass of volunteers was also significantly decreased by 1.4 and 2.4 kg from baseline in the 1- and 3-mg dose groups, respectively [1109660].

The effects of dulaglutide (1.5 mg sc, qw for 4 weeks) on gastric emptying would also be assessed by scintigraphy in a phase I, randomized, double-blind, placebo-controlled clinical trial (ClinicalTrials.gov identifier: NCT01215968). At the time of publication, patients (estimated $n = 40$) with T2DM were being recruited to this trial.

Phase II

A double-blind, placebo-controlled, parallel group, 5-week clinical trial assessed the effects of dulaglutide (0.05 to 8 mg sc, qw) in patients ($n = 43$) with T2DM. Statistically significant decreases in HbA1c (-0.69 to -1.34%) were observed at all dose levels. Increases in insulin and C-peptide AUC values were also observed, indicating an insulinotropic effect. Fasting and postprandial plasma glucose excursions were significantly reduced with dulaglutide doses ≥ 1 mg. At dulaglutide doses ≥ 5 mg, statistically significant effects on gastric emptying after the first dose and weight loss after the last dose were

A phase II, randomized, double-blinded, placebo-controlled, parallel assignment, multicenter clinical trial (EGO; NCT00630825) assessed the safety and efficacy of dulaglutide in patients ($n = 262$) with uncontrolled T2DM (baseline HbA1c = 8.2%) and a BMI of 33.9 kg/m². Patients were randomized into three dulaglutide groups or a matching placebo. The dulaglutide groups were: 0.5 mg (sc, qw) for 4 weeks titrated to 1.0 mg (sc, qw) for 12 weeks, 1.0 mg (sc, qw) for 16 weeks, or 1.0 mg (sc, qw) for 4 weeks titrated to 2.0 mg (sc, qw) for 12 weeks [1016672], [1087434], [1087444], [1109617], [1122363], [1140475]. At 16 weeks, the mean reduction from baseline in HbA1c was -1.28, -1.29 and -1.52% in the 0.5/1.0-, 1.0/1.0- and 1.0/2.0-mg dose groups, respectively, compared with -0.27% for placebo ($p < 0.001$). Reductions were also observed in fasting plasma glucose (-2.09, -2.04 and -2.64 versus -0.49 mm; $p < 0.001$), solid mixed meal test glucose excursions (30.71, 32.21 and 28.24 versus 36.36 mM·h; $p < 0.001$) and body mass (-1.58, -1.40 and -2.51 versus -0.07 kg; $p < 0.05$) [1016672], [1087444]. β -cell function was also significantly increased compared with placebo, as assessed by the homeostatic model assessment of β -cell function (HOMA%B: 39.20, 44.26 and 45.61 versus 1.04%; $p < 0.05$) [1087444].

In addition, the impact of Hispanic ethnicity was assessed [1109617], [1122363], [1140475]. At baseline, HbA1c levels were significantly greater ($p = 0.006$) in Hispanic patients (8.4%) compared with non-Hispanic Caucasian patients (8.1%); the decrease in HbA1c at week 16 was also greater in Hispanic patients (-1.5 versus -1.1%; $p = 0.02$). Furthermore, the reduction in postprandial glucose excursion was significantly greater in Hispanic patients (-2.8 versus -0.5 mM·h; $p = 0.003$), although fasting plasma glucose, insulin levels and β -cell function were not affected by ethnicity [1109617], [1122363], [1140475].

Further to these trials, additional phase II, randomized, double-blind, placebo-controlled, multicenter clinical trials of dulaglutide were listed in the NIH clinical trial registry at the time of publication. Trial NCT00791479 assessed the dose-dependent effects of dulaglutide (0.1, 0.5, 1.0 and 1.5 mg sc, qw for up to 12 weeks) on glycemic control in patients (estimated $n = 168$) with T2DM; this trial had been completed. Trial NCT01001104 was assessing the dose-response characteristics of dulaglutide (0.25, 0.50 and 0.75 mg sc, qw for up to 12 weeks) on HbA1c in Japanese patients (estimated $n = 144$) with inadequately controlled T2DM who were taking no more than one OAD (not DPP-4 inhibitors); patient recruitment to this trial was complete, although the trial was still ongoing. Data were not available from either trial.

Phase III

At the time of publication, a phase II/III, randomized, double-blind, placebo-controlled, multicenter clinical trial (NCT00734474) comparing dulaglutide (0.25, 0.5, 0.75, 1.0, 1.5, 2.0 and 3.00 mg sc, qw) with the DPP-4

patients (estimated $n = 1566$) with T2DM. Treatment would last for 2 years and the primary outcome was HbA1c change from baseline to 12 months.

Additionally, Eli Lilly has initiated a program of phase III, randomized, multicenter clinical trials known as AWARD. The placebo-controlled, double-blind AWARD-1 (NCT01064687) clinical trial was recruiting patients (estimated $n = 980$) with T2DM inadequately controlled with metformin and pioglitazone. This trial would determine the efficacy of dulaglutide (0.75 and 1.5 mg sc, qw), compared with placebo or exenatide, as an add-on to baseline therapy. The open-label AWARD-2 (NCT01075282) clinical trial was recruiting patients (estimated $n = 837$) with T2DM inadequately controlled with metformin and the SU agent glimepiride. The trial would compare the efficacy and safety of dulaglutide (0.75 and 1.5 mg sc, qw), compared with insulin glargine, as an add-on to baseline therapy. The placebo-controlled, double-blind AWARD-3 (NCT01126580) clinical trial was recruiting patients (estimated $n = 753$) with T2DM. The trial would compare the efficacy and safety of dulaglutide (0.75 and 1.5 mg/kg sc, qw) with metformin (1500 to 2000 mg/day po). The open-label AWARD-4 (NCT01191268) clinical trial would recruit patients (estimated $n = 837$) with T2DM. The trial would compare the efficacy and safety of dulaglutide (0.75 and 1.5 mg/kg sc, qw) with insulin glargine, both in combination with insulin lispro.

Side effects and contraindications

In the trial evaluating single escalating doses of dulaglutide (0.1 to 12 mg sc) in healthy volunteers, the most frequent adverse event was dyspepsia. Statistically significant increases in supine heart rate at doses ≥ 0.3 mg and in supine diastolic blood pressure at doses ≥ 1 mg compared with placebo were noted. Dose-dependent increases in the rates of headache, injection-site irritation, nausea and vomiting were also reported. Importantly, hypoglycemia or antibodies against dulaglutide were not reported [1013502], [1087432].

In the trial evaluating the effects of dulaglutide (1 or 3 mg) on gastric emptying in healthy volunteers, safety and tolerability were also assessed. Gastrointestinal disturbances were the most frequent adverse events. Furthermore, significant increases from baseline in pulse rate (7.8 and 9.6 bpm at 1 and 3 mg, respectively) and decreases from baseline in systolic blood pressure (4.1 and 7.7 mmHg at 1 and 3 mg, respectively) were also observed [1109660].

In the 5-week trial of dulaglutide (0.05 to 8 mg sc, qw) in patients with T2DM, dulaglutide was generally well tolerated. Nausea, vomiting, headache and diarrhea were the most common adverse events. At the 5-mg dose, a statistically significant increase in heart rate was reported. Antibodies against dulaglutide were not

In the EGO trial in patients with T2DM, dulaglutide (1 mg for 16 weeks, 0.5 mg for 4 weeks titrated to 1 mg for 12 weeks, or 1 mg for 4 weeks titrated to 2 mg for 12 weeks; all sc qw) was generally well tolerated. The most common adverse events were nausea (13%), diarrhea (8.8%) and abdominal distension (8.0%). The frequency of hypoglycemic episodes did not differ among treatment groups [1016672], [1087444].

Because of the effects on heart rate and blood pressure observed in the initial clinical trials, a phase II, randomized, double-blind, placebo-controlled, multicenter clinical trial (NCT01149421) was initiated to assess these parameters. Patients (estimated $n = 693$) with T2DM treated with one or more OAD were treated with dulaglutide (0.75 and 1.5 mg sc, qw) for up to 26 weeks. Inclusion criteria included HbA1c between 7 and 9.5%, blood pressure $> 90/60$ and $< 140/90$ mmHg, and BMI ≥ 23 kg/m².

Patent summary

The genesis of dulaglutide appears to have come from the GLP-1 fusion proteins claimed in Eli Lilly's WO-00246227, most likely protecting forms of the company's GLP-1 analog LY-548806 and involving some of the same inventors as listed on the product patent for dulaglutide. Although WO-00246227 has generic claims covering the GLP-1 analog and the peptide linker present in dulaglutide, the IgG4 Fc component does not have the amino acid substitutions present in the dulaglutide moiety that stabilize heavy chain dimer formation and eliminate their natural effector function.

The first two claims of WO-2005000892 describe dulaglutide, including its peptide linker. WO-2005000892 is part of the WO-2004110472 family covering a whole range of Fc fragment fusion proteins including one based on FGF-21. The granted equivalents relating specifically to GLP-1 fusion proteins are EA-00008831 and EP-01641483 both expiring in June 2024, and US-07452966 expiring in July 2024 after a short patent term extension.

Further patenting by Eli Lilly has concentrated on providing more stable formulations for dulaglutide. WO-2006068910 claims a buffer solution for the protein, which gives greater resistance to protease, and WO-2009009562 claims a solution giving greater physical stability. Only the earlier of the two applications has had any granted applications, by the European and Eurasian authorities. There is also WO-2009020802 claiming combinations of dulaglutide or LY-548806 with FGF-21 for the potential treatment of obesity.

The only patenting on dulaglutide by third parties has been by Amylin Pharmaceuticals, Eli Lilly's partner for the development and launch of exenatide. Amylin's WO-2009143014 claims a cell-based assay for measuring the activity of multiple GLP-1 agonists, including

Current opinion

Incretin-based therapies represent an important addition to the conventional antidiabetic treatments by targeting several key metabolic defects in T2DM. Even if the promising effects on β -cell proliferation and preservation observed in preclinical studies are not replicated in the clinic, the GLP-1 analogs as a class still represent strong drug candidates. Firstly, they represent a versatile physiological approach, targeting both pancreatic α - and β -cell dysfunction and obesity, combined with improvements in glycemic indices that are comparable with traditional OADs. Secondly, severe limitations associated with existing therapies, including the risk of hypoglycemia (as observed with insulin and SUs) and unsuitability for patients with renal impairment (metformin) or significant cardiovascular disease (TZDs), creates opportunity for incretin-based therapies in an expanding diabetic drug market. Thirdly, there are several potential future indications that may prove worthwhile to pursue, such as management of obesity, postmyocardial infarction size reduction [996601], adjunction to insulin therapy in patients with type 1 diabetes mellitus [996602] and, depending on the eventual trophic effects on β -cells, pancreatic islet transplantation patients.

Regarding the efficacy and safety of the GLP-1 analogs, there appears to be a class effect. The main difference between compounds appears to rely in the pharmacokinetic profile. In this regard, the relatively long $t_{1/2}$ value of dulaglutide (~ 90 h) could prove to be a significant advantage. Clinical data suggests that a more stable pharmacokinetic profile (ie, a longer $t_{1/2}$) leads to higher efficacy, and lower frequencies of nausea and vomiting [953142]. Furthermore, the benefits to patient convenience and compliance are obvious.

There are also limitations to consider. Firstly, there is a general problem concerning gastrointestinal side effects, especially nausea. Even if the nausea and vomiting were more infrequent with dulaglutide (because of an increased $t_{1/2}$) compared with some other GLP-1 analogs, its use will still be limited to patients who are able to manage these side effects and, for example, use them as a positive reinforcement strategy for weight loss. Ultimately, it appears that $\sim 5\%$ of patients with T2DM do not tolerate GLP-1 analogs currently on the market [976021], [996244], [996601]. Secondly, the consequences of antibody formation are not yet fully known. Evidence from clinical trials of exenatide suggests some significance with regard to glycemic control especially in patients exhibiting high antibody titers [996596]. Dulaglutide consists of GLP-1(7-37) covalently linked to an Fc fragment of human IgG4, thereby protecting it from DPP-4 cleavage and increasing its duration of pharmacological activity. One concern is that treating patients with engineered bioproducts could lead to the formation of antibodies against foreign epitopes. From the published data, it is not possible to ignore the potential formation of antidrug antibodies,

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