

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Byetta 10 micrograms solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose contains 10 micrograms (mcg) of exenatide in 40 microlitres (mcl), (0.25 mg exenatide per mL).

Excipient with known effect:

Byetta 10 mcg: Each dose contains 88 mcg metacresol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Byetta is indicated for treatment of type 2 diabetes mellitus in combination with:

- metformin

- sulphonylureas
- thiazolidinediones
- metformin and a sulphonylurea
- metformin and a thiazolidinedione

in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

Byetta is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these medicinal products.

4.2 Posology and method of administration

Posology

Immediate-release exenatide (Byetta) 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.

Immediate-release exenatide is available as either a 5 mcg or a 10 mcg exenatide per dose pre-filled pen.

Immediate-release 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). Immediate-release exenatide **should not** be administered after a meal. If an injection is missed, the treatment should be continued with the next scheduled dose.

Immediate-release exenatide is recommended for use in patients with type 2 diabetes mellitus who are already receiving metformin, a sulphonylurea, pioglitazone and/or a basal insulin. Immediate-release exenatide use can be continued when a basal insulin is added to existing therapy. When immediate-release exenatide is added to existing metformin and/or pioglitazone therapy, the current dose of metformin and/or pioglitazone can be continued as no increased risk of hypoglycaemia is anticipated, compared to metformin or pioglitazone alone. When immediate-release exenatide is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia (see section 4.4.). When immediate-release exenatide is used in combination with basal insulin, the dose of basal insulin should be evaluated. In patients at increased risk of hypoglycaemia reducing the dose of basal insulin should be considered (see section 4.8).

The dose of immediate-release exenatide does not need to be adjusted on a day-by-day basis depending on self-monitored glycaemia. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea or insulin, particularly when Byetta

therapy is started and insulin is reduced. A stepwise approach to insulin dose reduction is recommended.

Special populations

Elderly

Immediate-release 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.

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 (see section 5.2).

Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 mL/min) (see section 4.4).

Hepatic impairment

No dosage adjustment is necessary in patients with hepatic impairment (see section 5.2).

Paediatric population

The efficacy of exenatide in children and adolescents under 18 years of age was not demonstrated. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Each dose should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm. Immediate-release exenatide and basal insulin must be administered as two separate injections.

For instructions for using the pen, see section 6.6 and the user manual included with the leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Exenatide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Exenatide is not a substitute for insulin. Diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin (see section 4.2).

Immediate-release exenatide must not be administered by intravenous or intramuscular injection.

Renal impairment

In patients with end-stage renal disease receiving dialysis, single doses of immediate-release exenatide 5 mcg increased frequency and severity of gastrointestinal adverse reactions. 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 (see section 4.2).

There have been uncommon, spontaneously reported events of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis. Some of these events occurred in patients experiencing events that may affect hydration, including nausea, vomiting, and/or diarrhoea and/or receiving medicinal products known to affect renal function/hydration status. Concomitant medicinal products included angiotensin converting enzymes inhibitors, angiotensin-II antagonists, nonsteroidal anti-inflammatory medicinal products and diuretics. Reversibility of altered renal function has been observed with supportive treatment and discontinuation of potentially causative medicinal products, including exenatide.

Acute pancreatitis

Exenatide has not been studied in patients with a history of pancreatitis, and should be used with caution in these patients.

Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. There have been spontaneously reported events of acute pancreatitis with exenatide. Resolution of pancreatitis has been observed with supportive treatment but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported.

Patients should be informed of the characteristic symptoms of acute pancreatitis, including persistent, severe abdominal pain. Patients should be advised to seek immediate medical attention if they occur. If pancreatitis is suspected, exenatide should be discontinued. If the diagnosis of pancreatitis is confirmed, exenatide should not be restarted.

In the absence of other signs and symptoms, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis (see sections 4.8 and 5.1).

Severe gastrointestinal disease

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.

Hypoglycaemia

When immediate-release exenatide was used in combination with a sulphonylurea, the incidence of hypoglycaemia was increased over that of placebo in combination with a sulphonylurea. In the clinical studies patients on a sulphonylurea 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 sulphonylurea, reduction in the dose of sulphonylurea should be considered.

Rapid weight loss

Weight loss greater than 1.5 kg per week has been observed in approximately 5% of clinical trial patients treated with exenatide. Weight loss of this rate may have harmful consequences. Patients with rapid weight loss should be monitored for signs and symptoms of cholelithiasis.

Concomitant medicinal products

The effect of immediate-release exenatide to slow gastric emptying may reduce the extent and rate of absorption of orally administered medicinal products. Immediate-release 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 immediate-release exenatide is given in section 4.5.

The concurrent use of immediate-release exenatide with D phenylalanine derivatives (meglitinides), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors or other GLP-1 receptor agonists has not been studied and cannot be recommended.

Excipients

This medicinal product contains metacresol, which may cause allergic reactions.

This medicinal product contains less than 1 mmol sodium per dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

The effect of immediate-release 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 immediate-release 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 immediate-release exenatide is not administered.

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

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 immediate-release exenatide injection.

Digoxin, lisinopril and warfarin

A delay in $t_{\max}$ of about 2 h 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 (International Normalized Ratio) has been reported spontaneously during concomitant use of warfarin and exenatide. INR should be closely monitored during initiation and dose increase of immediate-release exenatide therapy in patients on warfarin and/or cumarol derivatives (see section 4.8).

Metformin or sulphonylureas

Immediate-release 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 immediate-release exenatide injection are needed.

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 immediate-release exenatide (0 h) and 1 h, 2 h and 4 h after immediate-release 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 0.6 h in the control period to 0.9 h, 4.2 h, 3.3 h, and 1.6 h, respectively. Paracetamol AUC, $C_{\max}$ and $t_{\max}$ were not significantly changed when paracetamol was given 1 hour before immediate-release exenatide injection. No adjustment to paracetamol dosing is required based on these study results.

Hydroxy Methyl Glutaryl Coenzyme A (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 immediate-release exenatide (10 mcg 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 immediate-release exenatide and HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles (see section 5.1). Changes in LDL-C or total cholesterol are possible, however, no predetermined dose adjustment is required. Lipid profiles should be monitored regularly.

Ethinyl estradiol and levonorgestrel

Administration of a combination oral contraceptive (30 mcg ethinyl estradiol plus 150 mcg levonorgestrel) one hour before immediate-release exenatide (10 mcg BID) did not alter the AUC, $C_{\max}$ or $C_{\min}$ of either ethinyl estradiol or levonorgestrel. Administration of the oral contraceptive 30 minutes after immediate-release exenatide did not affect AUC but resulted in a reduction of the $C_{\max}$ of ethinyl estradiol by 45 %, and $C_{\max}$ of levonorgestrel by 27-41 %, and a delay in $t_{\max}$ by 2-4 h due to delayed gastric emptying. The reduction in $C_{\max}$ is of limited clinical relevance and no adjustment of dosing of oral contraceptives is required.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

If a patient wishes to become pregnant, or pregnancy occurs, treatment with exenatide should be discontinued.

Pregnancy

There are no adequate data from the use of exenatide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Exenatide should not be used during pregnancy and the use of insulin is recommended.

Breast-feeding

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

Fertility

No fertility studies in humans have been conducted.

4.7 Effects on ability to drive and use machines

Exenatide has minor influence on the ability to drive and use machines. When exenatide is used in combination with a sulphonylurea or a basal insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions were mainly gastrointestinal related (nausea, vomiting and diarrhoea). The most frequently reported single adverse reaction was nausea which was associated with the initiation of treatment and decreased over time. Patients may experience hypoglycaemia when immediate-release exenatide is used with a sulphonylurea. Most adverse reactions associated with immediate-release exenatide were mild to moderate in intensity.

Since immediate-release exenatide has been marketed, acute pancreatitis has been reported with a frequency not known and acute renal failure has been reported uncommonly (see section 4.4).

Tabulated list of adverse reactions

Table 1 lists adverse reactions reported of immediate-release exenatide from clinical trials and spontaneous reports (not observed in clinical trials, frequency not known).

In clinical trials, background therapies included metformin, a sulphonylurea, a thiazolidinedione, or a combination of oral glucose-lowering medicinal products.

The reactions are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

Table 1: Adverse reactions of immediate-release exenatide identified from clinical trials and spontaneous reports

System organ class /adverse reaction terms	Frequency of occurrence					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders						
Drug-induced thrombocytopenia						X ³
Hepatobiliary disorders						
Cholecystitis			X ¹			
Cholelithiasis			X ¹			
Immune system disorders						
Anaphylactic reaction				X ¹		
Metabolism and nutrition disorders						
Hypoglycaemia (with metformin and a sulphonylurea) ²	X ¹					
Hypoglycaemia (with a sulphonylurea)	X ¹					
Decreased appetite		X ¹				
Dehydration, generally associated with nausea, vomiting and/or diarrhoea.			X ¹			
Nervous system disorders						
Headache ²		X ¹				
Dizziness		X ¹				
Dysgeusia			X ¹			
Somnolence			X ¹			

Gastrointestinal disorders						
Intestinal obstruction				X ¹		
Nausea	X ¹					
Vomiting	X ¹					
Diarrhoea	X ¹					
Dyspepsia		X ¹				
Abdominal pain		X ¹				
Gastroesophageal reflux disease		X ¹				
Abdominal distension		X ¹				
Acute pancreatitis (see section 4.4)						X ³
Eructation			X ¹			
Constipation		X ¹				
Flatulence		X ¹				
Delayed gastric emptying			X ¹			
Skin and subcutaneous tissue disorders						
Hyperhidrosis ²		X ¹				
Alopecia			X ¹			
Macular and papular rash						X ³
Pruritus, and/ or urticaria		X ¹				
Angioneurotic oedema						X ³
Renal and urinary disorders						
Altered renal function, including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine			X ¹			

General disorders and administration site conditions						
Feeling jittery		X ¹				
Asthenia ²		X ¹				
Injection site reactions			X ¹			
Investigations						
Weight decreased			X ¹			
International normalised ratio increased with concomitant warfarin, some reports associated with bleeding						X ³

¹ Rate based on immediate-release exenatide completed long-term efficacy and safety studies n=5763 total (patients on sulphonylurea n=2971).

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 immediate-release exenatide-treated patients.

³ Spontaneous reports data (unknown denominator). When immediate-release exenatide was used in combination with basal insulin therapy the incidence and types of other adverse events observed were similar to those seen in the controlled clinical trials with exenatide as monotherapy, with metformin and/or sulphonylurea or a thiazolidinedione, with or without metformin.

Description of selected adverse reactions

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia (DITP) with exenatide-dependent anti-platelet antibodies has been reported in the postmarketing setting. DITP is an immune-mediated reaction that is caused by drug-dependent platelet-reactive antibodies. These antibodies cause destruction of platelets in the presence of the sensitizing drug.

Hypoglycaemia

In studies in patients treated with immediate-release exenatide and a sulphonylurea (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 immediate-release exenatide and the sulphonylurea.

There were no clinically relevant differences in incidence or severity of hypoglycaemia with exenatide compared to placebo, in combination with a thiazolidinedione, with or without metformin. Hypoglycaemia was reported in 11 % and 7 % of patients treated with exenatide and placebo respectively.

Most episodes of hypoglycaemia were mild to moderate in intensity, and resolved with oral administration of carbohydrate.

In a 30-week study, when immediate-release exenatide or placebo was added to existing basal insulin therapy (insulin glargine), the dose of basal insulin was decreased by 20 % in patients with an $HbA_{1c} \leq 8.0$ %, per protocol design in order to minimize the risk of hypoglycaemia. Both treatment arms were titrated to achieve target fasting plasma glucose levels (see section 5.1). There were no clinically significant differences in the incidence of hypoglycaemic episodes in the immediate-release exenatide compared to the placebo group (25% and 29% respectively). There were no episodes of major hypoglycaemia in the immediate-release exenatide arm.

In a 24-week study, where either insulin lispro protamine suspension or insulin glargine was added to existing therapy of immediate-release exenatide and metformin or metformin plus thiazolidinedione the incidence of patients with at least one minor hypoglycaemic episode was 18% and 9% respectively and one patient reported major hypoglycaemia. In patients where existing therapy also included a sulphonylurea the incidence of patients with at least one minor hypoglycaemic episode was 48% and 54% respectively and one patient reported major hypoglycaemia.

Nausea

The most frequently reported adverse reaction was nausea. In patients treated with 5 mcg or 10 mcg immediate-release exenatide, 36 % 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 immediate-release 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 immediate-release 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.

Immediate-release 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

Injection site reactions have been reported in approximately 5.1 % of subjects receiving immediate-release exenatide in long-term (16 weeks or longer) controlled trials. These reactions have usually been mild and usually did not result in discontinuation of immediate-release exenatide.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-exenatide antibodies following treatment with immediate-release 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 develop antibodies to exenatide tend to have more injection site reactions (for example: redness of skin and itching), but otherwise 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 immediate-release exenatide in the controlled studies), had no apparent glycaemic response to immediate-release exenatide. In three insulin-comparator controlled trials (n=790) comparable efficacy and adverse events were observed in immediate-release 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucagon-like peptide-1 (GLP-1) analogues, ATC code: A10BJ01.

Mechanism of action

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that exhibits several antihyperglycaemic actions of glucagon-like peptide-1 (GLP-1). The amino acid sequence of exenatide partially 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 mediated by cyclic AMP and/or other intracellular signalling 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. (see section 4.4).

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

Immediate-release 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 and safety

Studies of immediate-release exenatide with metformin, a sulphonylurea or both as background therapy

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.

Immediate-release exenatide reduced HbA_{1c} and body weight in patients treated for 30 weeks in three placebo-controlled studies, whether the immediate-release exenatide was added to metformin, a sulphonylurea or a combination of both. These reductions in HbA_{1c} were generally observed at 12 weeks after initiation of treatment. See Table 2. 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).

Table 2: Combined results of the 30 week placebo controlled studies (intent to treat patients)

	Placebo	Immediate-release exenatide 5 mcg BID	Immediate-release exenatide 10 mcg BID
N	483	480	483
Baseline HbA _{1c} (%)	8.48	8.42	8.45
HbA _{1c} (%) change from base line	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

In insulin-comparator studies immediate-release exenatide (5 mcg BID for 4 weeks, followed by 10 mcg BID) in combination with metformin and sulphonylurea 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). Immediate-release 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 immediate-release 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 (immediate-release 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 immediate-release exenatide injection. Premeal blood glucose concentrations were generally lower in patients taking insulin compared to immediate-release exenatide. Mean daily blood glucose values were similar between immediate-release exenatide and insulin. In these studies the incidence of hypoglycaemia was similar for immediate-release exenatide and insulin treatment.

Studies of immediate-release exenatide with metformin, a thiazolidinedione or both as background therapy

Two placebo-controlled studies were conducted: one of 16 and one of 26 weeks duration, with 121 and 111 immediate-release exenatide and 112 and 54 placebo treated patients respectively, added to existing thiazolidinedione treatment, with or without metformin. Of the immediate-release exenatide patients, 12% were treated with a thiazolidinedione and immediate-release exenatide and 82% were treated with

a thiazolidinedione, metformin and immediate-release exenatide. Immediate-release exenatide (5 mcg BID for 4 weeks, followed by 10 mcg BID) resulted in statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.7% versus +0.1%) as well as significant reductions in body weight (-1.5 versus 0 kg) in the 16 week study. The 26 week study showed similar results with statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.8% versus -0.1%). There was no significant difference in body weight between treatment groups in change from baseline to endpoint (-1.4 versus -0.8 kg).

When immediate-release 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. The incidence and type of other adverse events observed were similar to those seen in the 30-week controlled clinical trials with a sulphonylurea, metformin or both.

Studies of immediate-release exenatide in combination with basal insulin

In a 30-week study, either immediate-release exenatide (5 mcg BID for 4 weeks, followed by 10 mcg BID) or a placebo was added to insulin glargine (with or without metformin, pioglitazone or both). During the study both treatment arms titrated insulin glargine using an algorithm reflecting current clinical practice to a target fasting plasma glucose of approximately 5.6 mmol/L. The mean age of subjects was 59 years and the mean duration of diabetes was 12.3 years.

At the end of the study, immediate-release exenatide (n=137) demonstrated a statistically significant reduction in the HbA_{1c} and weight compared to placebo (n=122). Immediate-release exenatide lowered HbA_{1c} by 1.7 % from a baseline of 8.3 % while placebo lowered HbA_{1c} by 1.0 % from a baseline of 8.5 %. The proportion of patients achieving HbA_{1c} <7% and HbA_{1c} ≤6.5% was 56 % and 42 % with immediate-release exenatide and 29 % and 13 % with placebo. Weight loss of 1.8 kg from a baseline of 95 kg was observed with immediate-release exenatide whereas a weight gain of 1.0 kg from a baseline of 94kg was observed with placebo.

In the immediate-release exenatide arm the insulin dose increased by 13 units/day compared to 20 units/ day on the placebo arm. Immediate-release exenatide reduced fasting serum glucose by 1.3 mmol/L and placebo by 0.9 mmol/L. The immediate-release exenatide arm compared to placebo had significantly lowered postprandial blood glucose excursions at the morning meal (- 2.0 versus - 0.2 mmol/L) and evening meal (- 1.6 versus + 0.1 mmol/L), there was no difference between treatments at midday.

In a 24-week study, where either insulin lispro protamine suspension or insulin glargine was added to existing therapy of immediate-release exenatide and metformin, metformin and sulphonylurea or metformin and pioglitazone, HbA_{1c} was lowered by 1.2 % (n=170) and by 1.4 % (n=167) respectively from a baseline of 8.2 %. Weight increase of 0.2 kg was observed for patients on insulin lispro protamine suspension and 0.6 kg for insulin glargine treated patients from a baseline of 102 kg and 103 kg respectively.

In a 30-week, open-label, active comparator-controlled, noninferiority study, the safety and efficacy of immediate-release exenatide (n=315) versus titrated insulin lispro three times daily (n=312) on a background of optimized basal insulin glargine and metformin in patients with type 2 diabetes was evaluated.

Following a basal insulin optimization (BIO) phase, patients with $\text{HbA}_{1c} > 7.0\%$ were randomized to add either immediate-release exenatide or insulin lispro to their existing regimen of insulin glargine and metformin. In both treatment groups, subjects continued to titrate their insulin glargine doses using an algorithm reflecting current clinical practice.

All patients assigned to immediate-release exenatide initially received 5 mcg BID for four weeks. After four weeks, their dose was increased to 10 mcg BID. Patients in the immediate-release exenatide-treated group with an $\text{HbA}_{1c} \leq 8.0\%$ at the end of the BIO phase decreased their insulin glargine dose by at least 10%.

Immediate-release exenatide lowered HbA_{1c} by 1.1% from a baseline of 8.3% and insulin lispro lowered HbA_{1c} by 1.1% from a baseline of 8.2% and noninferiority of immediate-release exenatide to titrated lispro was demonstrated. The proportion of patients achieving $\text{HbA}_{1c} < 7\%$ was 47.9% with immediate-release exenatide and 42.8% with insulin lispro. Weight loss of 2.6 kg from a baseline of 89.9 kg was observed with immediate-release exenatide whereas a weight gain of 1.9 kg from a baseline of 89.3 kg was observed with insulin lispro.

Fasting lipids

Immediate-release exenatide has shown no adverse effects on lipid parameters. A trend for a decrease in triglycerides has been observed with weight loss.

Beta-cell function

Clinical studies with immediate-release 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.

Body weight

A reduction in body weight was seen in patients treated with immediate-release 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.

Paediatric population

The efficacy and safety of immediate release exenatide was evaluated in a 28-week randomized, double-blind, placebo controlled study conducted in 120 patients aged 10

to 17 years with type 2 diabetes who had HbA_{1c} 6.5% to 10.5% and who were either naive to anti-diabetes agents or were treated with metformin alone, a sulfonylurea alone, or metformin in combination with a sulfonylurea. Patients received twice daily treatment with immediate release exenatide 5 µg, immediate release exenatide 10 µg or equivalent dose of placebo for 28 weeks. The primary efficacy endpoint was the change in HbA_{1c} from baseline to 28 weeks of treatment; the treatment difference (pooled doses) from placebo was not statistically significant [-0.28% (95% CI: -1.01, 0.45)]. No new safety findings were identified in this paediatric study.

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2 h. 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 of exenatide is 28 L.

Biotransformation 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 2.4 h. These pharmacokinetic characteristics of exenatide are independent of the dose.

Special populations

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 (see section 4.2).

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

Long-term controlled data in elderly are limited, but suggest no marked changes in exenatide exposure with increased age up to about 75 years old. In a pharmacokinetic study in patients with type 2 diabetes, administration of exenatide (10 mcg) resulted in a mean increase of exenatide AUC by 36 % in 15 elderly subjects aged 75 to 85 years compared to 15 subjects aged 45 to 65 years likely related to reduced renal function in the older age group (see section 4.2).

Paediatric population

In a single-dose pharmacokinetic study in 13 patients with type 2 diabetes and between the ages of 12 and 16 years, administration of exenatide (5 mcg) resulted in slightly lower mean AUC (16% lower) and C_{max} (25% lower) compared to those observed in adults.

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

metacresol

mannitol
glacial acetic acid
sodium acetate trihydrate
water for injections

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

In use pen: 30 days

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).

Do not freeze.

In use

Store below 25 °C.

The pen must not be stored with the needle attached.

Replace cap on pen in order to protect from light.

6.5 Nature and contents of container

Type I glass cartridge with a (bromobutyl) rubber plunger, rubber disc, and aluminium seal. Each cartridge is assembled into a disposable pen-injector (pen).

10 mcg: Each pre-filled pen contains 60 doses (approximately 2.4 mL of solution).

Pack size of 1 and 3 pens. Not all pack sizes may be marketed.

Injection needles are not included.

Becton, Dickinson and Company needles are suitable to use with the Byetta pen.

6.6 Special precautions for disposal

The patient should be instructed to discard the needle after each injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for use

Byetta is for use by one person only.

The instructions for using the pen, included with the leaflet, must be followed carefully.

The pen must not be stored with the needle attached.

Byetta should not be used if particles appear or if the solution is cloudy and/or coloured.

Do not use Byetta if it has been frozen.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,
1 Francis Crick Avenue,
Cambridge,
CB2 0AA,

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