

Exenatide: A Review of Pharmacology and Therapeutic Uses

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ABSTRACT

Type 2 diabetes is generally characterized by two principal abnormalities: insulin resistance and progressive failure of pancreatic β -cell function that leads to inadequate insulin secretion. The current approach to the management of type 2 diabetes is generally stepwise. No currently available therapy has been shown to slow the decline in β -cell function in established type 2 diabetes. Expectedly, such management modalities should demonstrate a unique mode of action to enable additive and / or synergistic use with current therapies; produce no weight gain, hypoglycemia, or other limiting or unmanageable side effects; preserve or enhance β -cell function; and reduce associated risk factors that lead to complications and therefore increase morbidity and mortality. Exenatide is a novel incretin mimetic agent that exhibits many of these desired aspects of antidiabetic therapy. [IJEM 2007;11(1&2):43-49]

Keywords: Exenatide, Type 2 diabetes mellitus, GLP-1, HbA1c

INTRODUCTION

Type 2 diabetes is generally characterized by two principal abnormalities: insulin resistance and progressive failure of pancreatic β -cell function that leads to inadequate insulin secretion. The current approach to the management of type 2 diabetes is generally stepwise (1). Early treatment consists of diet management, exercise, and weight control. As glucose control deteriorates, in addition to the lifestyle interventions, pharmacological therapy is initiated with one or two oral antidiabetic agents and later another additional oral agent or insulin may be added. Ultimately, many if not most individuals with type 2 diabetes require insulin as primary therapy with adjunctive therapy to achieve glycemic goals (2). Despite the introduction of a number of novel agents for the treatment of type 2 diabetes, glucose control remains unsatisfactory because average hemoglobin A1c (HbA1c) values well above the target values are reported in many studies (3). In addition, many therapies have limiting side effects such as weight gain, hypoglycemia, and edema which restricts their use (4). The data from United Kingdom Prospective Diabetes Study (UKPDS) indicates that β -cell failure is progressively downhill despite

intensive therapy with insulin, sulfonylurea, or biguanide agents (5-6). In contrast, insulin resistance does not appear to progress in parallel with β -cell failure (7). Consistent with this, many subjects in the UKPDS who were treated originally with diet management or oral agents eventually required insulin therapy for glucose control (8). No currently available therapy has been shown to slow the decline in β -cell function in established type 2 diabetes. All of these data suggest that ideal therapies for the long-term treatment of type 2 diabetes are needed to delay, arrest, and / or reverse progressively declining β -cell function (9-12). Expectedly, such management modalities should demonstrate a unique mode of action to enable additive and / or synergistic use with current therapies; produce no weight gain, hypoglycemia, or other limiting or unmanageable side effects; preserve or enhance β -cell function; and reduce associated risk factors that lead to complications and therefore increase morbidity and mortality. Exenatide is a novel incretin mimetic agent that exhibits many of these desired aspects of antidiabetic therapy.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mechanism of action

Exenatide is an incretin mimetic that exhibits several antihyperglycaemic actions of glucagon-like peptide-1 (GLP-1). The amino acid sequence of exenatide partially

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overlaps that of human GLP-1. Exenatide has been shown to bind to and activate the known human GLP-1 receptor *in vitro*, its mechanism of action is mediated by cyclic AMP and/or other intracellular signaling pathways.

Exenatide increases, on a glucose-dependent basis, the secretion of insulin from pancreatic beta cells. As blood glucose concentrations decrease, insulin secretion subsides. When exenatide was used in combination with metformin alone, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin which may be due to this glucose-dependent insulinotropic mechanism.

Exenatide suppresses glucagon secretion which is known to be inappropriately elevated in type 2 diabetes. Lower glucagon concentrations lead to decreased hepatic glucose output. However, exenatide does not impair the normal glucagon response and other hormone responses to hypoglycaemia.

Exenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.

Pharmacodynamic effects

Exenatide improves glycaemic control through the immediate and sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes.

Clinical efficacy

The clinical studies comprised 3945 subjects (2997 treated with exenatide), 56% men and 44% women, 319 subjects (230 treated with exenatide) were ≥ 70 years of age and 34 subjects (27 treated with exenatide) were ≥ 75 years of age.

Exenatide reduced HbA_{1c} and body weight in patients treated for 30 weeks in three placebo-controlled studies, whether the Exenatide was added to metformin, a sulfonylurea or a combination of both. These reductions in HbA_{1c} were generally observed at 12 weeks after initiation of treatment (Table 1). The reduction in HbA_{1c} was sustained and the weight loss continued for at least

82 weeks in the subset of 10 mcg BID patients completing both the placebo-controlled studies and the uncontrolled study extensions (n=137).

In a placebo-controlled study of 16 weeks duration, Exenatide (n=121) or placebo (n=112) was added to existing thiazolidinedione treatment, with or without metformin. Exenatide (5mcg BID for 4 weeks, followed by 10 mcg BID) resulted in statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.8% versus +0.1 %) as well as significant reductions in body weight (-1.5 versus -0.2 kg).

When Exenatide was used in combination with a thiazolidinedione, the incidence of hypoglycaemia was similar to that of placebo in combination with a thiazolidinedione. The experience in patients >65 years and in patients with impaired renal function is limited.

In insulin-comparator studies Exenatide (5mcg BID for 4 weeks, followed by 10mcg BID) in combination with metformin and sulfonylurea significantly (statistically and clinically) improved glycaemic control, as measured by decrease in HbA_{1c}. This treatment effect was comparable to that of insulin glargine in a 26 week study (mean insulin dose 24.9 IU/day, range 4-95 IU/day, at the end of study) and biphasic insulin aspart in a 52-week study (mean insulin dose 24.4 IU/day, range 3-78 IU/day, at the end of study). Exenatide lowered HbA_{1c} from 8.21 (n=228) and 8.6% (n=222) by 1.13 and 1.01% while insulin glargine lowered from 8.24 (n=227) by 1.10% and biphasic insulin aspart from 8.67 (n=224) by 0.86%. Weight loss of 2.3 kg (2.6%) was achieved with Exenatide in the 26 week study and a loss of 2.5 kg (2.7%) in a 52-week study whereas treatment with insulin was associated with weight gain. Treatment differences (Exenatide minus comparator) were -4.1 kg in the 26-week study and -5.4 kg in the 52-week study. Seven-point self monitored blood glucose profiles (before and after meals and at 3 am) demonstrated significantly reduced glucose values compared to insulin in the postprandial periods after Exenatide injection. Premeal blood glucose concentrations were generally lower in patients taking insulin compared to Exenatide. Mean daily blood glucose values were similar between Exenatide and insulin. In these studies the incidence of hypoglycaemia was similar for Exenatide and insulin treatment.

Exenatide has shown no adverse effects on lipid parameters. A trend for a decrease in triglycerides has been observed with weight loss. Clinical studies with Exenatide have indicated improved beta-cell function, using measures such as the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio. A pharmacodynamic study demonstrated in patients with type 2 diabetes (n=13) a restoration of first phase insulin secretion and improved second phase insulin secretion in response to an intravenous bolus of glucose.

Table 1: Combined results of the 30 week placebo controlled studies (intent to treat patients)

	Placebo (n=483)	EXENATIDE 5µg BID (n=480)	EXENATIDE 10µg BID (n=483)
HbA _{1c} Baseline(%)	8.48	8.42	8.45
HbA _{1c} (%) change from baseline	-0.08	-0.59	-0.89
Proportion of patients (%) achieving HbA _{1c} ≤ 7%	7.9	25.3	33.6
Proportion of patients (%) achieving HbA _{1c} ≤ 7% (patients completing studies)	10.0	29.6	38.5
Baseline weight (kg)	99.26	97.10	98.11
Change of weight from baseline (kg)	-0.65	-1.41	-1.91

A reduction in body weight was seen in patients treated with Exenatide irrespective of the occurrence of nausea although the reduction was larger in the group with nausea (mean reduction 2.4 kg versus 1.7 kg) in the long-term controlled studies of up to 52 weeks.

Administration of exenatide has been shown to reduce food intake, due to decreased appetite and increased satiety.

SUSTAINABILITY OF EFFECTS.

In the published data the glycemic control and the decrease in weight was found to be maintained for upto 2 years⁽¹⁴⁾.

At week 104, 283 subjects completing 2 years of exenatide treatment had mean (SEM) reductions from baseline of HbA_{1c} value (-1.1% [0.1%]; 95% CI, -1.3 to -1.0; P<0.001), FPG (-25.2 [2.8] mg/dL; 95% CI, -31 to -20; P<0.001), weight (-4.7[0.3] kg; 95% CI, -5.4 to -4.0; P<0.001), and BMI (-1.6[0.1] kg/m²; 95% CI, -1.8 to -1.4; P<0.001). The mean (SEM) reductions in HbA_{1c} and FPG were evident as early as week 12 (-1.1% [0.1%] and -25.1 [2.4] mg/dL, respectively), indicating a sustained glycemic effect. Change in mean (SEM) weight was -1.6[0.1] kg at week 12 and continued to decrease progressively over the observation period; 81% of subjects lost weight over 2 years of exenatide treatment. Mean (SEM) changes from baseline to week 104 in the ITT population were similar; HbA_{1c}, -0.8% (0.1%); FPG, -16(2) mg/dL; and weight, -3.6(0.2) kg.

PHARMACOKINETIC PROPERTIES

Absorption

Following subcutaneous administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2h. Mean peak exenatide concentration (C_{max}) was 211 pg/ml and overall mean area under the curve (AUC_{0-inf}) was 1036 pg.h/ml following subcutaneous administration of a 10 mcg dose of exenatide. Exenatide exposure increased proportionally over the therapeutic dose range of 5 mcg to 10 mcg. Similar exposure is achieved with subcutaneous administration of exenatide in the abdomen, thigh, or arm.

Distribution

The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose exenatide is 28l.

Metabolism and Elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. In clinical studies the mean apparent clearance of exenatide is 9 l/h and the mean terminal half-life is 2.4h. These pharmacokinetic characteristics of exenatide are independent of the dose.

Special populations

Patients with renal impairment

In patients with mild (creatinine clearance 50 to 80 ml/min) or moderate renal impairment (creatinine clearance 30 to 50 ml/min), exenatide clearance was mildly reduced compared to clearance in individuals with normal renal function (13% reduction in mild and 36% reduction in moderate renal impairment). Clearance was significantly reduced by 84% in patients with end-stage renal disease receiving dialysis.

Patients with hepatic insufficiency

No pharmacokinetic study has been performed in patients with hepatic insufficiency. Exenatide is cleared primarily by the kidney, therefore hepatic dysfunction is not expected to affect blood concentrations of exenatide.

Gender and race

Gender and race have no clinically relevant influence on exenatide pharmacokinetics.

Elderly

Data in elderly are limited, but suggest no marked changes in exenatide exposure with increased age up to about 75 years old. There are no pharmacokinetic data in patients >75 years.

Children and adolescents

Pharmacokinetics of exenatide has not been investigated in children and adolescents below 18 years of age.

Preclinical Safety Data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, or genotoxicity.

In female rats given exenatide for 2 years, an increased incidence of benign thyroid C-cell adenomas was observed at the highest dose, 250 mcg/kg/day, a dose that produced an exenatide plasma exposure 130-fold the human clinical exposure. This incidence was not statistically significant when adjusted for survival. There was no tumorigenic response in male rats or either sex of mice.

Animal studies did not indicate direct harmful effects with respect to fertility or pregnancy. High doses of exenatide during mid-gestation caused skeletal effects and reduced-foetal growth in mice and reduced foetal growth in rabbits. Neonatal growth was reduced in mice exposed to high doses during late gestation and lactation.

THERAPEUTIC USES⁽¹³⁾

Exenatide is indicated for treatment of type 2 diabetes mellitus in combination with metformin, and / or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

EXENATIDE therapy should be initiated at 5 mcg

exenatide per dose administered twice daily (BID) for at least one month in order to improve tolerability. The dose of exenatide can then be increased to 10 mcg BID to further improve glycaemic control. Doses higher than 10 mcg BID are not recommended. Exenatide is available as either a 5 mcg or a 10 mcg exenatide per dose prefilled pen. Exenatide can be administered at any time within the 60-minute period before the morning and evening meal (or two main meals of the day, approximately 6 hours or more apart). Exenatide should not be administered after a meal. If an injection is missed, the treatment should be continued with the next scheduled dose. Each dose should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm.

Exenatide is recommended for use in patients with type 2 diabetes mellitus who are already receiving metformin and /or a sulfonylurea. When Exenatide is added to existing metformin therapy, the current dose of metformin can be continued as no increased risk of hypoglycaemia is anticipated, compared to metformin alone. When added to sulfonylurea therapy, a reduction in the dose of sulfonylurea should be considered to reduce the risk of hypoglycaemia.

The dose of Exenatide does not need to be adjusted on a day-by-day basis depending on self-monitored glycaemia. However, blood glucose self-monitoring may become necessary to adjust the dose of sulphonylureas. Limited experience exists concerning the combination of Exenatide with thiazolidinediones.

Specific Patient Groups

Elderly : Exenatide should be used with caution and dose escalation from 5 mcg to 10 mcg should proceed conservatively in patients >70 years. The clinical experience in patients >75 years is very limited.

Patients with renal impairment : No dosage adjustment is necessary in patients with mild renal impairment (creatinine clearance 50-80 ml/min). In patients with moderate renal impairment (creatinine clearance: 30-50 ml/min), dose escalation from 5 mcg to 10 mcg should proceed conservatively. Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 ml/min).

Patients with hepatic impairment : No dosage adjustment of Exenatide is necessary in patients with hepatic impairment.

Children and adolescents : There is no experience in children and adolescents below 18 years.

Special Warnings and Precautions

Exenatide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. It should not be used in type 2 diabetes patients who require insulin therapy due to beta cell failure. Intravenous or intramuscular injection of

Exenatide is not recommended.

In patients with end-stage renal disease receiving dialysis, single doses of Exenatide 5mcg increased frequency and severity of undesirable gastrointestinal effects. Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 ml/min). The clinical experience in patients with moderate renal impairment is very limited.

Exenatide has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhoea. Therefore, the use of Exenatide is not recommended in patients with severe gastrointestinal disease.

The concurrent use of Exenatide with insulin, D-phenylalanine derivatives, meglitinides, or alpha-glucosidase inhibitors has not been studied and cannot be recommended.

The experience in patients with BMI ≤ 25 is limited.

Hypoglycaemia

When Exenatide was used in combination with a sulfonylurea, the incidence of hypoglycaemia was increased over that of placebo in combination with a sulfonylurea. In the clinical studies patients on a sulfonylurea combination, with mild renal impairment had an increased incidence of hypoglycaemia compared to patients with normal renal function. To reduce the risk of hypoglycaemia associated with the use of a sulfonylurea, reduction in the dose of sulfonylurea should be considered.

Interactions

The effect of Exenatide to slow gastric emptying may reduce the extent and rate of absorption of orally administered medicinal products. Exenatide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption and medicinal products with a narrow therapeutic ratio.

Specific recommendations regarding intake of such medicinal products in relation to Exenatide is given below:

Interaction with other medicinal products and other forms of interaction:

The effect of Exenatide to slow gastric emptying may reduce the extent and rate of absorption of orally administered medicinal products. Patients receiving medicinal products of either a narrow therapeutic ratio or medicinal products that require careful clinical monitoring should be followed closely. These medicinal products should be taken in a standardised way in relation to Exenatide injection. If such medicinal products are to be administered with food, patients should be advised to, if possible, take them with a meal when Exenatide is not administered.

For oral medicinal products that are particularly dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those medicinal products at least 1 hour before Exenatide injection.

Exenatide is not expected to have any clinically relevant effects on the pharmacokinetics of metformin or sulphonylureas. Hence no restriction in timing of intake of these medicinal products in relation to Exenatide - injection are needed.

Gastroresistant formulations containing substances sensitive for degradation in the stomach, such as proton pump inhibitors, should be taken at least 1 hour before or more than 4 hours after Exenatide injection.

Paracetamol

Paracetamol was used as a model medicinal product to evaluate the effect of exenatide on gastric emptying. When 1000 mg paracetamol was given with 10 mcg Exenatide (0 h) and 1h, 2h and 4h after Exenatide injection, paracetamol AUCs were decreased by 21%, 23%, 24% and 14% respectively; C_{max} was decreased by 37 %, 56%, 54% and 41% respectively; T_{max} was increased from 0.6h in the control period to 0.9h, 4.2h, 3.3h, and 1.6h, respectively. Paracetamol AUC, C_{max} and T_{max} were not significantly changed when paracetamol was given 1 hour before Exenatide injection. No adjustment to paracetamol dosing is required based on these study results.

HMG CoA reductase inhibitors

Lovastatin AUC and C_{max} were decreased approximately 40% and 28%, respectively, and T_{max} was delayed about 4 h when Exenatide (10mcg BID) was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone. In the 30-week placebo-controlled clinical trials, concomitant use of Exenatide and HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles. Although no predetermined dose adjustment is required, one should be aware of possible changes in LDL-C or total cholesterol. Lipid profiles should be monitored regularly.

Digoxin, lisinopril and warfarin

A delay in T_{max} of about 2h was observed when digoxin, lisinopril or warfarin was administered 30 min after exenatide. No clinically relevant effects on C_{max} or AUC were observed. However, since market introduction, increased INR has been reported during concomitant use of warfarin and Exenatide. INR should be closely monitored during initiation and dose increase of Exenatide therapy in patients on warfarin and/or cumarol derivatives.

Pregnancy and Lactation

Pregnancy: There are no adequate data from the use of Exenatide in pregnant women. Studies in animals have

shown reproductive toxicity. The potential risk for humans is unknown. Exenatide should not be used during pregnancy and the use of insulin is recommended. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Exenatide should be discontinued.

Breast feeding. It is unknown whether exenatide is excreted in human milk. Exenatide should not be used in breast feeding women.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. When Exenatide is used in combination with a sulphonylurea, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

Undesirable effects

Table 2 lists adverse reactions reported from phase 3 studies. The table presents adverse reactions that occurred with an incidence $\geq 5\%$ and more frequently among Exenatide-treated patients than insulin- or placebo-treated patients. The table also includes adverse reactions that occurred with an incidence $\geq 1\%$ and with a statistically significantly higher and/or $\geq 2X$ incidence among Exenatide - treated patients than insulin- or placebo-treated patients.

Table 2: Adverse reactions reported in long term phase 3 controlled studies^{1*}

Body system/adverse reaction	Frequency of occurrence	
	Common	Very common
Metabolism and nutrition disorders		
Hypoglycaemia (with metformin and sulphonylurea) ²		X
Hypoglycaemia (with a sulphonylurea)		X
Decreased appetite	X	
Nervous system disorders		
Headache ²	X	
Dizziness	X	
Gastrointestinal disorders		
Nausea		X
Vomiting		X
Diarrhoea		X
Dyspepsia	X	
Abdominal pain	X	
Gastroesophageal reflux disease	X	
Abdominal distension	X	
Skin and subcutaneous tissue disorders		
H ^y perhidrosis ²	X	
General disorders and administrative site conditions		
Feeling jittery	X	
Asthenia ²	X	

*N= 1788 EXENATIDE-treated intent-to-treat patients.

1. Data from Phase 3 comparator-controlled studies versus placebo, insulin glargine or 30% soluble insulin aspart/70% insulin aspart protamine crystals (biphasic insulin aspart) in which patients also received metformin, thiazolidinediones or sulphonylurea in addition to Exenatide or comparator.
2. In insulin-comparator controlled studies in which metformin and a sulphonylurea were concomitant medicinal products, the incidence for these adverse reactions was similar for insulin and Exenatide treated patients.

The reactions are listed below as MedDRA preferred term by system organ class and absolute frequency. Patient frequencies are defined as: very common ($\geq 1/10$) and common ($> 1/100, < 1/10$) (Table 1)

Hypoglycemia

In studies in patients treated with Exenatide and a sulfonylurea (with or without metformin), the incidence of hypoglycaemia was increased compared to placebo (23.5% and 25.2% versus 12.6% and 3.3%) and appeared to be dependent on the doses of both Exenatide and the sulfonylurea. Most episodes of hypoglycaemia were mild to moderate in intensity, and all resolved with oral administration of carbohydrate.

Nausea

The most frequently reported adverse reaction was nausea. In patients treated with 5mcg or 10mcg Exenatide, generally 40-50% reported at least one episode of nausea. Most episodes of nausea were mild to moderate and occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased in most patients who initially experienced nausea.

The incidence of withdrawal due to adverse events was 8% for Exenatide-treated patients, 3% for placebo-treated and 1% for insulin-treated patients in the long-term controlled trials (16 weeks or longer). The most common adverse events leading to withdrawal for Exenatide-treated patients were nausea (4% of patients) and vomiting (1%). For placebo-treated or insulin-treated patients, < 1% withdrew due to nausea or vomiting.

Exenatide treated patients in the open-label extension studies at 82 weeks experienced similar types of adverse events observed in the controlled trials. Injection site reactions have been reported in approximately 5.1% of subjects receiving Exenatide in long-term (16 weeks or longer) controlled trials. These reactions have usually been mild and usually did not result in discontinuation of Exenatide.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-exenatide antibodies following treatment with Exenatide. In most patients who develop antibodies, antibody titres diminish over time and remain low through 82 weeks.

Overall the percentage of antibody positive patients was consistent across clinical trials. Patients who developed anti-exenatide antibodies had similar rates and types of adverse events as those with no anti-exenatide antibodies. In the three placebo-controlled trials (n=963) 38% of patients had low titre anti-exenatide antibodies at 30 weeks. For this group, the level of glycaemic control (HbA_{1c}) was generally comparable to that observed in

those without antibody titres. An additional 6% of patients had higher titre antibodies at 30 weeks. About half of this 6% (3% of the total patients given Exenatide in the controlled studies), had no apparent glycaemic response to Exenatide. In two insulin-comparator controlled trials (n=475) comparable efficacy and adverse events were observed in Exenatide-treated patients regardless of antibody titre. Examination of antibody-positive specimens from one long-term uncontrolled study revealed no significant cross-reactivity with similar endogenous peptides (glucagon or GLP-1).

Spontaneous reports

Since market introduction of Exenatide, the following additional adverse reactions have been reported:

Immune system disorders: anaphylactic reaction, very rarely.

Metabolism and nutritional disorders: dehydration, generally associated with nausea, vomiting and/or diarrhoea, some reports associated with elevation of serum creatinine.

Nervous system disorders: dysgeusia, somnolence.

Gastrointestinal disorders: eructation, constipation, flatulence. Cases of pancreatitis have been reported.

Skin and subcutaneous tissue disorders: macular rash, papular rash, pruritis, urticaria, angioneurotic oedema. *Investigations:* international normalised ratio increased with concomitant warfarin, some reports associated with bleeding.

Overdose

Signs and symptoms of overdose may include severe nausea, severe vomiting and rapidly declining blood glucose concentrations. In the event of overdose, appropriate supportive treatment (possibly given parenterally) should be initiated according to the patient's clinical signs and symptoms.

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