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Exenatide

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Contents

Abstract

▲ Exenatide is an incretin mimetic. It improves glycaemic control via various glucoregulatory mechanisms, including glucose-dependent insulinotropism, suppression of inappropriately high glucagon levels, delayed gastric emptying and reduction of food intake.

▲ In three large, well designed, phase III trials in adults with type 2 diabetes mellitus and suboptimal glycaemic control despite treatment with metformin and/or a sulfonylurea, mean changes from baseline in glycosylated haemoglobin (HbA_{1c}) significantly favoured subcutaneous exenatide 5 or 10μg twice daily over placebo after 30 weeks' treatment (primary endpoint).

▲ Relative to placebo, reductions from baseline in bodyweight were significantly greater with twice-daily exenatide 5μg (in two studies) or 10μg (in all three studies).

▲ *Post hoc* completer analyses revealed that the beneficial effects of exenatide on HbA_{1c} and bodyweight were maintained for up to 82 weeks.

▲ Adjunctive therapy with subcutaneous exenatide 10μg twice daily improved glycaemic control to a similar extent as insulin glargine in patients with type 2 diabetes suboptimally controlled with metformin plus a sulfonylurea in a large, well designed, 26-week, phase III trial.

▲ Subcutaneous exenatide was generally well tolerated in patients with type 2 diabetes. The incidence of hypoglycaemia in patients receiving exenatide plus metformin was similar to that seen in placebo plus metformin recipients; however, in patients receiving a sulfonylurea (with or without metformin), the incidence of hypoglycaemia was numerically higher with exenatide than with placebo.

Features and properties of exenatide (synthetic exendin-4; AC2993; Byetta™)	
Indication	
Adjunctive therapy in patients with type 2 diabetes mellitus who have suboptimal glycaemic control despite treatment with metformin and/or a sulfonylurea	
Mechanism of action	
Incretin mimetic	Glucoregulatory actions such as the glucose-dependent stimulation of insulin secretion, suppression of glucagon levels, delayed gastric emptying and reduction of food intake
Dosage and administration	
Starting dose	5μg
Target dose	5 or 10μg
Route of administration	Subcutaneous injection
Frequency of administration	Twice daily
Pharmacokinetic profile (subcutaneous exenatide 10μg)	
Mean maximum plasma concentration (C_{max})	211 pg/mL
Mean area under the plasma concentration-time curve from time zero to infinity	1036 pg • h/mL
Time to median C_{max}	2.1h
Mean terminal elimination half-life	2.4h
Adverse events	
Most frequent	Nausea, hypoglycaemia, vomiting, diarrhoea, feeling jittery, dizziness and headache

H–His–Gly–Glu–Gly–Thr–Phe–Thr–Ser–Asp–Leu–Ser–Lys–Gln–Met–Glu–Glu–Glu–Ala–Val–Arg–Leu–Phe–Ile–Glu–Trp–Leu–Lys–Asn–Gly–Gly–Pro–Ser–Ser–Gly–Ala–Pro–Pro–Pro–Ser–NH_2

Exenatide: amino acid sequence

The UK Prospective Diabetes Study demonstrated that improved glycaemic control reduces the risk of microvascular complications in patients with type 2 diabetes mellitus.[1] The American Diabetes Association (ADA) recommends treatment targets of <7% for glycosylated haemoglobin (HbA_{1c}), 5.0–7.2 mmol/L for fasting capillary plasma glucose and <10 mmol/L for postprandial capillary plasma glucose.[2] A slightly lower HbA_{1c} target of ≤6.5% is recommended by the American College of Endocrinology.[3]

A stepwise management approach is generally used to achieve improved glycaemic control in patients with type 2 diabetes.[4] Initial management involves lifestyle modification (e.g. dietary change and exercise) and treatment with oral antihyperglycaemic agents such as metformin, sulfonylureas, meglitinides, thiazolidinediones and α-glucosidase inhibitors. Patients often require two or more drugs to achieve glycaemic control, and the progressive nature of the disease means that many patients will eventually need insulin.[5] Sulfonylureas, metformin and insulin have not been shown to alter the progressive β-cell failure that characterises type 2 diabetes,[6] and current combination therapy may be associated with an increased risk of adverse effects such as hypoglycaemia and bodyweight gain.[5]

The incretin hormone glucagon-like peptide-1 (GLP-1) exhibits glucoregulatory effects, such as enhancing insulin secretion in a glucose-dependent manner, suppressing glucagon secretion, delaying gastric emptying and suppressing appetite.[5] However, a drawback of GLP-1 is that it is rapidly degraded *in vivo* by dipeptidyl peptidase-IV (DPP-IV).[5] Exendin-4 is a 39-amino acid peptide originally isolated from the saliva of the Gila monster (*Heloderma suspectum*). It shares some of the glucoregulatory actions of GLP-1 and is resistant to DPP-IV degradation.[7] Exendin-4 is not an analogue of GLP-1, although the amino acid sequence of exendin-4 has a 53% overlap with mammalian GLP-1.[7] Exenatide (Byetta™)[1] is the synthetic peptide of exendin-4,[7] and is the first incretin mimetic to reach the market.

This article examines the pharmacological properties of exenatide and its use in patients with type 2 diabetes who have suboptimal glycaemic control despite receiving treatment with metformin and/or a sulfonylurea.

1. Pharmacodynamic Profile

This section provides an overview of the pharmacodynamic activity of exenatide. Although numerous studies have examined the activity of exenatide in animals, this section concentrates on human data, where available. Well designed studies were conducted in healthy volunteers (n = 4–39)[8-11] and/or patients with type 2 diabetes (n = 4–24).[8,12-16] Some papers reported more than one study protocol.[8,12,13] Some studies are only available as abstracts and/or posters.[14,15,17,18]

- Exenatide binds to and stimulates the human pancreatic GLP-1 receptor; this receptor mediates its insulinotropic actions.[7] The *in vivo* potency of exenatide has been shown to be much greater than that of native GLP-1.[8,19,20] Unlike GLP-1, exenatide is not a substrate for the DPP-IV enzyme, so exenatide has a longer half-life than GLP-1.[7] Although some of the glucoregulatory effects of exenatide are similar to those of mammalian GLP-1, the actions of the two peptides do differ in some respects (e.g. GLP-1 suppresses gastric acid secretion, whereas exenatide does not).[21]

Effect on Glycaemic Control

- Exenatide rapidly reduced fasting and postprandial plasma glucose levels in patients with type 2

1 The use of trade names is for product identification purposes only and does not imply endorsement.

diabetes in several small studies.[12-14,16] The effects of exenatide on glycaemic control in patients with type 2 diabetes who were enrolled in large (n >100), well designed, longer-term trials (including pivotal phase III trials) are discussed in section 3.

- Single doses of subcutaneous exenatide 0.05, 0.1 or 0.2 μg/kg reduced mean fasting plasma glucose levels from baseline to a significantly ($p < 0.0001$) greater extent than placebo in patients with type 2 diabetes (mean values at 3 hours postdose of 7.6, 6.7 and 6.0 vs 10.8 mmol/L) [baseline plasma glucose level of ≈12 mmol/L; value estimated from graph].[12]

- Postprandial plasma glucose levels were significantly ($p < 0.05$) lower with subcutaneous exenatide than with placebo in patients with type 2 diabetes.[12,13] For example, mean postprandial plasma glucose levels decreased to a nadir of 7 mmol/L at 180 minutes postdose in exenatide 0.1 μg/kg recipients, compared with an increase to a peak of 16 mmol/L at 120 minutes postdose in placebo recipients.[12] Patient in these studies received exenatide 0.1 μg/kg or placebo twice daily for 5 days[12] or single-dose exenatide 0.02–0.4 μg/kg or placebo.[13]

- Twice-daily administration of subcutaneous exenatide is needed to provide adequate glycaemic control in patients with type 2 diabetes.[16] Four patients in a 1-month study initially received once-daily exenatide (up to 0.4 μg/kg/day) in the evening, but loss of glycaemic control was seen by lunchtime the next day. When these patients, and the remaining six patients, subsequently received exenatide twice daily, significant reductions from baseline in HbA_{1c} (from 9.1% to 8.3%; $p = 0.009$) and fasting and postprandial capillary blood glucose levels ($p < 0.05$) were seen.

- The timing of exenatide administration is flexible within the 60-minute period before a meal in patients with type 2 diabetes.[14] Relative to placebo, subcutaneous exenatide 10μg administered with, or 15 or 60 minutes before, a meal reduced peak postprandial plasma glucose levels by 3.93, 4.27 and 4.40 mmol/L; reductions of only 1.24 and 0.62 mmol/L occurred when exenatide was administered 30 or 60 minutes after a meal. Peak plasma glucose levels were significantly lower with exenatide than with placebo ($p < 0.05$), except when exenatide was administered 60 minutes after the meal. The manufacturer's prescribing information states that exenatide should be not administered after a meal, but rather should be administered in the 60-minute period before morning and evening meals.[22]

Mechanisms of Improved Glycaemic Control

The mechanisms by which exenatide improves glycaemic control are discussed in this section. Some of these mechanisms are acute (e.g. glucose-dependent stimulation of insulin secretion, suppression of inappropriately high glucagon secretion, delayed gastric emptying), and some are longer term (e.g. increased β-cell mass in *in vitro* and animal studies, reduction in food intake).[13]

Insulin Secretion

- Exenatide enhanced insulin release only if glucose levels were elevated (i.e. glucose-dependent insulinotropism) in both healthy volunteers and patients with type 2 diabetes.[8,9,12] In a 5-hour hyperglycaemic clamp study, intravenous infusion of exenatide 0.15 pmol/kg/min for 1 hour (from minute 60 to minute 120 of the study) potentiated the insulin response in both healthy volunteers and patients with type 2 diabetes.[8] When the glucose infusion was discontinued at the end of the third hour, glucose levels decreased only to basal levels and plasma insulin levels decreased.

- The glucose-dependent effect of exenatide on insulin secretion was also shown in healthy fasted volunteers who received intravenous exenatide 0.4 μg/kg/day or placebo during a stepwise hypoglycaemic clamp.[9] Serum insulin levels were significantly ($p < 0.05$) higher in exenatide than in placebo recipients during the euglycaemic step, but similar in both treatment arms during the hyperinsulinaemic-hypoglycaemic step.

- In patients with type 2 diabetes, single doses of subcutaneous exenatide 0.05, 0.1 or 0.2 μg/kg significantly ($p < 0.001$ vs placebo) and dose-dependently increased serum insulin levels during

the first 3 hours postdose, when fasting plasma glucose levels were elevated.[12] However, once plasma glucose levels approached the normal range (from 3 hours onwards), serum insulin levels gradually fell to near basal levels.

- Exenatide restored the first-phase insulin response in patients with type 2 diabetes, suggesting improved β-cell function.[15] A 5-hour intravenous infusion of exenatide or placebo was started once euglycaemia was achieved with an insulin infusion (stopped 30 minutes prior to the glucose load). Three hours after the start of the infusion of exenatide or placebo, a 2-hour intravenous glucose tolerance test was performed. Both first- and second-phase insulin secretion were significantly ($p < 0.005$) increased in patients receiving exenatide versus placebo.
- Results of large clinical trials support the finding that exenatide improves β-cell secretory function in patients with type 2 diabetes (see section 3 for study design details).[17,23] In patients receiving subcutaneous exenatide 0.08 μg/kg twice or three times daily as an adjunct to metformin and/or a sulfonylurea, the homeostasis model assessment for β-cell function improved by ≈50–100% at day 14 or 28, compared with at baseline or day 1.[23] Improvement in β-cell function also occurred in patients receiving subcutaneous exenatide 5 or 10μg twice daily as an adjunct to metformin with or without a sulfonylurea.[17]

Glucagon Secretion

- Plasma glucagon levels were suppressed (i.e. ≈50% lower with exenatide than with placebo) during the hyperinsulinaemic-euglycaemic step in healthy volunteers receiving intravenous exenatide 0.4 μg/kg/day or placebo during a stepwise hypoglycaemic clamp.[9] However, during hypoglycaemia, peak plasma glucagon levels were significantly ($p < 0.05$) higher with exenatide than with placebo. Thus, glucagon is not suppressed when needed during hypoglycaemia.
- Subcutaneous exenatide 0.05–0.2 μg/kg suppressed plasma glucagon levels in both the fasting and postprandial states in patients with type 2 diabetes.[12] Similar to the effect of exenatide on insulin levels, the suppression of plasma glucagon levels in the fasting state appeared to be glucose-dependent, in that glucagon levels were markedly suppressed for the first 3 hours postdose when fasting plasma glucose levels were elevated, but similar to the levels seen in placebo recipients thereafter.

Gastric Emptying

- Exenatide delayed gastric emptying in healthy volunteers[10] and patients with type 2 diabetes,[12,13] as shown by the results of paracetamol (acetaminophen) absorption studies (see section 2). Gastric emptying is a major factor determining postprandial glycaemic control, given that the rate-limiting step for the absorption of glucose is the passage of nutrients from the stomach to the small intestine.[10,13]

Other Mechanisms

- Exendin-4 has been shown to reduce food intake in healthy volunteers.[11] Intravenous exendin-4 0.05 pmol/kg/min reduced calorie intake by 19%, compared with saline (867 vs 1075 kcal; $p = 0.012$). Subcutaneous exenatide is also associated with bodyweight reduction in the longer term (see section 3).
- In *in vitro* and animal studies, exendin-4 has been shown to increase β-cell mass by stimulating β-cell neogenesis and proliferation, and suppressing β-cell apoptosis (reviewed by Nielsen et al.[7]). Exendin-4 may also have an insulin-sensitising effect in patients with type 2 diabetes, although more data are needed.[7,24]

Other Effects

- No malignant islet cell tumours were found in the pancreatic tissue of mice and rats ($n = 130$) administered subcutaneous exenatide 18, 70 or 250 μg/kg/day for 2 years (≈6, 25 and 90 times the systemic exposure that would be seen with a 20 μg/day human dose).[18] There were also no significant differences between rodents receiving exenatide or placebo in the incidence of islet cell hyperplasia or benign islet cell adenomas.[18]

2. Pharmacokinetic Profile

This section briefly summarises the pharmacokinetic properties of exenatide, focusing on the ap-

proved doses (5 and 10μg) where possible. Pharmacokinetic studies were conducted in healthy volunteers (n = 21–40)[10,25] and in patients with type 2 diabetes (n = 8–28),[12,13,26] treated hypertension (n = 19)[27] or renal dysfunction (n = 31).[28] Three studies are only available as abstracts.[25,27,28] Additional data were obtained from the manufacturer's prescribing information.[22]

- The mean maximum plasma concentration (C_{max}) of exenatide following a subcutaneous 10μg dose was 211 pg/mL and the mean area under the plasma concentration-time curve from time zero to infinity (AUC_∞) was 1036 pg • h/mL.[22] In patients with type 2 diabetes, the time to reach median C_{max} (t_{max}) was 2.1 hours. AUC increased proportionally with an increase in the exenatide dose from 5 to 10μg, although the increase in C_{max} was less than proportional.[22]

- Subcutaneous exenatide 10μg exhibited similar bioavailability when injected into the upper arm, abdomen or thigh in patients with type 2 diabetes.[26] Exenatide had a mean apparent volume of distribution of 28.3L following subcutaneous administration of a single dose.[22]

- Elimination of exenatide primarily occurs via glomerular filtration, followed by proteolytic degradation, according to the results of nonclinical studies.[22] In humans, exenatide has a mean apparent clearance of 9.1 L/h, and a mean terminal elimination half-life ($t_{1/2}$) of 2.4 hours. Both clearance and $t_{1/2}$ are independent of dose. Exenatide concentrations are detectable for about 10 hours following administration, in most people.[22]

- Race, obesity, age and sex do not appear to significantly alter the pharmacokinetics of exenatide.[22]

- Exenatide clearance was not altered to a clinically significant extent in patients with mild-to-moderate renal impairment (creatinine clearance 1.86–4.8 L/h [31–80 mL/min]) [n = 15] administered a single dose of subcutaneous exenatide 5 or 10μg.[28] However, in eight patients with end-stage renal disease requiring haemodialysis who were receiving exenatide 5μg, mean exenatide clearance was significantly lower than in eight healthy volunteers receiving exenatide 10μg (0.9 vs 3.4 L/h; $p \leq 0.0001$).[28] Exenatide is not recommended for use in patients with a creatinine clearance of <1.8 L/h (<30 mL/min).[22]

- Administration of exenatide with or preceding paracetamol slowed the absorption of paracetamol in healthy volunteers[10] and patients with type 2 diabetes mellitus.[12,13] For example, the t_{max} of paracetamol was 0.6 hours when it was administered 1 hour before exenatide, compared with t_{max} values of 0.9, 4.2 and 3.3 hours when paracetamol was administered with, or 1 or 2 hours after, exenatide; this reflects the delay in gastric emptying seen with exenatide (see section 1).[10] However, overall paracetamol exposure was not altered to a clinically relevant extent by the timing of exenatide administration.[10]

- Because of this delayed gastric emptying, oral drugs, such as oral contraceptives and antibacterials, whose efficacy is dependent on threshold concentrations should be administered at least 1 hour before exenatide.[22]

- At steady state, the mean C_{max} of oral digoxin (1mg loading dose followed by 0.25 mg/day) decreased by 17% and the median t_{max} was delayed by 2.5 hours with concomitant administration of subcutaneous exenatide 10μg twice daily.[25] However, these changes were not considered clinically relevant.

- Concomitant administration of subcutaneous exenatide 10μg twice daily decreased the C_{max} and AUC of a single dose of lovastatin 40mg by ≈28% and ≈40%, and delayed the lovastatin t_{max} by ≈4 hours.[22] However, these changes were not considered clinically relevant as no consistent changes from baseline in lipid levels were seen in exenatide recipients who were also receiving HMG CoA reductase inhibitors in pivotal clinical trials.[22]

- Subcutaneous exenatide 10μg twice daily did not alter lisinopril C_{max} or AUC at steady state, although lisinopril t_{max} was delayed by 2 hours, in patients with hypertension who were receiving lisinopril 5–20 mg/day.[27] Mean systolic and diastolic blood pressure (24-hour) values were not significantly altered.

• Negligible placental transfer of exenatide was seen in an *ex vivo* study.[29] In a human *ex vivo* placental perfusion system, the ratio of the fetal : maternal exenatide concentration was ≤0.017 for all experiments.

3. Therapeutic Efficacy

Comparisons with Placebo

Short-Term Trials

The results of two 28-day trials are briefly discussed in this section.[23,30] These randomised, triple-blind, placebo-controlled studies included adults with type 2 diabetes and suboptimal glycaemic control despite receiving metformin and/or a sulfonylurea (n = 109)[23] or metformin (n = 117) or diet plus exercise alone (n = 39).[30] Patients in one study received subcutaneous exenatide 0.08 μg/kg twice daily (either before breakfast and dinner, or before breakfast and at bedtime) or three times daily (before breakfast and dinner and at bedtime) or placebo three times daily,[23] and patients in the other study received subcutaneous exenatide 2.5–10μg twice daily or placebo (administered 15 minutes before breakfast and dinner).[30] Both studies had 2-week, single-blind, placebo lead-in periods.

Mean baseline HbA_{1c} was 9.1–9.4%[23] and 7.4–7.7%,[30] mean baseline serum fructosamine levels were 331–346 μmol/L[23] and mean baseline bodyweight was 97–98[23] and 92–104kg.[30]

Primary efficacy endpoints were the change from baseline in serum fructosamine levels[23] (reflecting glycaemic control over the prior 2 weeks) and HbA_{1c}[30] (reflecting glycaemic control over the prior 2–3 months). Analyses used the intent-to-treat (ITT) population.[23,30]

• At day 28, mean serum fructosamine levels were reduced from baseline to a significantly greater extent in patients receiving adjunctive therapy with exenatide before breakfast and dinner, before breakfast and at bedtime, or before breakfast and dinner and at bedtime than with placebo (−45, −39 and −46 vs −5 μmol/L; all $p \leq 0.004$).[23] Moreover, significantly greater reductions in mean HbA_{1c} (−1.1%, −0.7% and −1.0% vs −0.3%; all $p \leq 0.006$) and mean postprandial plasma glucose levels (−4.4, −3.2 and −3.4 vs −0.6 mmol/L; all $p \leq 0.004$) occurred with the exenatide regimens than with placebo at day 28.

• Significant ($p < 0.0001$) dose-dependent reductions in HbA_{1c} were seen in exenatide recipients after 28 days of treatment.[30] Mean changes from baseline in HbA_{1c} (−0.33% and −0.45% vs + 0.04%; both $p < 0.05$) and bodyweight (−0.6 and −1.7 vs 0kg; $p < 0.05$) significantly favoured twice-daily treatment with exenatide 5 or 10μg versus placebo at day 28 among the subgroup of patients receiving metformin (values estimated from graphs).

Phase III Trials

The longer-term efficacy of subcutaneous exenatide in adults with type 2 diabetes and suboptimal glycaemic control despite treatment with metformin,[31] a sulfonylurea[32] or metformin plus a sulfonylurea[33] was examined in three large (n = 336–733), 30-week, randomised, triple-blind, placebo-controlled, multicentre, phase III trials.[31-33]

The studies had a 4-week, single-blind, placebo lead-in period.[31-33] Patients were randomised to receive adjunctive therapy with subcutaneous exenatide 5 or 10μg twice daily or placebo (patients assigned to the 10μg twice-daily dosage received exenatide 5μg twice daily for the first 4 weeks before the dosage was increased to 10μg twice daily).[31-33] Patients self-injected the study drug 15 minutes before morning and evening meals.[31-33]

In each study, mean patient age was 52–54,[31] 55–56[32] or 55–56[33] years and the mean duration of diabetes was 4.9–6.6,[31] 5.7–6.6[32] or 8.7–9.4[33] years. At baseline, mean HbA_{1c} was 8.2–8.3%,[31] 8.5–8.7%[32] or 8.5%,[33] mean fasting plasma glucose levels were 9.3–9.8,[31] 9.9–10.8,[32] or 9.9–10.1 mmol/L[33] and mean bodyweight was 100–101,[31] 95–99[32] or 97–99kg.[33]

The primary efficacy endpoint in all three studies was the change from baseline in HbA_{1c}.[31-33] Prespecified secondary efficacy endpoints included changes from baseline in fasting[31-33] and postprandial[31,33] plasma glucose levels, fasting plasma insulin and proinsulin levels,[31,32] bodyweight,[31-33] and

the proportion of patients achieving an HbA_{1c} of ≤7%[31] (reflecting the ADA target for HbA_{1c}[2]). Analyses were based on the ITT population using a last-observation-carried-forward method[31-33] (except for the change in postprandial plasma glucose levels and the proportion of patients achieving an HbA_{1c} of ≤7%, which were examined in the evaluable patient populations).

Following completion of the three 30-week trials, patients could continue exenatide therapy in open-label extension phases (results available as abstracts).[34-37] All patients (including those who received exenatide 10μg twice daily in the initial trials) received exenatide 5μg twice daily for 4 weeks followed by 10μg twice daily. The number of patients completing 82 weeks' therapy was 118 among those receiving metformin,[34] 70 among those receiving a sulfonylurea[35] and 205 among those receiving metformin and a sulfonylurea.[36] An additional pooled analysis of this open-label extension phase (n = 265) examined the effect of exenatide on lipid levels and blood pressure.[37] Statistical analyses were not provided.[34-37]

- Adjunctive therapy with exenatide improved glycaemic control in patients with type 2 diabetes who were not adequately controlled with metformin and/or a sulfonylurea.[31-33] After 30 weeks' treatment, mean changes from baseline in HbA_{1c} in all three studies significantly favoured twice-daily exenatide 5μg (−0.40% to −0.55%) or 10μg (−0.77% to −0.86%) versus placebo (+0.08% to +0.23%) [figure 1]. A significant ($p < 0.0005$) difference between exenatide and placebo recipients in the change from baseline in HbA_{1c} was seen as early as 4 weeks after the start of treatment.[31]
- Moreover, among patients with a baseline HbA_{1c} of >7%, a significantly ($p < 0.01$) greater proportion of exenatide 5 or 10μg twice daily versus placebo recipients achieved an HbA_{1c} of ≤7% (32% and 46% vs 13% in patients receiving metformin,[31] 33% and 41% vs 9% in patients receiving a sulfonylurea[32] and 27% and 34% vs 9% in patients receiving metformin plus a sulfonylurea[33]). These analyses included 240,[31] 237[32] and 554[33] evaluable patients.

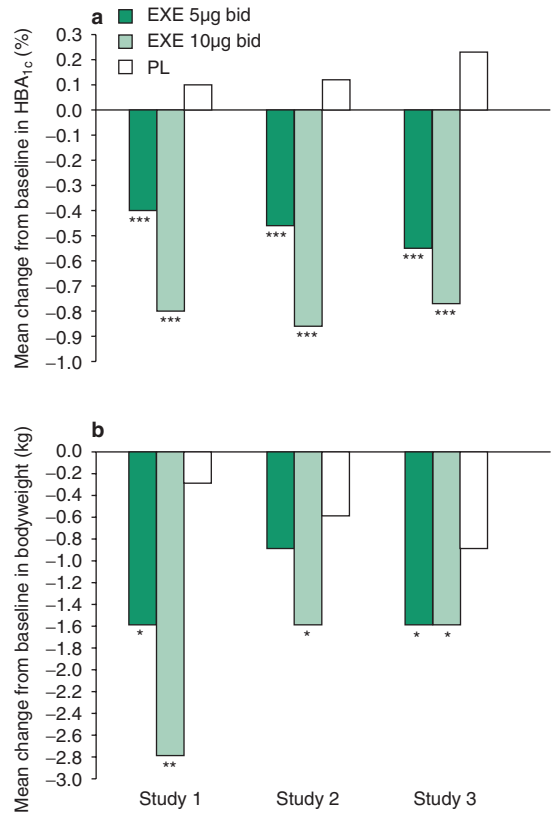

Fig. 1. Mean change from baseline in (**a**) glycosylated haemoglobin (HbA_{1c}) [primary endpoint] and (**b**) bodyweight with exenatide (EXE) at 30 weeks. Results of three randomised, triple-blind, placebo (PL)-controlled, multicentre, phase III studies in adults with type 2 diabetes mellitus and suboptimal glycaemic control despite treatment with metformin (study 1; n = 336),[31] a sulfonylurea (study 2; n = 377),[32] or metformin plus a sulfonylurea (study 3; n = 733).[33] Patients received subcutaneous EXE 5 or 10μg twice daily (bid) or PL for 30 weeks. * $p \leq 0.05$, ** $p \leq 0.001$, *** $p < 0.0005$ vs PL.

- Significantly greater reductions from baseline in bodyweight were observed with exenatide 5 or 10μg twice daily than with placebo in patients receiving metformin alone (−1.6 and −2.8 vs −0.3kg)[31] or metformin plus a sulfonylurea (−1.6 and −1.6 vs −0.9kg)[33] [figure 1]. In patients receiving a sulfonylurea, only recipients of exenatide 10μg twice daily achieved a significantly greater reduction in bodyweight than placebo recipients (−1.6 vs −0.6kg) [figure 1].[32] Weight loss was progressive over the entire 30 weeks in exenatide 5[31,33] and 10μg[31-33] twice daily recipients.

- At week 30, the mean change from baseline in fasting plasma glucose levels significantly favoured recipients of exenatide 5 or 10μg twice daily versus placebo in patients receiving concomitant therapy with metformin (−0.4 and −0.6 vs +0.8 mmol/L; both $p < 0.005$)[31] or with metformin plus a sulfonylurea (−0.5 and −0.6 vs +0.8 mmol/L; both $p < 0.0001$).[33] In patients receiving a sulfonylurea alone, fasting plasma glucose levels decreased by 0.3 and 0.6 mmol/L with exenatide 5 and 10μg twice daily and increased by 0.4 mmol/L with placebo; only the difference between exenatide 10μg twice daily and placebo was statistically significant ($p < 0.05$).[32]

- Postprandial glucose levels were significantly ($p < 0.05$) lower in recipients of exenatide 5 or 10μg twice daily than in placebo recipients at week 30.[31,33] These analyses involved subgroups of patients who underwent a standardised meal tolerance test (n = 36[31] and 77[33]).

- Changes from baseline in fasting plasma insulin levels did not significantly differ between exenatide and placebo recipients.[31,32] However, fasting proinsulin levels were reduced to a significantly greater extent with exenatide 10μg twice daily than with placebo in one study.[32] Moreover, in both studies assessing this endpoint, the proinsulin **:** insulin ratio was significantly reduced with exenatide 10mg twice daily versus placebo ($p \leq 0.001$).[31,32]

- *Post hoc* completer analyses revealed that the beneficial effects of exenatide on HbA_{1c} and bodyweight were maintained for up to 82 weeks.[34-36] At week 82, reductions from baseline in HbA_{1c} in patients who received exenatide 10μg twice daily for the entire 82 weeks compared with those who received placebo for weeks 0–30 were 1.2% versus 1.3% in patients receiving metformin,[34] 1.5% versus 1.3% in patients receiving a sulfonylurea[35] and 1.0% versus 1.2% in patients receiving metformin plus a sulfonylurea.[36] Among patients with an HbA_{1c} of >7% at baseline, 62%,[34] 65%[35] and 39%[36] of exenatide 10μg twice daily recipients had achieved an HbA_{1c} of ≤7% at week 82.

- In addition, at week 82, reductions from baseline in bodyweight in patients who received exenatide 10μg twice daily for the entire 82 weeks compared with those who received placebo for weeks 0–30 were 4.8 versus 3.3kg in patients receiving metformin,[34] 4.1 versus 3.9kg in patients receiving a sulfonylurea[35] and 4.4 versus 3.1kg in patients receiving metformin plus a sulfonylurea.[36]

- At week 82, exenatide recipients had mean reductions from baseline of 36.9, 2.5 and 1.4 mg/dL in triglyceride, total cholesterol and low-density lipoprotein cholesterol levels, with a mean increase from baseline of 4.5 mg/dL in high-density lipoprotein cholesterol levels (baseline levels of 239.2, 185.9, 115.1 and 38.0 mg/dL, respectively).[37] Systolic and diastolic blood pressure values were reduced by a mean of 1.5 and 3.2mm Hg (128.6 and 78.7mm Hg at baseline).

Comparison with Insulin Glargine

The efficacy of adjunctive therapy with exenatide was compared with that of insulin glargine in a 26-week, randomised, multicentre, phase III study in patients with type 2 diabetes and suboptimal glycaemic control despite receiving metformin plus a sulfonylurea.[38] Patients received subcutaneous exenatide 5μg twice daily for 4 weeks followed by 10μg twice daily (n = 283) or insulin glargine once daily (titrated to a target fasting plasma glucose level of <100 mg/dL) [n = 268]. At baseline, HbA_{1c} was 8.2% in exenatide recipients and 8.3% in insulin glargine recipients. This study is currently available as an abstract.

- Adjunctive therapy with exenatide improved glycaemic control to a similar extent as insulin glargine in patients with type 2 diabetes who were not adequately controlled with metformin plus a sulfonylurea.[38] At 26 weeks, reductions from baseline in HbA_{1c} were similar in exenatide and insulin glargine recipients (−1.0% vs −1.1%), and a similar proportion of patients achieved an HbA_{1c} of ≤7% (48% vs 46%).

- The change in bodyweight at 26 weeks significantly favoured exenatide over insulin glargine recipients (−2.3 vs +1.8kg; $p < 0.001$).[38]

4. Tolerability

Safety was designated a primary endpoint in the three placebo-controlled phase III trials[31-33] and was also examined in the phase III trial comparing exenatide with insulin glargine[38] (see section 3 for study design details). In general, only descriptive analyses were reported.

- Subcutaneous exenatide was generally well tolerated. The most frequent treatment-emergent adverse events in exenatide recipients were of mild-to-moderate severity and gastrointestinal in nature.[31-33] Excluding hypoglycaemia, the most commonly occurring treatment-emergent adverse events in the placebo-controlled trials included nausea, vomiting, diarrhoea, feeling jittery, dizziness and headache (figure 2).[31-33] Withdrawal because of nausea occurred in 2% of patients receiving exenatide 5μg twice daily, 4% of patients receiving exenatide 10μg twice daily and <1% of placebo recipients.[32,33]
- The incidence of nausea[31-33,38] and hypoglycaemia[32] peaked in the initial weeks of treatment and then decreased over time. A *post hoc* analysis, available as an abstract, revealed that the weight loss seen in exenatide recipients (see section 3) was unlikely to be due to nausea.[39] Gradual dose escalation has been shown to attenuate nausea in exenatide recipients.[40]
- Hypoglycaemia occurred rarely in patients receiving exenatide 5 or 10μg twice daily plus metformin, with an incidence similar to that in placebo plus metformin recipients (4.5% and 5.3% vs 5.3% of patients) [figure 2].[31] A numerically higher incidence of hypoglycaemia occurred in patients receiving exenatide 5 or 10μg twice daily plus a sulfonylurea versus placebo plus a sulfonylurea (14.4% and 35.7% vs 3.3%),[32] and in patients receiving exenatide 5 or 10μg twice daily plus metformin and a sulfonylurea versus placebo plus metformin and a sulfonylurea (19.2% and 27.8% vs 12.6%)[33] [statistical analysis not reported; figure 2].
- No cases of severe hypoglycaemia occurred in patients receiving exenatide as an adjunct to metformin[31] or a sulfonylurea,[32] although one case of severe hypoglycaemia was reported in a patient receiving exenatide 5μg twice daily as an adjunct to metformin plus a sulfonylurea.[33]
- The mean rate of nocturnal hypoglycaemia was significantly lower in exenatide than in insulin glargine recipients (0.9 vs 2.4 events/patient-year; $p < 0.001$).[38]
- Few patients experienced serious treatment-emergent adverse events (3–6% of exenatide 5μg twice daily recipients, 3–5% of exenatide 10μg twice daily recipients and 4–8% of placebo recipients).[31-33]
- In general, no clinically relevant between-group differences were observed in terms of changes in vital signs,[31,32] ECG recordings[31] or laboratory parameters.[31]
- Anti-exenatide antibodies, which are of unknown clinical relevance, were present in 41–49% of exenatide recipients at week 30.[31-33] Antibodies were generally of low titre and did not appear to be predictive of glycaemic control or adverse events.[31-33]

5. Dosage and Administration

Exenatide should be administered by subcutaneous injection (in the thigh, abdomen or upper arm) in the 60-minute period prior to the morning and evening meals.[22] Exenatide should be initiated at a dosage of 5μg twice daily; the dosage can be increased to 10μg twice daily after 1 month of treatment, depending on the clinical response.

Exenatide is recommended for use in patients receiving metformin and/or a sulfonylurea who have suboptimal glycaemic control.[22] Consideration may be given to reducing the sulfonylurea dosage to reduce the risk of hypoglycaemia. Exenatide should not be used as an insulin substitute in patients who require insulin, or in the treatment of patients with type 1 diabetes or diabetic ketoacidosis. Local prescribing information should be consulted for information regarding contraindications, other precautions and drug interactions.

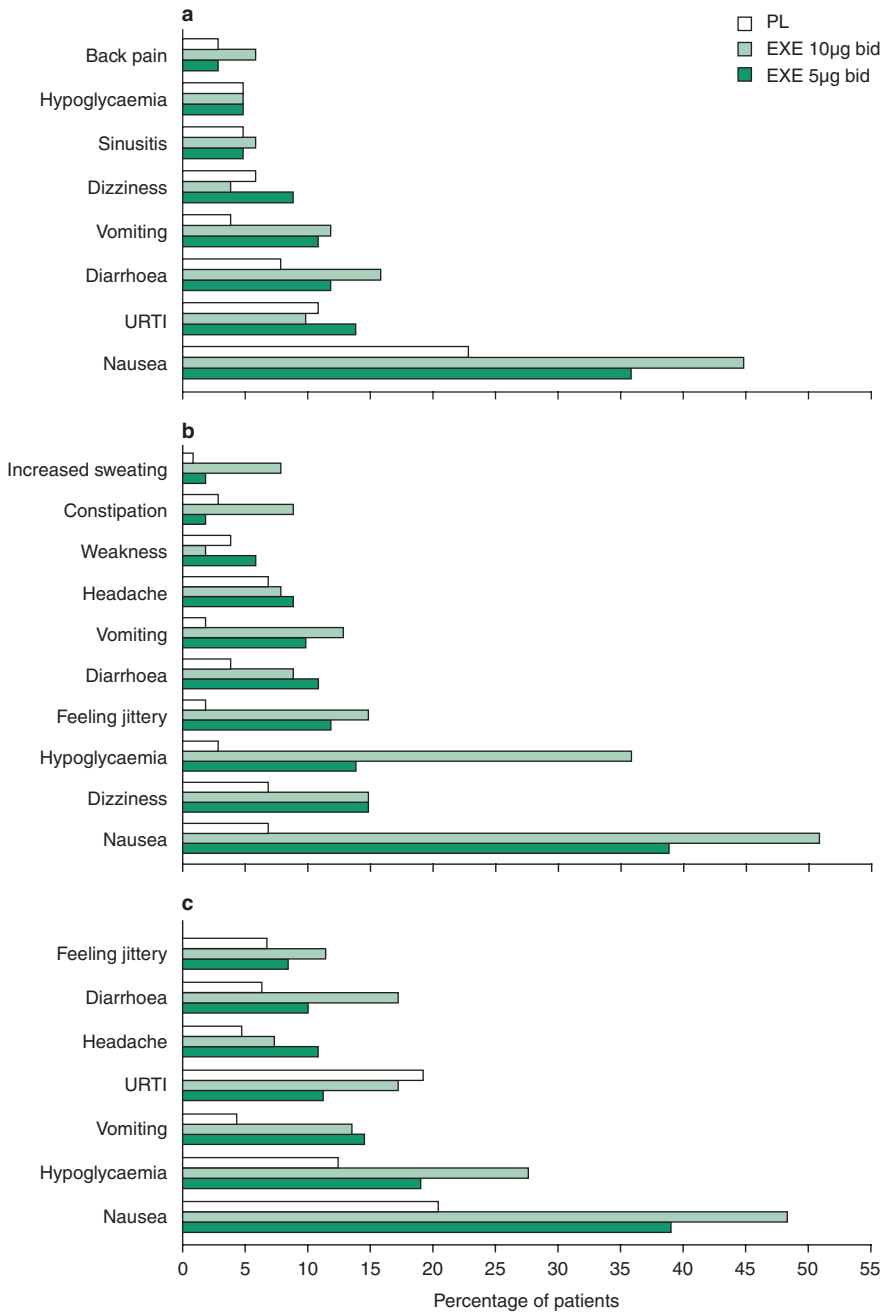

Fig. 2. Treatment-emergent adverse events in patients receiving exenatide (EXE). In three phase III, randomised, triple-blind, placebo (PL)-controlled, multicentre studies, adults with type 2 diabetes mellitus and suboptimal glycaemic control despite treatment with (**a**) metformin (n = 336),[31] (**b**) a sulfonylurea (n = 377)[32] or (**c**) metformin plus a sulfonylurea (n = 733)[33] received subcutaneous EXE 5 or 10μg twice daily (bid) or PL for 30wk. Adverse events shown in: (**a**) DeFronzo et al.[31] are those occurring with an incidence of ≥5% and a higher incidence in EXE than PL recipients; (**b**) Buse et al.[32] are those related to the gastrointestinal tract and hypoglycaemia; and (**c**) Kendall et al.[33] are those occurring with an incidence of ≥10% in any treatment arm. **URTI** = upper respiratory tract infection.

6. Exenatide: Current Status

Subcutaneous exenatide is approved in the US for use in patients with type 2 diabetes who have suboptimal glycaemic control despite treatment with metformin and/or a sulfonylurea. It is the first incretin mimetic to reach the market and has been shown to improve glycaemic control in patients who have not achieved optimal glycaemic control with metformin and/or a sulfonylurea in well designed, phase III trials; preliminary data indicate that the improvement in glycaemic control achieved with exenatide was similar to that seen with insulin glargine. Exenatide is generally well tolerated.

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