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ADIS DRUG EVALUATION

Insulin Glargine 300 U/mL: A Review in Diabetes Mellitus

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Abstract Insulin glargine 300 U/mL (Toujeo®) is a long-acting basal insulin analogue approved for the treatment of diabetes mellitus. Insulin glargine 300 U/mL has a more stable and prolonged pharmacokinetic/pharmacodynamic profile than insulin glargine 100 U/mL (Lantus®), with a duration of glucose-lowering activity exceeding 24 h. In several 6-month phase III trials, insulin glargine 300 U/mL achieved comparable glycaemic control to that seen with insulin glargine 100 U/mL in patients with type 1 or type 2 diabetes, albeit with consistently higher daily basal insulin requirements. These improvements in glycaemic control were maintained during longer-term (12 months) treatment. Insulin glargine 300 U/mL was generally associated with a lower risk of nocturnal hypoglycaemia than insulin glargine 100 U/mL in insulin-experienced patients with type 2 diabetes, while the risk of nocturnal hypoglycaemia did not significantly differ between treatment groups in insulin-naïve patients with type 2 diabetes or in patients with type 1 diabetes. To conclude, once-daily subcutaneous insulin glargine 300 U/mL is an effective and generally well tolerated basal insulin therapy option for patients with type 1 or type 2 diabetes.

Insulin glargine 300 U/mL: clinical considerations in diabetes mellitus
Long-acting insulin analogue with duration of glucose-lowering activity of >24 h
More stable and prolonged pharmacokinetic/pharmacodynamic profile than insulin glargine 100 U/mL
Provides comparable glycaemic control to insulin glargine 100 U/mL over 6 months in patients with type 1 or type 2 diabetes
Improvements in glycaemic control are maintained during longer-term therapy
Generally well tolerated
Lower risk of nocturnal hypoglycaemia than with insulin glargine 100 U/mL in insulin-experienced patients with type 2 diabetes

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1 Introduction

Insulin therapy continues to play an important role in the management of diabetes mellitus. The primary goal of insulin therapy is to achieve the best possible glycaemic control without hypoglycaemia or unacceptable weight gain [1]. Most patients with type 1 diabetes should receive basal and prandial insulin or continuous subcutaneous insulin infusion therapy, with treatment guidelines recommending the use of insulin analogues in most patients [2].

Due to progressive β-cell dysfunction, many patients with type 2 diabetes will eventually require insulin therapy [1–3]. While most patients with type 2 diabetes can be treated with basal insulin as the only insulin agent (usually in combination with metformin and sometimes another non-insulin agent), some require the addition of a rapid-acting mealtime insulin [1, 3].

Long-acting insulin analogues such as insulin glargine and insulin detemir were developed to overcome some of the limitations associated with early basal insulins such as neutral protamine Hagedorn (NPH) insulin (e.g. variable absorption, hypoglycaemia) [1, 4]. Insulin glargine was the first long-acting basal insulin analogue to be approved for use in clinical practice, and has a well-established record of efficacy and safety [4]. Insulin glargine and other long-acting insulins are associated with lower rates of nocturnal hypoglycaemia than NPH insulin [5, 6]. Nevertheless, hypoglycaemia remains a substantial challenge, particularly in type 1 diabetes, preventing many patients from achieving optimal glycaemic control. Therefore, long-acting basal insulin analogues with stable glucose-lowering profiles, a longer duration of action and less day-to-day variability are sought after [5, 6]. Insulin degludec is an ultra-long-acting insulin with a duration of action of >42 h [7] and a long-acting 300 U/mL formulation of insulin glargine (hereafter referred to as insulin glargine 300 U/mL; Toujeo®) has also been developed. Insulin glargine 300 U/mL forms a smaller subcutaneous depot than the 100 U/mL formulation (hereafter referred to as insulin glargine 100 U/mL; Lantus®), resulting in slower and more prolonged insulin release [8, 9].

This article reviews pharmacological, efficacy and tolerability data relevant to the use of subcutaneous once-daily insulin glargine 300 U/mL as basal insulin therapy in patients with type 1 or type 2 diabetes.

2 Pharmacodynamic Properties of Insulin Glargine 300 U/mL

Insulin glargine differs structurally from human insulin by the addition of two arginines after position B30 and the replacement of asparagine with glycine at position A21 [10]. Insulin glargine is soluble at an acidic pH and precipitates when injected into subcutaneous tissue due to the neutral pH of the tissue; the precipitated drug is then gradually released into the circulation [10]. The more sustained release of insulin glargine from the precipitate seen with insulin glargine 300 U/mL compared with insulin glargine 100 U/mL reflects the fact that the injection volume is reduced by two-thirds, which results in a smaller precipitate surface area [11]. This smaller precipitate surface area is associated with a reduced redissolution rate [8].

Like other insulins, the primary function of insulin glargine is regulation of glucose metabolism [10]. Blood glucose levels are lowered through inhibition of glucose production in the liver and stimulation of peripheral glucose uptake by skeletal muscle and fat. Insulin glargine also enhances protein synthesis and inhibits lipolysis and proteolysis [10].

Subcutaneous insulin glargine 300 U/mL is long-acting with a more even and prolonged pharmacodynamic profile than insulin glargine 100 U/mL [8, 9, 12]. For example, during euglycaemic clamp in patients with type 1 diabetes ($n = 18$), the steady-state glucose infusion rate (GIR) profile of insulin glargine 300 U/mL was flatter, more constant and more evenly distributed over 24 h than that of insulin glargine 100 U/mL [8]. The median steady-state maximum smoothed bodyweight-standardized GIR was 2.5 $mg \cdot kg^{-1} \cdot min^{-1}$ with subcutaneous insulin glargine 300 U/mL 0.4 U/kg/day and 3.2 $mg \cdot kg^{-1} \cdot min^{-1}$ with the same dosage of insulin glargine 100 U/mL, yielding a treatment ratio of 0.81 (90 % CI 0.68–0.97). The more even activity profile and longer duration of action was supported by the ≈3 h longer time to 50 % of GIR area under the curve (AUC) from time zero to 36 h with insulin glargine 300 U/mL compared with insulin glargine 100 U/mL. After the final dose of 0.4 U/kg on day 8, tight blood glucose control (≤5.8 mmol/L) was maintained for a median of 30 h with insulin glargine 300 U/mL and 25 h with insulin glargine 100 U/mL [8].

In a 16-week, open-label phase II study using continuous glucose monitoring (CGM) in patients with type 1 diabetes ($n = 59$), the proportion of time spent within a glucose range of 4.4–7.8 mmol/L during the last 2 weeks of each treatment period (primary endpoint) was not significantly different between insulin glargine 300 U/mL and insulin glargine 100 U/mL [least squares (LS) mean difference 0.75 %; 95 % CI –3.61 to 5.12] [13]. However, pooled average glucose profiles showed that insulin glargine 300 U/mL provided more stable glucose levels throughout the day than insulin glargine 100 U/mL for both morning and evening injections, and measures of intra-subject variability tended to be lower with insulin glargine 300 U/mL than with insulin glargine 100 U/mL [13]. In another study using CGM in Japanese patients with type 1 diabetes ($n = 20$), there was no significant difference in glucose variability with insulin glargine 300 U/mL versus insulin glargine 100 U/mL ($AUC_{mean\_24\ h}$ treatment ratio 0.96; 90 % CI 0.79–1.16) [14].

Dose adjustment and more frequent glucose monitoring may be needed when insulin glargine 300 U/mL is used concurrently with certain drugs [11, 15]. There have been reports of cardiac failure during coadministration of insulin

and pioglitazone [11]. If insulin glargine 300 U/mL and pioglitazone are used concurrently, it is recommended that patients are observed for signs and symptoms of heart failure, weight gain and oedema [11]. Local prescribing information should be consulted for additional details and a more comprehensive list of potential drug interactions with insulin glargine 300 U/mL.

3 Pharmacokinetic Properties of Insulin Glargine 300 U/mL

Consistent with the pharmacodynamic activity of insulin glargine 300 U/mL, the pharmacokinetic profile of insulin glargine 300 U/mL was more even and prolonged compared with insulin glargine 100 U/mL [8, 9, 16]. Following subcutaneous injection in healthy subjects and in patients with diabetes, insulin glargine 300 U/mL has a slower and more prolonged absorption profile than insulin glargine 100 U/mL [11]. Subcutaneous insulin glargine 300 U/mL and insulin glargine 100 U/mL were not bioequivalent when administered as single equal doses in healthy volunteers [17].

During euglycaemic clamp in Japanese ($n = 18$) and European ($n = 24$) patients with type 1 diabetes receiving single subcutaneous doses of insulin glargine 300 U/mL 0.4 or 0.6 U/kg or insulin glargine 100 U/mL 0.4 U/kg, maximum serum concentration (C_{max}) and area under the serum concentration-time curve from time zero to 24 h values were significantly higher for insulin glargine 100 U/mL than for insulin glargine 300 U/mL (all $p < 0.05$) [9]. The median time to C_{max} ranged from 12–16 h with all doses of insulin glargine 300 U/mL and from 8–12 h with insulin glargine 100 U/mL. Corresponding values for the median time to 50 % of insulin glargine exposure over the whole clamp period were 15–19 h and 13–14 h, respectively [9].

During euglycaemic clamp in patients with type 1 diabetes ($n = 50$), insulin glargine 300 U/mL was associated with a low level of diurnal fluctuation in insulin concentrations and a high level of day-to-day reproducibility in insulin glargine exposure, indicating that it is suitable for effective basal insulin use [12].

Steady-state concentrations were reached after at least 5 days in patients with type 1 diabetes who received 8 days of once-daily subcutaneous insulin glargine 300 U/mL 0.4–0.6 U/kg [15]. Intra-subject variability (defined as the coefficient of variation for the insulin exposure during 24 h) is 17.4 % [11] or 21.0 % [15] at steady state.

Following subcutaneous injection, insulin glargine is rapidly metabolized at the carboxyl terminus of the β-chain to form the active metabolites M1 (21^{A}-Gly-insulin) and M2 (21^{A}-Gly-des-30^{B}-Thr-insulin) [11, 15]. M1 is the principal component circulating in plasma [11]. In patients with type 1 diabetes, insulin glargine metabolism was found to be the same for insulin glargine 300 U/mL and insulin glargine 100 U/mL, with M1 confirmed as the main circulating active moiety in the blood [16]. The half-life of insulin glargine 300 U/mL following subcutaneous injection is 18–19 h independent of dose, and is determined by the rate of absorption from the subcutaneous tissue [11].

There is a lack of data concerning the effects of renal or hepatic impairment on the pharmacokinetics of insulin glargine 300 U/mL [15]. Patients with renal or hepatic impairment receiving insulin glargine 300 U/mL may require frequent glucose monitoring and dose adjustment [15]. Insulin requirements may be reduced in patients with renal impairment (because of reduced insulin metabolism) or hepatic impairment (because of reduced insulin metabolism and reduced capacity for gluconeogenesis) [11]. Due to progressive deterioration of renal function, insulin requirements may be reduced in elderly patients (aged ≥65 years) [11]. Caution is recommended when insulin glargine 300 U/mL is administered to geriatric patients [15].

4 Therapeutic Efficacy of Insulin Glargine 300 U/mL

The therapeutic efficacy of subcutaneous insulin glargine 300 U/mL in patients with diabetes was examined in several 6-month, randomized, open-label, multicentre studies forming the phase III EDITION trial programme [18–23], two of which are available as abstracts [22, 23]. The EDITION 1, 2 and 3 trials were conducted in patients with type 2 diabetes [18–20] (Sect. 4.1), while EDITION 4 was conducted in patients with type 1 diabetes [21] (Sect. 4.2). EDITION JP 1 [22, 24] and JP 2 [23, 25] were conducted in Japanese patients with type 1 and type 2 diabetes, respectively (Sect. 4.3). Where specified, the trials enrolled patients aged ≥18 years [18–21, 24, 25] with glycated haemoglobin (HbA_{1c}) levels of 7–10 % [18, 19, 21–23] or 7–11 % [20]; patients had a mean age of 45–61 years [18–23], a mean body mass index (BMI) of 25.3–36.6 kg/m^2 [18–21, 23] and a mean disease duration of 10–21 years [18–23]. The primary endpoint of all studies was the change from baseline in HbA_{1c} levels after 6 months of treatment [18–23]. The EDITION 1–4 studies were non-inferiority trials, with insulin glargine 300 U/mL shown to be noninferior to insulin glargine 100 U/mL if the upper limit of the 95 % CI for the between-treatment difference in HbA_{1c} was <0.4 % [18–21].

4.1 In Type 2 Diabetes

In EDITION 1 and 2, patients were receiving current basal therapy with ≥42 U/day of either insulin glargine 100 U/mL or NPH insulin, together with mealtime insulin

(lispro, aspart or glulisine, with or without metformin) [18] or oral antidiabetic drugs (OADs) [19]. In EDITION 3, insulin-naïve patients were receiving background therapy with OADs [20]. Patients were randomized to receive insulin glargine 300 U/mL or insulin glargine 100 U/mL once daily in the evening (i.e. from before the evening meal until bedtime, but at the same time each day for each individual) [18–20]. In EDITION 3, the starting dose was 0.2 U/kg in both treatment groups [20]. For patients previously using once-daily basal insulin in EDITION 1 and 2, the starting dose was the basal insulin dose used before randomization; the new daily basal dose was reduced by ≈20 % for patients previously taking NPH insulin more than once daily [18, 19]. Basal insulin doses were adjusted once weekly to achieve a pre-breakfast self-measured plasma glucose (SMPG) level of 4.4–5.6 mmol/L [18–20]. In EDITION 1, mealtime insulin doses were adjusted at the discretion of the investigator [18]. The use of sulfonylureas was not permitted in EDITION 2 or 3 [19, 20].

Both insulin glargine 300 U/mL and 100 U/mL improved glycaemic control in insulin-experienced [18, 19] and -naïve [20] patients with type 2 diabetes. In terms of HbA_{1c}, insulin glargine 300 U/mL was noninferior to insulin glargine 100 U/mL after 6 months of treatment (Table 1) [18–20]. Other glycaemic endpoints, including the proportion of patients achieving an HbA_{1c} of <7 or ≤6.5 % and the change from baseline in fasting plasma glucose (FPG), generally supported these findings (Table 1). Across the three trials, patients gained <1 kg in bodyweight regardless of the insulin glargine formulation; however, in EDITION 2 [19], insulin glargine 300 U/mL was associated with significantly less weight gain than insulin glargine 100 U/mL (Table 1). The mean daily basal insulin dose at study end was ≈10 % higher in insulin glargine 300 U/mL recipients than in insulin glargine 100 U/mL recipients in EDITION 1 and 2 and ≈17 % higher in EDITION 3 [18–20]; the between-group difference was statistically significant in EDITION 2 [19].

Across trials, changes in pre-injection SMPG, pre-injection SMPG variability and the 8-point SMPG profile were generally similar in patients receiving insulin glargine 300 U/mL and those receiving insulin glargine 100 U/mL [18–20].

Treatment satisfaction, as measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ), improved from baseline to month 6 with both treatments [18–20]. In EDITION 3, no change in health-related quality of life (HR-QOL) was observed in either treatment group as measured by the EuroQol 5 Dimensions (EQ-5D) questionnaire [20].

The efficacy of insulin glargine 300 U/mL in patients with type 2 diabetes was confirmed by patient-level data from a prespecified pooled analysis of EDITION 2 and 3 ($n = 1670$) and a post-hoc pooled analysis of EDITION 1, 2 and 3 ($n = 2496$) [26]. For instance, in the larger analysis, the LS mean change from baseline in HbA_{1c} at 6 months was −1.02 % in both treatment groups and ≈36 % of patients achieved an HbA_{1c} of <7 %. The LS mean change from baseline in FPG was −2.04 mmol/L with insulin glargine 300 U/mL and −2.26 mmol/L with insulin glargine 100 U/mL; corresponding reductions in pre-injection SMPG were 1.43 and 1.34 mmol/L, respectively. Results for glycaemic control were consistent in the prespecified pooled dataset of EDITION 2 and 3. In the pooled analysis of EDITION 1, 2 and 3, the mean daily basal insulin dose at study end was 12 % higher with insulin glargine 300 U/mL than with insulin glargine 100 U/mL (0.85 vs. 0.76 U/kg). Insulin glargine 300 U/mL was associated with significantly ($p = 0.039$) less weight gain than insulin glargine 100 U/mL (+0.51 vs. +0.79 kg) [26].

Post hoc patient-level pooled analyses of EDITION 2 and 3, with or without EDITION 1, confirmed the glycaemic efficacy of insulin glargine 300 U/mL, regardless of age (<65 and ≥65 years), BMI (<30 and ≥30 kg/m^2), diabetes duration (<10 and ≥10 years) or the concomitant administration of dipeptidyl peptidase-IV inhibitors (available as abstracts) [27–29]. According to a post hoc analysis of EDITION 1 and 2, patients who switched from a twice-daily basal insulin to once-daily insulin glargine 300 U/mL achieved comparable glycaemic control to those who switched to once-daily insulin glargine 100 U/mL (available as an abstract) [30].

4.1.1 Long-Term Results

The timing of insulin glargine 300 U/mL administration can be varied by ±3 h without compromising glycaemic control in patients with type 2 diabetes, according to 3-month sub-studies of EDITION 1 and 2 (available as an abstract) [31]. Patients who received insulin glargine 300 U/mL in the original trials were further randomized at month 6 to either a fixed 24-h dosing interval or a flexible dosing regimen which allowed 24 ± 3 h intervals between each injection. After 3 months' therapy, mean HbA_{1c} was reduced by 0.05 % with flexible-dose insulin glargine and by 0.00 % with fixed-dose insulin glargine (treatment difference of 0.05 %; 95 CI −0.13 to 0.23) (mean baseline HbA_{1c} of 7.3 % in both groups) [31].

The efficacy of insulin glargine 300 U/mL in patients with type 2 diabetes was maintained in the longer term, according to 6-month extensions of EDITION 1 and 2 [32, 33] and a pooled analysis of 1-year patient-level data from EDITION 1, 2 and 3 (available as an abstract) [34]. In the extension studies, patients continued to receive their originally assigned treatment for a further 6 months [32, 33].

Glycaemic control was sustained over 12 months with both treatments, as evidenced by durable HbA_{1c}- and FPG-

Table 1 Efficacy of once-daily subcutaneous insulin glargine in patients with diabetes. Results are from randomized, open-label, multicentre, 6-month trials in the phase III EDITION programme (between-group statistical analyses presented where available)

Study	Treatment (U/mL) + background regimen	No. of pts[a]	Changes[b] from BL [BL values][c]			Pts at target HbA_{1c} at study end (%)		Mean daily basal ins dose at study end (U/kg/day) [BL value][c]
			HbA_{1c} (%)[d]	FPG (mmol/L)	BW (kg)	<7.0 %	≤6.5 %	
In insulin-experienced pts with type 2 diabetes								
EDITION 1 [18]	Gla 300 + MT ins	404	−0.83[e] [8.15]	−1.3 [8.7]	+0.9 [106.2]	39.6	21.0	0.97 [0.67]
	Gla 100 + MT ins	400	−0.83 [8.16]	−1.4 [8.9]	+0.9 [106.4]	40.9	21.6	0.88 [0.67]
EDITION 2 [19]	Gla 300 + OADs	403	−0.57[e] [8.26]	−1.1 [8.2]	+0.1* [98.7]	30.6	14.5	0.92[f] [0.64]
	Gla 100 + OADs	405	−0.56 [8.22]	−1.1 [7.9]	+0.7 [98.0]	30.4	14.8	0.84 [0.66]
In insulin-naïve pts with type 2 diabetes								
EDITION 3 [20]	Gla 300 + OADs	432	−1.42[e] [8.51]	−3.4 [9.9]	+0.5[g] [95.1]	43.1	25.0	0.62
	Gla 100 + OADs	430	−1.46 [8.57]	−3.8 [10.2]	+0.7 [95.6]	42.1	27.4	0.53
In pts with type 1 diabetes								
EDITION 4 [21]	Gla 300 + MT ins	273	−0.42[e] [8.11]	−0.4 [10.3]	+0.5* [81.9]	16.8		0.47 [0.38]
	Gla 100 + MT ins	273	−0.44 [8.14]	−1.5 [11.1]	+1.0 [81.8]	15.0		0.40 [0.37]

Where required, results were converted to SI units using established conversion factors

BL baseline, *BW* bodyweight, *FPG* fasting plasma glucose, *Gla* insulin glargine, *HbA_{1c}* glycated haemoglobin, *ins* insulin, *mITT* modified intent-to-treat, *MT* mealtime, *OADs* oral antidiabetic drugs, *pts* patients

* $p < 0.05$ vs. Gla 100

[a] Efficacy analyses were conducted in the mITT populations

[b] Changes are mean changes or least squares mean changes at 6 months

[c] Some BL values relate to the randomized population rather than the mITT population

[d] Primary endpoint

[e] Noninferiority of Gla 300 vs. Gla 100 was shown

[f] Statistically significant vs. Gla 100 (*p* value not reported)

[g] Not statistically significant vs. Gla 100

lowering effects [32–34]. However, the LS mean change from baseline in HbA_{1c} at 12 months was significantly greater with insulin glargine 300 U/mL than with insulin glargine 100 U/mL in EDITION 1 (−0.86 vs. −0.69 %; $p = 0.007$) [32] and in the pooled analysis of EDITION 1, 2 and 3 (−0.91 vs. −0.80 %; $p = 0.0174$) [34]; corresponding changes in HbA_{1c} in EDITION 2 were −0.55 and −0.50 % [33]. Furthermore, mean weight gain was significantly lower in insulin glargine 300 U/mL recipients than in insulin glargine 100 U/mL recipients (+0.4 vs. +1.2 kg; $p = 0.009$) in EDITION 2 [33] and in the pooled analysis of EDITION 1, 2 and 3 (+1.2 vs. +1.5 kg; $p = 0.0117$) [34]. In EDITION 1, the mean change in bodyweight from baseline to the last on-treatment value was +1.2 and +1.4 kg in the respective treatment groups [32].

4.2 In Type 1 Diabetes

In EDITION 4, patients receiving mealtime and basal insulin were randomized to receive insulin glargine 300 U/mL or insulin glargine 100 U/mL once daily in the morning (between pre-breakfast and pre-lunch) or evening (at the evening meal until bedtime), while continuing mealtime insulin [21]. The dose of insulin glargine was titrated to achieve a pre-breakfast SMPG of 4.4–7.2 mmol/L, with dose adjustments made weekly [21].

In patients with type 1 diabetes, insulin glargine 300 U/mL was noninferior to insulin glargine 100 U/mL in terms of the improvement in glycaemic control (HbA_{1c}) at 6 months (Table 1) [21]. Other glycaemic endpoints, including the change from baseline in FPG and the proportion of patients achieving an HbA_{1c} of <7 %, generally supported these findings (Table 1). Reductions from baseline in HbA_{1c} or FPG were not affected by the time of administration (i.e. morning or evening) of insulin glargine. Weight gain was significantly lower in insulin glargine 300 U/mL recipients than in insulin glargine 100 U/mL recipients. The mean daily basal insulin dose at study end was ≈18 % higher with insulin glargine 300 U/mL than with insulin glargine 100 U/mL [21].

There were no clinically relevant differences between insulin glargine 300 U/mL and insulin glargine 100 U/mL in pre-injection SMPG, variability in pre-injection SMPG or 8-point SMPG profile [21]. As seen for HbA_{1c} and FPG,

the 8-point SMPG profiles for insulin glargine 300 U/mL were indistinguishable when administered in the morning or evening. Conversely, there was evidence of a difference in pre-breakfast SMPG for insulin glargine 100 U/mL. Treatment satisfaction, as measured by the DTSQ, improved from baseline to month 6 in both treatment groups. However, there was no change in HR-QOL in either treatment group as measured by the EQ-5D questionnaire [21].

4.3 In Japanese Patients

Insulin glargine 300 U/mL also improved glycaemic control in Japanese patients with type 1 ($n = 243$) [22] or type 2 ($n = 241$) [23] diabetes. Patients in EDITION JP 1 had been receiving basal and mealtime insulin [22] and patients in EDITION JP 2 had been receiving basal insulin and OADs [23]. Patients were randomized to receive insulin glargine 300 U/mL or insulin glargine 100 U/mL in combination with mealtime insulin [22] or OADs [23], and the dose of basal insulin glargine was titrated to achieve a target FPG of 4.4–7.2 [22] or 4.4–5.6 [23] mmol/L. Baseline HbA_{1c} values were 8.1 % in EDITION JP 1 [22] and 8.0 % in EDITION JP 2 [23]. In EDITION JP 1, the LS mean change from baseline in HbA_{1c} at 6 months was −0.30 % with insulin glargine 300 U/mL and −0.43 % with insulin glargine 100 U/mL (LS mean treatment difference 0.13 %; 95 % CI −0.03 to 0.29) [22]. Corresponding changes in EDITION JP 2 were −0.45 and −0.55 % (LS mean treatment difference 0.10 %; 95 % CI −0.08 to 0.27) [23]. Where reported, LS mean changes from baseline in bodyweight were −0.6 kg with insulin glargine 300 U/mL and +0.4 kg with insulin glargine 100 U/mL in EDITION JP 2 [23].

The efficacy of insulin glargine 300 U/mL in Japanese patients with diabetes was maintained in the longer-term, according to 6-month extensions of EDITION JP 1 and JP 2 (available as abstracts) [35, 36].

5 Tolerability of Insulin Glargine 300 U/mL

5.1 General Adverse Event Profile

Subcutaneous insulin glargine 300 U/mL was generally well tolerated in patients with diabetes [18–21]. Tolerability was maintained in the long term, with no new safety concerns identified at 12 months in the EDITION 1 and 2 extensions [32, 33].

The most commonly reported treatment-emergent adverse events (TEAEs) in patients with type 2 diabetes receiving insulin glargine 300 U/mL in EDITION 1, 2 and 3 were infections [18–20], nervous system disorders [19], gastrointestinal (GI) events [18–20], cardiac events [20] and musculoskeletal disorders [18–20]. For example, in EDITION 2, infections and infestations (most commonly nasopharyngitis and upper respiratory tract infection) were reported in 33 % of insulin glargine 300 U/mL recipients versus 32 % of insulin glargine 100 U/mL recipients, nervous system disorders were reported in 12 versus 9 %, GI disorders were reported in 11 versus 8 % and musculoskeletal and connective tissue disorders were reported in 11 versus 10 % [19]. The most commonly reported treatment-related adverse event was injection-site reactions, which occurred in 0.7 % of insulin glargine 300 U/mL recipients and 2.7 % of insulin glargine 100 U/mL recipients [19]. There were no treatment-related deaths in any of these trials [18–20].

A pooled analysis of EDITION 1, 2 and 3 found that the overall incidence of TEAEs was 57.3 % with insulin glargine 300 U/mL and 53.7 % with insulin glargine 100 U/mL [26]. Injection-site reactions occurred in 2.4 % of insulin glargine 300 U/mL recipients and 3.1 % of insulin glargine 100 U/mL recipients. Serious TEAEs were reported in 5.2 % of insulin glargine 300 U/mL recipients and 5.0 % of insulin glargine 100 U/mL recipients. Overall, 1.4 % of patients receiving insulin glargine 300 U/mL and 1.3 % of those receiving insulin glargine 100 U/mL discontinued treatment because of TEAEs [26].

In EDITION 4, TEAEs occurred in 61 % of patients with type 1 diabetes receiving insulin glargine 300 U/mL and 58 % of those receiving insulin glargine 100 U/mL [21]. Serious TEAEs were reported in 6.2 % of patients in the insulin glargine 300 U/mL group and 8.0 % of patients in the insulin glargine 100 U/mL group. Injection-site reactions occurred in 2.2 % of insulin glargine 300 U/mL recipients and 1.5 % of insulin glargine 100 U/mL recipients. TEAEs led to treatment discontinuation in 1.1 % of patients in each group [21]. Immunogenicity results from EDITION 4 found that 79 % of insulin glargine 300 U/mL recipients tested positive for anti-insulin antibodies (AIA) on at least one occasion, including 62 % who were positive at baseline and 44 % of patients who developed anti-drug antibodies (i.e. anti-insulin glargine antibodies) during the study[15]. Most patients (80 %) who were AIA positive at baseline remained AIA positive at study end [15].

5.2 Hypoglycaemia

Hypoglycaemia is generally the most common adverse event associated with insulin therapy [11, 15]. In EDITION 1, 2 and 3, the main prespecified secondary endpoint was the proportion of patients experiencing ≥1 confirmed or severe nocturnal (0000–0559 h) hypoglycaemic event between week 9 and study end (month 6), where confirmed hypoglycaemia was defined as an SMPG of ≤3.9 mmol/L

[18–20]. Hypoglycaemia was also assessed in EDITION 4, JP 1 and JP 2, but was not a prespecified endpoint [21–23]. Where specified, documented symptomatic hypoglycaemia was defined as symptomatic events with an SMPG of ≤3.9 mmol/L [18–21] and severe hypoglycaemia was defined as events requiring assistance by another person to administer carbohydrate, glucagon or other therapy [18, 20]. All of these studies also analyzed hypoglycaemic events with an SMPG of <3.0 mmol/L; however, these events are not discussed in this review. Statistical significance was determined using relative risks (for incidence) and rate ratios (for annualized event rates).

5.2.1 *In Type 2 Diabetes*

In insulin-experienced patients with type 2 diabetes, insulin glargine 300 U/mL was generally associated with a significantly lower incidence of nocturnal hypoglycaemia than insulin glargine 100 U/mL [18, 19, 23]. For example, the incidence of confirmed or severe nocturnal hypoglycaemia from week 9 to month 6 was significantly lower in patients who received insulin glargine 300 U/mL than in those who received insulin glargine 100 U/mL (Table 2) [18, 19, 23].

In general, the risk of nocturnal hypoglycaemia did not significantly differ between insulin-naïve patients with type 2 diabetes receiving insulin glargine 300 U/mL and those receiving insulin glargine 100 U/mL, when either the incidence or annualized rate were considered [20]. For example, there was no significant between-group difference in the incidence of confirmed or severe nocturnal hypoglycaemia from week 9 to month 6 (Table 2), although the incidence of confirmed or severe nocturnal hypoglycaemia over the entire 6-month treatment period was significantly lower with insulin glargine 300 U/mL than with insulin glargine 100 U/mL (relative risk 0.76; 95 % CI 0.59–0.99) [20].

Over the first 8 weeks or over the entire 6 months of the study, the incidence [18, 19] (but not the annualized rate [18]) of hypoglycaemia (confirmed or severe hypoglycaemia, documented symptomatic hypoglycaemia or any hypoglycaemia) at any time over 24 h was generally significantly lower in insulin-experienced patients who received insulin glargine 300 U/mL than in those who received insulin glargine 100 U/mL. In insulin-naïve patients, the incidence of confirmed or severe hypoglycaemia or documented symptomatic hypoglycaemia at any time over 24 h did not significantly differ between treatments, although significant differences in favour of insulin glargine 300 U/mL were seen over the first 8 weeks or over the entire 6 months of the study when annualized rates were calculated [20].

When reported, the incidence or annualized rate of hypoglycaemia during the day (0600–2359 h) was not significantly higher in patients receiving insulin glargine 300 U/mL than in those receiving insulin glargine 100 U/mL [18].

The pooled analysis of EDITION 1, 2 and 3 found that over the 6-month treatment period, annualized rates of confirmed or severe hypoglycaemia were significantly ($p < 0.05$) lower with insulin glargine 300 U/mL than with insulin glargine 100 U/mL during the night (2.10 vs. 3.06 events per patient-year; rate ratio 0.69; 95 % CI 0.57–0.84) and at any time of day (15.22 vs. 17.73 events per patient-year; rate ratio 0.86; 95 % CI 0.77–0.97) [26]. Corresponding rates at 1 year were 2.0 versus 2.4 events per patient-year (rate ratio 0.82; 95 % CI 0.67–0.99) and 13.7 versus 14.1 events per patient-year (rate ratio 0.97; 95 % CI 0.87–1.09) [34]. Of note, annualized rates of hypoglycaemia were significantly lower with insulin glargine 300 U/mL than with insulin glargine 100 U/mL even during the first 8 weeks of treatment, corresponding to the time when the greatest basal insulin dose titration occurred [26]. When only the titration period was considered, the rate ratio for confirmed or severe hypoglycaemia was 0.58 (95 % CI 0.47–0.73) during the night and 0.77 (95 % CI 0.68–0.89) at any time of day [26].

Over 24 h, most episodes of confirmed or severe hypoglycaemia occurred between 0600 and 1000 h [26]. For example, between 0600 and 0800 h there were ≈4 events per patient-year with insulin glargine 300 U/mL and ≈3 events per patient-year with insulin glargine 100 U/mL (values estimated from a graph). These findings suggest that the beneficial effects of insulin glargine extend beyond the predefined nocturnal period of 0000–0559 h [26]. It should be noted that the beneficial effects of insulin glargine 300 U/mL on nocturnal hypoglycaemia were also evident when the nocturnal period was clinically defined as 2200 h to pre-breakfast SMPG (available as an abstract) [37].

A post hoc patient-level pooled analysis of EDITION 1, 2 and 3 demonstrated that the significantly lower risk of confirmed or severe hypoglycaemia with insulin glargine 300 U/mL versus insulin glargine 100 U/mL was not affected by age (<65 or ≥65 years) or BMI (<30 or ≥30 kg/m^2) [28]. Similarly, in a pooled analysis of EDITION 1, 2 and 3 ($n = 2488$) and the EDITION 1 and 2 extensions ($n = 1994$), the rate of documented symptomatic hypoglycaemia was 4.4 events/year with insulin glargine 300 U/mL and 5.2 events/year with insulin glargine 100 U/mL (rate ratio 0.84; 95 % CI 0.76–0.92; $p < 0.001$), independent of such patient characteristics as gender, BMI, diabetes duration and comorbidity (available as an abstract) [38].

Table 2 Hypoglycaemic events between week 9 and study end in patients with diabetes receiving once-daily subcutaneous insulin glargine. Results are from randomized, open-label, multicentre, 6-month trials in the phase III EDITION programme

Study	Treatment (U/mL) + background regimen	No. of pts[a]	Confirmed[b] or severe nocturnal[c] hypoglycaemia		
			Incidence (% pts)	RR (95 % CI)	Annualized rate (no. events per pt-year)
In insulin-experienced pts with type 2 diabetes					
EDITION 1 [18]	Gla 300 + MT ins	404	36	0.79 (0.67–0.93)**	2.97
	Gla 100 + MT ins	402	46		4.05
EDITION 2 [19]	Gla 300 + OADs	403	22	0.77 (0.61–0.99)*	1.94
	Gla 100 + OADs	405	28		3.19
EDITION JP 2 [23]	Gla 300 + OADs	118	25	0.58 (0.40–0.85)	2.15
	Gla 100 + OADs	119	44		6.03
In insulin-naïve pts with type 2 diabetes					
EDITION 3 [20]	Gla 300 + OADs	432	16	0.89 (0.66–1.20)	1.56
	Gla 100 + OADs	430	17		1.44
In pts with type 1 diabetes					
EDITION 4 [21]	Gla 300 + MT ins	274	59	1.06 (0.92–1.23)	
	Gla 100 + MT ins	275	56		
EDITION JP 1 [22]	Gla 300 + MT ins	120	62	0.84 (0.70–1.00)	7.45
	Gla 100 + MT ins	118	74		10.53

Gla insulin glargine, *ins* insulin, *mITT* modified intent-to-treat, *MT* mealtime, *OADs* oral antidiabetic drugs, *pt(s)* patient(s), *RR* relative risk

* $p < 0.05$, ** $p < 0.01$ vs. Gla 100

[a] Analyses were conducted in the mITT [19, 20] or safety [18, 21–23] populations

[b] Plasma glucose ≤3.9 mmol/L

[c] Time of onset between 0000 and 0559 h

Severe hypoglycaemia was infrequent in both insulin glargine 300 U/mL and insulin glargine 100 U/mL recipients [18, 19, 23]. In the post hoc, pooled analysis of EDITION 1, 2 and 3, the annualized rate of severe hypoglycaemia at any time was 0.11 events per patient-year in both treatment groups (rate ratio 0.98; 95 % CI 0.51–1.86) [26].

5.2.2 In Type 1 Diabetes

The incidence of confirmed or severe nocturnal hypoglycaemia between week 9 and month 6 did not significantly differ between patients with type 1 diabetes receiving insulin glargine 300 U/mL and those receiving insulin glargine 100 U/mL (Table 2) [21, 22]. Similar results were seen in EDITION JP 1 for the annualized rate of confirmed or severe nocturnal hypoglycaemia between week 9 and month 6 [22]. However, the risk of hypoglycaemia with this definition during the first 8 weeks of treatment was significantly lower with insulin glargine 300 U/mL than with insulin glargine 100 U/mL in EDITION 4 (risk ratio 0.69; 95 % CI 0.53–0.91) [21] and EDITION JP 1 (relative risk 0.71; 95 % CI 0.56–0.91) [22]. The incidence and annualized rate of confirmed or severe hypoglycaemia at any time of day (24 h) between week 9 and month 6 did not significantly differ between insulin glargine 300 U/mL and insulin glargine 100 U/mL [21, 22].

Over the entire 6-month treatment period, the majority (93–98 %) of patients in both treatment groups experienced ≥1 episode of confirmed or severe hypoglycaemia [21, 22]. The frequency of severe hypoglycaemia was low in both treatment groups [21, 22]. Of note, in EDITION 4, the risk of hypoglycaemia was not affected by the timing of insulin glargine administration (i.e. morning or evening injection) [21].

6 Dosage and Administration of Insulin Glargine 300 U/mL

Insulin glargine 300 U/mL is approved in the USA [15], the EU [11] and several other countries to improve glycaemic control in adults with diabetes. It is administered via a pre-filled pen [11]. Insulin glargine 300 U/mL is indicated for once-daily subcutaneous administration at the same time each day [15] or at any time (preferably at the same time) of the day [11]. When necessary, insulin glargine 300 U/mL may be administered up to 3 h before or after the usual time of administration [11]. Injection-site rotation within the same region (deltoid, abdominal wall or

thigh) is recommended to reduce the risk of lipodystrophy [11, 15].

In patients with type 1 diabetes, insulin glargine 300 U/mL must be used in combination with a short- or rapid-acting insulin to cover mealtime insulin requirements [11]. Insulin glargine 300 U/mL can be administered in combination with other glucose-lowering medications in patients with type 2 diabetes [11].

The recommended starting dose of insulin glargine 300 U/mL in insulin-naïve patients with type 1 diabetes is approximately 33–50 % of the total daily insulin requirements [15]. The recommended starting dose of insulin glargine 300 U/mL in insulin-naïve patients with type 2 diabetes is 0.2 U/kg once daily [11, 15].

In insulin-experienced patients, switching to insulin glargine 300 U/mL from a once-daily intermediate- or long-acting insulin can be done on a unit-to-unit basis [11, 15]. However, patients switching from insulin glargine 100 U/mL may require a higher daily dose of insulin glargine 300 U/mL to achieve glycaemic control. When switching from twice-daily NPH insulin, the recommended starting dose of insulin glargine 300 U/mL is 80 % of the total daily insulin dose [11, 15].

The dose of insulin glargine 300 U/mL should be adjusted according to individual patient needs [11, 15]. The dose ranges from 1–80 U per injection with insulin glargine 300 U/mL [15]. Dose titration is recommended no more frequently than every 3–4 days to reduce the risk of hypoglycaemia [15].

Local prescribing information should be consulted for detailed information regarding the use of insulin glargine 300 U/mL in special populations, contraindications, warnings and precautions.

7 Place of Insulin Glargine 300 U/mL in the Management of Type 1 and Type 2 Diabetes

The recent development of new long-acting basal insulin analogues such as insulin degludec (approved in the USA and the EU) and insulin glargine 300 U/mL represents an advance in the management of diabetes. Development of insulin peglispro, another long-acting insulin analogue, has been discontinued [39]. Insulin glargine 300 U/mL has a more stable and prolonged pharmacokinetic/pharmacodynamic profile than insulin glargine 100 U/mL, with a half-life of 18–19 h (Sect. 3) and a duration of glucose-lowering activity exceeding 24 h (Sect. 2). This activity is more constant and evenly distributed with insulin glargine 300 U/mL than with insulin glargine 100 U/mL, with low within-day variability and high day-to-day reproducibility in insulin exposure (Sect. 3). These are important characteristics of an effective basal insulin [40], since unpredictable fluctuations in systemic exposure may cause hypoglycaemia and hyperglycaemia, both of which are barriers to optimal glycaemic control [12, 40]. However, it should be noted that the pharmacodynamic/pharmacokinetic properties of insulin glargine 300 U/mL observed in euglycaemic clamp studies did not necessarily lead to differences being seen between insulin glargine 300 U/mL and insulin glargine 100 U/mL in the clinical setting. For example, the prolonged duration of action of insulin glargine 300 U/mL did not result in lower pre-injection SMPG values in clinical trials, and there did not appear to be a difference between insulin glargine 300 U/mL and insulin glargine 100 U/mL in terms of the variability in pre-injection SMPG (Sects. 4.1, 4.2).

A phase III trial programme (EDITION) comprising six individual studies has demonstrated the efficacy of once-daily subcutaneous insulin glargine 300 U/mL as a basal insulin therapy in patients with type 1 or type 2 diabetes (Sect. 4). It is worth noting that all studies in the EDITION programme utilized an open-label design because of differences in the pen devices used; this may have biased the reporting of events. Insulin glargine 300 U/mL was shown to provide noninferior HbA_{1c}-lowering compared with insulin glargine 100 U/mL (Sect. 4), with glycaemic control maintained over 12 months in several extension studies (Sects. 4.1.1, 4.3). In EDITION 2 and 4, patients receiving insulin glargine 300 U/mL experienced less weight gain than those receiving insulin glargine 100 U/mL. However, the differences were small and not likely to be clinically relevant. The effect of insulin glargine 300 U/mL on bodyweight is unlikely to be explained by factors such as glycaemic control, use of OADs or insulin dose [19, 21]; further investigation is warranted.

Daily basal insulin requirements were 10–18 % higher with insulin glargine 300 U/mL than with insulin glargine 100 U/mL across EDITION 1–4 (Sects. 4.1, 4.2). This reflects the lower exposure of insulin glargine 300 U/mL in pharmacokinetic studies (Sect. 3) and may be attributable to the lower bioavailability of insulin glargine 300 U/mL due to increased residence time in the subcutaneous tissue, resulting in longer exposure to enzymatic inactivation by tissue peptidases [19, 21, 26].

In a euglycaemic clamp study, insulin glargine 300 U/mL provided more stable glucose levels throughout the day than insulin glargine 100 U/mL, irrespective of morning or evening administration (Sect. 2). Consistent with this, the 8-point SMPG profiles of insulin glargine 300 U/mL in patients with type 1 diabetes were indistinguishable when given in the morning or evening (Sect. 4.2). Allowing patients the option of a morning or evening injection schedule may help to reduce the treatment burden associated with the disease [21]. In addition,

the higher concentration of insulin glargine 300 U/mL means that a smaller injection volume can be used. Although it is preferable that insulin glargine 300 U/mL be injected at the same time each day, it does allow for occasional flexibility around the time of dosing (Sect. 6). Indeed, the timing of insulin glargine 300 U/mL administration can be varied by ± 3 h without compromising glycaemic control in patients with type 2 diabetes (Sect. 4.1.1).

Insulin glargine 300 U/mL was generally well tolerated in patients with diabetes (Sect. 5.1). The most common treatment-related adverse event was injection-site reactions. The risk of nocturnal hypoglycaemia between week 9 and month 6 was generally significantly lower in insulin-experienced patients with type 2 diabetes receiving insulin glargine 300 U/mL than in those receiving insulin glargine 100 U/mL (Sect. 5.2), suggesting that insulin glargine 300 U/mL may be particularly useful for patients who have issues with nocturnal hypoglycaemia on their current insulin regimen. Of note, lower rates of hypoglycaemia with insulin glargine 300 U/mL versus insulin glargine 100 U/mL were apparent even during the titration period (i.e. baseline to week 8). This may offer the clinical advantage of smoother, safer and more reliable insulin titration [19, 20, 26], thereby reducing the fear of hypoglycaemia [19]. Reductions in nocturnal hypoglycaemia were seen over the entire 6-month study period in insulin-naïve patients with type 2 diabetes (Sect. 5.2.1), but not in patients with type 1 diabetes (Sect. 5.2.2). This may be explained by several factors present in patients with type 1 diabetes, including lifestyle changes, variability in insulin absorption and the lack of endogenous insulin secretion [21].

Insulin glargine 300 U/mL is administered using a disposable prefilled injector pen [11, 15]. Insulin- and pen-naïve patients with type 2 diabetes ($n = 40$) found the insulin glargine SoloSTAR® disposable pen reliable, easy to learn and easy to use [41]. In an interview-based survey, the insulin glargine 300 U/mL SoloSTAR® pen was ranked first by more patients with type 1 ($n = 26$) or type 2 ($n = 228$) diabetes as being the easiest to use and inject than three other disposable insulin pens (insulin glargine 100 U/mL SoloSTAR®, insulin aspart FlexPen® and insulin lispro KwikPen®) [42].

The relative position of insulin glargine 300 U/mL in the management of diabetes remains to be fully determined. Studies comparing insulin glargine 300 U/mL with long-acting insulin analogues (e.g. insulin degludec) would be of interest. A "real world" trial comparing efficacy and health outcomes of insulin glargine 300 U/mL with other commercially available long-acting basal insulins (insulin glargine 100 U/mL and insulin detemir) is currently underway in insulin-naïve patients with type 2 diabetes ($n = 3270$) [43].

In conclusion, once-daily subcutaneous insulin glargine 300 U/mL is an effective and generally well tolerated basal insulin therapy option for patients with type 1 or type 2 diabetes. This new formulation has a stable and more prolonged time-action profile than insulin glargine 100 U/mL and provides consistent and sustained glycaemic control in patients with type 1 or type 2 diabetes. In addition, insulin glargine 300 U/mL is generally associated with a lower risk of nocturnal hypoglycaemia than insulin glargine 100 U/mL in insulin-experienced patients with type 2 diabetes.

Data selection sources: Relevant medical literature (including published and unpublished data) on insulin glargine 300 U/mL was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 19 Jan 2016], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Insulin, 300 U/mL, Glar300 U/mL, glargine 300, Gla300, Toujeo, Lantus XR.
Study selection: Studies in patients with type 1/type 2 diabetes who received insulin glargine 300 U/mL. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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Compliance with Ethical Standards

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