AUSTRALIAN PRODUCT INFORMATION
BYETTA® (exenatide) solution for injection

1. NAME OF THE MEDICINE

Exenatide.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BYETTA 5 micrograms solution for injection

BYETTA 5 µg pre-filled pen contains 60 doses of sterile, preserved isotonic solution (approximately 1.2 mL). Each dose contains 5 µg exenatide in 20 microlitres (0.25 mg synthetic exenatide per mL).

BYETTA 10 micrograms solution for injection

BYETTA 10 µg pre-filled pen contains 60 doses of sterile, preserved isotonic solution (approximately 2.4 mL). Each dose contains 10 µg exenatide in 40 microlitres (0.25 mg synthetic exenatide per mL).

Each millilitre of BYETTA contains 250 µg of synthetic exenatide.

For a full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Solution for injection. BYETTA is a clear colourless solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BYETTA is indicated as adjunctive therapy to improve glycaemic control in adult patients with type 2 diabetes mellitus who are taking:

- metformin
- a sulfonylurea
- metformin and a sulfonylurea
- metformin and a basal insulin

4.2 DOSE AND METHOD OF ADMINISTRATION

BYETTA therapy should be initiated at 5 µg exenatide per dose administered twice daily (BID) for at least one month in order to improve tolerability. The dose of

BYETTA can then be increased to 10 µg BID to further improve glycaemic control. Doses higher than 10 µg BID are not recommended.

BYETTA can be administered at any time within the 60-minute period before the morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). BYETTA should not be administered after a meal. If an injection is missed, the treatment should be continued with the next scheduled dose.

Each dose of BYETTA should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm. BYETTA is not recommended to be administered by intravenous or intramuscular injection. BYETTA and basal insulin must be administered as two separate injections.

Concomitant therapy

Metformin

When BYETTA is added to metformin therapy, the current dose of metformin can be continued as no increased risk of hypoglycaemia is anticipated, compared to metformin alone.

Sulfonylurea

When BYETTA is added to sulfonylurea therapy, a reduction in the dose of sulfonylurea may be considered to reduce the risk of hypoglycaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Insulin

When BYETTA is used in combination with insulin, the dose of insulin should be evaluated. In patients at increased risk of hypoglycaemia consider reducing the dose of insulin (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials).

The concurrent use of BYETTA with prandial insulin has not been studied and cannot be recommended. BYETTA treatment should be ceased prior to commencing a basal bolus regimen.

Specific patient groups

Gender, age, race or obesity

No dosage adjustment is necessary for gender, for age, for race or for obese patients (BMI >30 kg/m^2) (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Patients with renal impairment

No dosage adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min) (see Section 5.2 PHARMACOKINETIC PROPERTIES).

In patients with moderate renal impairment (creatinine clearance: 30 to 50 mL/min), dose escalation from 5 µg to 10 µg should proceed conservatively (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES).

BYETTA should not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min) (see Sections 4.3 CONTRAINDICATIONS and 5.2 PHARMACOKINETIC PROPERTIES).

Patients with hepatic impairment

BYETTA can be given to patients with hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric patients

BYETTA is not indicated for use in children and adolescents. Currently available data for patients aged 10 to less than 18 years old are described in Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Safety and efficacy in patients below the age of 10 years have not been studied. No recommendations on dosage can be made.

Instructions for use and handling

Each BYETTA pen is for use by one person only. Instructions on how to use the pen are provided in the User Manual. The instructions for using the pen must be followed carefully.

BYETTA should not be used if particles appear or if the solution is cloudy and coloured. Exenatide that has been frozen must not be used.

The patient should be advised to discard the needle after each injection. Used needles should be disposed of in appropriate needle bin and returned to pharmacists or given to diabetes nurse educators for disposal. The pen is stored without the needle attached. The cartridge must not be refilled.

4.3 CONTRAINDICATIONS

BYETTA is contraindicated in patients with known hypersensitivity to this product or any of its components, including metacresol (see Section 6.1 LIST OF EXCIPIENTS).

BYETTA should not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Compared with healthy subjects, renal clearance of exenatide was significantly reduced in patients with end-stage renal disease receiving dialysis, resulting in poor gastrointestinal tolerability.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

The concurrent use of exenatide with D-phenylalanine derivatives, meglitinides, alpha-glucosidase inhibitors, orlistat, opioids, and anticholinergics has not been

studied. Exenatide in combination with a thiazolidinedione is not recommended as there is limited experience.

Exenatide is not a substitute for insulin in insulin-requiring patients. Exenatide should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. The substitution of exenatide for insulin in insulin-requiring patients has not been extensively studied. In a 16 week exploratory study, which evaluated the safety of substituting exenatide for insulin in 33 patients with type 2 diabetes using insulin in combination with oral antidiabetic agents, almost 40% of subjects were unable to maintain glycaemic control (experienced an increase of HbA_{1c} ≥0.5%) while on exenatide.

Since market introduction there have been some spontaneously reported cases of increased INR (International Normalised Ratio) with concomitant use of warfarin and exenatide, sometimes associated with bleeding (see Sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS – Spontaneous Data).

Exenatide should be used with caution and dose escalation from 5 µg to 10 µg should proceed conservatively in patients >70 years. The clinical experience in patients >75 years is very 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 may be considered (see Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Due to the glucose-dependent insulinotropic mechanism of action of exenatide, when used in combination with metformin alone, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin (see Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Exenatide did not alter the counter-regulatory hormone response to insulin-induced hypoglycaemia in a randomised, double-blind, controlled study in healthy subjects.

Interaction with warfarin

Since market introduction there have been some spontaneously reported cases of increased INR (International Normalised Ratio) with concomitant use of warfarin and exenatide, sometimes associated with bleeding (see Sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Spontaneous data).

Altered renal function

There have been rare, spontaneously reported events of acute renal failure, worsened chronic renal failure, renal impairment, or increased serum creatinine among patients using exenatide. These events mostly occurred in patients also receiving one or more pharmacologic agents known to potentially affect renal function or hydration status and/or experiencing events of nausea, vomiting, diarrhoea, and/or dehydration. Concomitant agents included angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, and diuretics. For many events, reversibility has been observed with appropriate treatment (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Spontaneous data).

Pancreatitis

Recognised risk factors for pancreatitis include a past history of pancreatitis, gallstones, alcoholism and severe hypertriglyceridaemia. Clinical judgement should be exercised when selecting anti-diabetic treatments, including exenatide, for these patients. The change in risk of recurrent pancreatitis in patients with a past history of pancreatitis who receive exenatide is not known. There have been rare, spontaneously reported events of acute pancreatitis, including fatal cases of haemorrhagic or necrotising pancreatitis in patients who have received exenatide. Cases of haemorrhagic or necrotising pancreatitis have been reported across the adult age range (18 years and over, including the elderly). There are no early signs or symptoms that distinguish cases that will become acute haemorrhagic or necrotising pancreatitis from the less severe form of pancreatitis. This potential should be considered in patients treated with exenatide who manifest symptoms and signs suggestive of pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Patients and their caregivers should be advised to report immediately to their doctor such abdominal pain particularly if associated with vomiting or diarrhoea. Generally, resolution of pancreatitis has been observed with supportive treatment. If pancreatitis is suspected, exenatide and other potentially suspect medications should be discontinued and not recommenced unless pancreatitis has been excluded.

Weight loss

Rapid weight loss at a rate of >1.5 kg per week has been reported in patients treated with exenatide. Weight loss of this rate may have harmful consequences.

Use in renal impairment

In patients with mild to moderate renal impairment (creatinine clearance >30 to 80 mL/min), exenatide clearance was only mildly reduced compared to clearance in individuals with normal renal function. Patients with moderate renal impairment (creatinine clearance >30 to 50 mL/min) have been noted to have an increase in the AUC of exenatide. As the risk of adverse events is dose-dependent, caution is recommended in this population (see Section 4.3 CONTRAINDICATIONS).

Use in the elderly

No dosage adjustments are necessary for use of exenatide in elderly patients. Subjects aged up to 75 years were enrolled in the 5 placebo- and active comparator-controlled pivotal clinical studies. A total of 333 subjects aged 65 years or older

received exenatide in these studies. There were no apparent age-related differences in the change in HbA_{1c} values from baseline to endpoint for subjects treated with exenatide during these studies.

Paediatric use

BYETTA is not indicated for use in children and adolescents. Currently available data for patients aged 10 to less than 18 years old are described in Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Safety and efficacy in patients below the age of 10 years have not been studied.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Exenatide stimulates insulin release. This should be considered when insulin secretagogues are used (for use with sulfonylurea, see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials).

Exenatide slows gastric emptying, as part of its mechanism of action. This has the potential for interaction with orally administered medicines. Exenatide should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption or medication associated with local gastrointestinal irritation such as bisphosphonates or tetracyclines. Gastro-resistant formulations containing substances sensitive to 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. For oral medications that are particularly dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those medicines at least 1 hour before exenatide injection. If such medicines are to be administered with food, patients should be advised to take them with a meal or snack when exenatide is not administered.

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 µg exenatide (0 hour) and 1 hour, 2 hours and 4 hours 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 0.6 hour in the control period to 0.9 hour, 4.2 hours, 3.3 hours and 1.6 hours 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

The AUC and C_{max} of lovastatin, a HMG CoA reductase inhibitor, were decreased approximately 40% and 28%, respectively, and T_{max} was delayed by about 4 hours when Exenatide (10 µg 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.

Warfarin

In a controlled clinical pharmacology study in healthy volunteers, a delay in warfarin T_{max} of about 2 hours was observed when warfarin was administered 30 min after exenatide. No clinically relevant effects on C_{max} or AUC were observed (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Spontaneous data).

Digoxin and lisinopril

No clinically relevant interactions were observed with digoxin and lisinopril.

Ethinyl estradiol and levonorgestrel

Administration of a combination oral contraceptive (30 µg ethinyl estradiol plus 150 µg levonorgestrel) one hour before BYETTA did not alter the AUC, C_{max} or C_{min} of either ethinyl estradiol or levonorgestrel. Administration of the oral contraceptive 30 minutes after BYETTA 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 hours 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Animal studies did not indicate direct harmful effects with respect to fertility. Male and female fertility was unaffected in mice treated with exenatide at SC doses up to 760 µg/kg/day, 500 times the clinical exposure at 20 µg/day based on AUC.

Use in pregnancy – Category C

Exenatide is not recommended for use during pregnancy. No specific studies have been conducted in pregnant women.

Data on a limited number of exposed pregnancies indicate no adverse effects of exenatide on pregnancy or on the health of the foetus/new born child. To date, no other relevant epidemiological data are available.

Potential embryofetal effects were assessed with SC doses of exenatide during organogenesis in mice at 6, 68 and 760 µg/kg/day and in rabbits at 0.2, 2, 22, 156 and 260 µg/kg/day, giving respective exposures approximately 3, 30 and 500 times (mouse) and 0.2, 5, 200, 1400 and 3500 times (rabbit) the clinical exposure at 20 µg/day. A low incidence of abortions and decreased fetal growth occurred in mice and rabbits at ≥68 and 22 µg/day, respectively, which also caused a decrease in food consumption and body weight gain in dams. Alterations of skeletal ossification were observed in rabbits at ≥2 µg/kg/day as a result of decreased food intake. Wavy ribs were seen in mice at 760 µg/kg/day. Fetal umbilical hernias were increased in

rabbits at ≥22 µg/kg/day. There was minimal placental transfer of exenatide in animal studies *in vivo* or in human placental tissues *in vitro*. The fetal findings were probably secondary to effects on the dam.

High doses of exenatide administered to mice during gestation and lactation caused stillbirths, an increase in neonatal deaths and a decrease in neonatal growth at exposures 500 times the clinical exposure at 20 µg/day. The no observable effect level for peri-neonatal effects was 68 µg/kg/day, giving exposures 30 times the clinical exposure.

Use in lactation

It is unknown whether exenatide is excreted in human milk. In lactating mice given high doses of exenatide, low concentrations of exenatide were detected in milk (2.5% of plasma level). Neonatal deaths were increased in lactating mice at high doses (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in pregnancy). Exenatide should be administered to nursing women only if the potential benefit to the mother justifies the potential risk to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

When exenatide is used in combination with a sulfonylurea, or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Use with metformin and/or a sulfonylurea

The safety of exenatide has been evaluated in over 2500 exenatide-treated subjects in the completed clinical pharmacology, efficacy and safety studies, comprising 1729 subject years. Overall, 87% of exenatide-treated subjects experienced at least one treatment emergent adverse event, compared with 72% of insulin- and 64% of placebo-treated subjects. Among exenatide-treated subjects, nausea was the most common event (52%), followed by hypoglycaemia (27%) and vomiting (19%).

The incidence of withdrawal due to adverse events was 8% for exenatide-treated patients and 2% for placebo-treated or insulin-treated patients in the long-term controlled trials (26 weeks or longer). The most common adverse events leading to withdrawal for exenatide-treated patients were nausea (3% of patients) and vomiting (1%). For placebo-treated or insulin-treated patients, <1% withdrew due to nausea and 0% due to vomiting.

Exenatide-treated patients in the open-label extension studies at 82 weeks experienced similar types of adverse events to those observed in the long term-controlled trials of 26 weeks or more.

Table 5 lists the adverse reactions reported from Phase 3 placebo, insulin glargine and 30% soluble insulin aspart/70% insulin aspart protamine crystal (biphasic insulin aspart) - comparator controlled studies in which the patients received metformin, a sulfonylurea or a combination of both in addition to exenatide or comparator.

The table presents adverse reactions that occurred with an incidence ≥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 ≥1% and with a statistically significantly higher and/or ≥2X incidence among exenatide-treated patients than insulin- or placebo-treated patients.

The reactions are listed below as MedDRA preferred term by system organ class and absolute frequency.

Table 1 Adverse reactions reported in phase 3 placebo or active-comparator controlled studies

Body System/Adverse Reaction Terms	**Frequency of occurrence**		
Events	**Exenatide N=1498**	**Insulin N=515**	**Placebo N=483**
Metabolism and nutrition disorders			
Hypoglycaemia (with metformin and a sulfonylurea) [1,2]	39.6%	55.9%	12.6%
Hypoglycaemia (with a sulfonylurea)[3]	25.2%	data not available	3.3%
Decreased appetite	3.1%	0.2%	0.2%
Nervous system disorders			
Headache[1]	7.9%	7.0%	6.2%
Dizziness	6.9%	1.6%	6.2%
Gastrointestinal disorders			
Nausea	44.3%	4.7%	18.0%
Vomiting	14.0%	3.5%	3.7%
Diarrhoea	12.0%	2.5%	6.8%
Dyspepsia	4.7%	0.4%	2.1%
Abdominal pain[4]	3.4%	1.0%	2.5%
Gastroesophageal reflux disease	2.5%	0.2%	0.8%
Abdominal distension	1.5%	0.2%	0.8%
Skin and subcutaneous tissue disorders			
Hyperhidrosis[1]	2.5%	1.0%	1.2%
General disorders and administrative site conditions			
Feeling jittery	6.0%	0.2%	4.1%
Asthenia[1]	2.8%	1.4%	1.7%

1 In insulin comparator controlled studies in which metformin and a sulfonylurea were concomitant medications, the incidence for these terms was similar for insulin and Exenatide treated patients.

2 Includes data from placebo-controlled and insulin-controlled studies, for which the definition of hypoglycaemia differed. N=1021 for subjects using metformin and sulfonylurea.

3 N=254 for subjects using a sulfonylurea.

4 Includes reported events of abdominal pain and upper abdominal pain

In the three 30-week controlled trials of exenatide add-on to metformin and/or sulfonylurea, adverse events with an incidence ≥5% (excluding hypoglycaemia; see Table 6) that occurred more frequently in exenatide-treated patients compared with placebo-treated patients are summarised in Table 2.

Table 2 Frequent treatment-emergent adverse events (≥5% incidence and greater incidence with exenatide treatment) excluding hypoglycaemia*

	Placebo BID N=483 %	All Exenatide BID N=963 %
Nausea	18	44
Vomiting	4	13
Diarrhoea	6	13
Feeling Jittery	4	9
Dizziness	6	9
Headache	6	9
Dyspepsia	3	6

* In three 30-week placebo-controlled clinical trials.

Paediatric study

The efficacy and safety of BYETTA was evaluated in a 28-week randomised, double-blind, placebo-controlled study with extension period 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 naïve 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 BYETTA 5 µg, BYETTA 10 µg or 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. No new safety findings were identified in this paediatric study.

Hypoglycaemia

Use with a sulfonylurea, metformin or both

In 30-week placebo-controlled studies in patients treated with exenatide in combination with a sulfonylurea, or exenatide in combination with a sulfonylurea and metformin, the incidence of hypoglycaemia was increased over that of placebo in combination with a sulfonylurea, or placebo in combination with a sulfonylurea and metformin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

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 (see Table 3). In contrast, when exenatide was used in combination with metformin, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin.

Table 3 Incidence of hypoglycaemia by concomitant antidiabetic therapy in 30-week placebo controlled studies

	Placebo	Exenatide		Placebo	Exenatide		Placebo	Exenatide	
	BID	5 µg BID	10 µg BID	BID	5 µg BID	10 µg BID	BID	5 µg BID	10 µg BID
	With metformin			With sulfonylurea			With met/sfu		
N	113	110	113	123	125	129	247	245	241
Hypoglycaemia	5.3%	4.5%	5.3%	3.3%	14.4 %	35.7 %	12.6%	19.2 %	27.8%

Exenatide and placebo were administered before the morning and evening meals.

Abbreviations: BID, twice daily; met/sfu, metformin and a sulfonylurea.

In the long-term active comparator (26 weeks or greater) studies in which all patients also received both metformin and a sulfonylurea the incidence of hypoglycaemia was similar for exenatide and insulin treatment (either insulin glargine or biphasic insulin aspart). Exenatide patients reported fewer episodes of nocturnal hypoglycaemia than insulin patients in both insulin glargine-comparator study ($p<0.001$) and the biphasic insulin aspart-comparator study ($p=0.0384$).

To reduce the risk of hypoglycaemia associated with the use of a sulfonylurea, reduction in the dose of sulfonylurea may be considered (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use with insulin

When exenatide was added to existing titrated basal insulin therapy (insulin glargine), the incidence and types of adverse events observed were similar to those seen in the controlled clinical trials with exenatide in combination with metformin and/or sulfonylurea (see Table 4).

Table 4 Treatment-emergent adverse events (≥5% incidence in exenatide treated patients)

System Organ Class Preferred Term	Frequency of occurrence	
Events	Exen + Ins Glar	Placebo + Ins Glar
	N=137	N=122
Gastrointestinal disorders		
Nausea	41%	8%

System Organ Class Preferred Term	Frequency of occurrence	
Events	**Exen + Ins Glar**	**Placebo + Ins Glar**
	N=137	**N=122**
Vomiting	18%	4%
Diarrhoea	18%	8%
Dyspepsia	7%	2%
Constipation	10%	2%
General disorders and administrative site conditions		
Asthenia	5%	1%
Infections and infestations		
Nasopharyngitis	6%	5%
Upper respiratory tract infection	8%	7%
Musculoskeletal and connective tissue disorders		
Back pain	7%	2%
Nervous system disorders		
Headache	14%	4%
Respiratory, thoracic, and mediastinal disorders		
Cough	5%	6%

Abbreviations: Exen = exenatide; ILPS = insulin lispro protamine suspension; Ins Glar = insulin glargine.

Nausea

The most frequently reported adverse reaction, mild to moderate nausea, occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased in most patients who initially experienced nausea.

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.

In the three long-term placebo controlled trials in adults 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. In about half of this 6% (3% of the total patients given exenatide in the controlled studies), the glycaemic response to exenatide appeared diminished; the remainder had a glycaemic response consistent with that of patients without antibodies. Patients who developed anti-exenatide antibodies tend to have more injection site reactions (for example: redness of skin and itching), but otherwise had similar rates and types of adverse events as those with no anti-exenatide antibodies. In the insulin-comparator

controlled trials comparable efficacy and adverse events were observed in exenatide treated patients with and without antibody titres. Examination of antibody-positive specimens from one long-term uncontrolled study revealed no significant cross-reactivity with related endogenous peptides (glucagon or GLP-1).

Injection site reactions

Injection site reactions have been reported in approximately 5.7% of subjects receiving exenatide in long term (26 weeks or longer) controlled clinical trials. These reactions have usually been mild and usually did not result in discontinuation of exenatide.

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia (DITP) with exenatide-dependent anti-platelet antibodies has been reported in the post-marketing 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 sensitising drug.

Spontaneous data

General: Common (≥1% and <10%): injection-site reactions.

Gastrointestinal disorders: Uncommon (≥0.1% and <1%): abdominal distension, abdominal pain, eructation, constipation, flatulence, delayed gastric emptying. Rare (≥0.01% and <0.1%): acute pancreatitis, intestinal obstruction including ileus. Very rare (<0.01%): cases of ischaemic colitis and gut ischaemia have been reported.

Nervous System disorders: Uncommon (≥0.1% and <1%): dysgeusia. Rare (≥0.01% and <0.1%): somnolence.

Investigations: Rare (≥0.01% and <0.1%): INR increased with concomitant warfarin use, some reports associated with bleeding (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Immune system disorder: Very rare (<0.01%): anaphylactic reaction.

Skin and subcutaneous disorders: Rare (≥0.01% and <0.1%): angioedema, generalised pruritus and/or urticaria, macular or papular rash, alopecia.

Metabolism and nutritional disorders: Rare (≥0.01% and <0.1%): dehydration, generally associated with nausea, vomiting, and/or diarrhoea, weight decreased (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Weight loss).

Renal and urinary disorders: Rare (≥0.01% and <0.1%): acute renal failure, chronic renal failure, renal impairment, increased serum creatinine (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Weight loss).

Blood and lymphatic system disorders: Frequency not known: Drug-induced thrombocytopenia.

Hepatobiliary disorders: Uncommon (≥0.1% and <1%): cholelithiasis, cholecystitis.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In a clinical study of exenatide, three patients with type 2 diabetes each experienced a single overdose of 100 µg SC (10 times the maximum recommended dose). One of the three patients experienced severe hypoglycaemia requiring parenteral glucose administration. The three patients recovered without complication.

In a spontaneously reported case of overdose, a patient was administered the total contents of an exenatide pen (approximately 300 µg) that had been transferred to a syringe. The patient subsequently experienced severe nausea and vomiting, which resolved within 24 hours. The patient did not experience hypoglycaemia or a decline in blood glucose.

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

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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*. This leads to an increase in both the glucose-dependent insulin synthesis and secretion from pancreatic beta-cells, by mechanisms involving cyclic AMP and/or other intracellular signalling pathways. As blood glucose concentrations decrease, insulin secretion subsides thereby reducing the potential risk of hypoglycaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

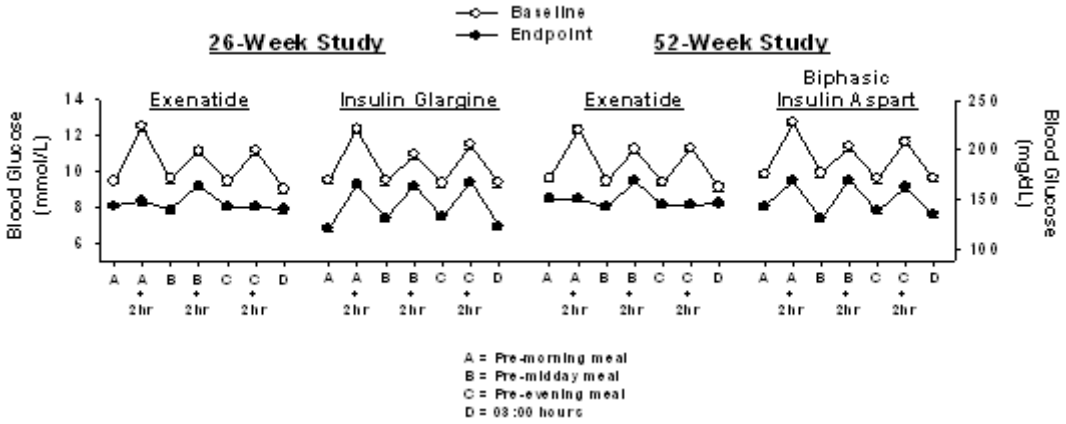
Exenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.

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. These pharmacodynamic actions occur through various mechanisms including stimulation of insulin secretion during hyperglycaemia, suppression of glucagon, and slowing of gastric emptying.

In the insulin-comparator controlled studies, exenatide was associated with a significant reduction in postprandial blood glucose excursions compared with insulin glargine ($p<0.0001$) and biphasic insulin aspart ($p<0.0001$) (see Figure 1).

Figure 1 Summary of 7-point self-monitored blood glucose profiles at baseline and study endpoint in the insulin-comparator controlled studies



26-week study (ITT patients (n=549)) and 52-week study (ITT patients (n=501), last observation carried forward)

Beta-cell function: exenatide stimulates insulin release – clinical trial data show that this happens acutely with benefits in glycosylated haemoglobin evident within six weeks. No clinical data are available to suggest an improvement over time in beta-cell function. Most clinical benefit in glycaemic control is seen within 12 weeks of commencement. An increase in pancreatic islet cell mass has not been consistently demonstrated in animal models.

Clinical trials

Use in combination with metformin and/or a sulfonylurea

Efficacy of exenatide in treatment of type 2 diabetes has been established in 5 pivotal placebo- or active comparator-controlled clinical trials, involving 2,496 patients, 1,498 of whom received exenatide. The primary objectives of these clinical trials were to evaluate glycaemic control, primarily as assessed by HbA_{1c}. The secondary objectives included examining the effects of exenatide on fasting and postprandial plasma glucose concentrations, body weight, and fasting concentrations of circulating insulin, proinsulin, and lipids.

Exenatide treatment results in improvement in glycaemic control as measured by HbA_{1c} over the dosing period with most benefit obtained by about the twelfth week of treatment (see Figure 2 and Table 1). In the three placebo controlled clinical trials, the mean (±SD) change from baseline in fasting plasma glucose was -0.4 ± 2.8 mmol/L and -0.6 ± 2.7 mmol/L with exenatide 5 and 10 µg BID, respectively, compared to an increase of 0.7 ± 2.9 mmol/L in the placebo arm at week 30. In addition, sustained reductions in postprandial glucose concentrations were observed during meal challenge tests at weeks 4 and 30.

In insulin comparator trials, exenatide reduced postprandial glucose excursions more than insulin glargine or biphasic insulin aspart, while insulin glargine reduced fasting glucose concentrations ($p<0.0001$) more than exenatide.

Patients treated with exenatide may exhibit progressive weight reduction. No specific studies on appetite or weight loss have been conducted. The precise mechanism of weight loss is unknown. The administration of exenatide is also associated with nausea and vomiting (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

In three separate clinical trials when exenatide was used in combination with metformin, sulfonylurea, or a combination of both, significant improvements in glucose control were observed compared to placebo (see Table 5).

Table 5 Summary of efficacy results in placebo-controlled studies (ITT subjects)

		Change From Baseline to Week 30 (LS Mean ± SE)1
	N	**HbA_{1c} (%)**
2993-112 (metformin)		
Placebo	113	0.00 ± 0.106
Exenatide 5 µg[2]	110	-0.46 ± 0.112**
Exenatide 10 µg[3]	113	-0.86 ± 0.110**
2993-113 (sulfonylurea)		
Placebo	123	0.06 ± 0.115
Exenatide 5 µg[2]	125	-0.51 ± 0.111**
Exenatide 10 µg[3]	129	-0.91 ± 0.110**
2993-115 (metformin + sulfonylurea)		
Placebo	247	0.12 ± 0.079
Exenatide 5 µg[2]	245	-0.66 ± 0.079**
Exenatide 10 µg[3]	241	-0.88 ± 0.080**

Abbreviations: N=number of subjects; OAD=oral antidiabetic agent(s); SE=standard error of the mean; SU=sulfonylurea.

Note: The last observation carried forward method was applied to impute missing values at Week 4 through Week 30.

1 Based on a general linear model with treatment, baseline HbA_{1c} strata, and site as fixed effects for 2993-112 and 2993-113; based on a general linear model with treatment, baseline HbA_{1c} strata, SU management group, and site as fixed effects for 2993-115.

2 Exenatide 5 µg is exenatide 5 µg BID (4 weeks) followed by exenatide 5 µg BID (26 weeks);

3 Exenatide 10 µg is exenatide 5 µg BID (4 weeks) followed by exenatide 10 µg BID (26 weeks).

*p<0.05, **p<0.01 for difference from placebo (p-values for the HbA_{1c} endpoint are adjusted based on Fisher's Protected Testing procedure).

When exenatide was used in combination with metformin and sulfonylurea similar improvements in glucose control were observed in two clinical trials, one comparing with insulin glargine and the other comparing with biphasic insulin aspart (see Table 6).

Table 6 Summary of efficacy results for exenatide active-comparator controlled studies (ITT subjects)

		Change From Baseline to Endpoint Least Squares Mean ± Standard Error
Study	**N**	**HbA_{1c} (%)1**
H80-MC-GWAA (metformin + sulfonylurea) – 26 weeks of treatment		
Insulin glargine^	260	-1.05 ± 0.06*
Exenatide 10 µg[2]	275	-1.00 ± 0.06*
LS Mean Difference		0.05
(95% CI (E-I))		(-0.09 to 0.20)
H80-MC-GWAD (metformin + sulfonylurea) – 52 weeks of treatment		
Biphasic insulin aspart^^	246	-0.88 ± 0.07*
Exenatide 10 µg[2]	248	-0.98 ± 0.07*
LS Mean Difference		-0.10
(95% CI (E-I))		(-0.28 to 0.08)

Abbreviations: N=number of subjects; SE=standard error of the mean; LS=least squares

Note: The last observation carried forward method was applied to impute missing values for HbA_{1c} and fasting glucose.

1 Based on a general linear model with treatment, country, and baseline value of the dependent variable as fixed effects.

2 Exenatide 10 µg is exenatide 5 µg BID (4 weeks) followed by exenatide 10 µg BID for the remaining duration of the study.

CI (E-I)=the 2-sided, 95% Confidence Interval for the least squares (LS) mean difference between treatments (exenatide-insulin).

*p<0.0001 for difference within treatment, **p<0.0001 difference between treatment

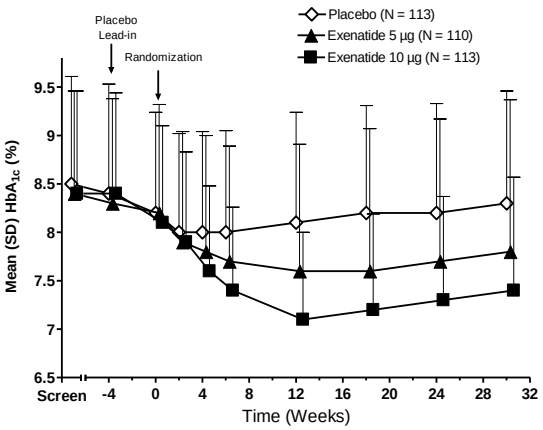
^ GWAA: At week 26, the mean dose of insulin glargine was 25.0 Units/day.

^^ GWAD: At week 52, the mean dose of premixed biphasic insulin aspart was 24.4 Units/day.

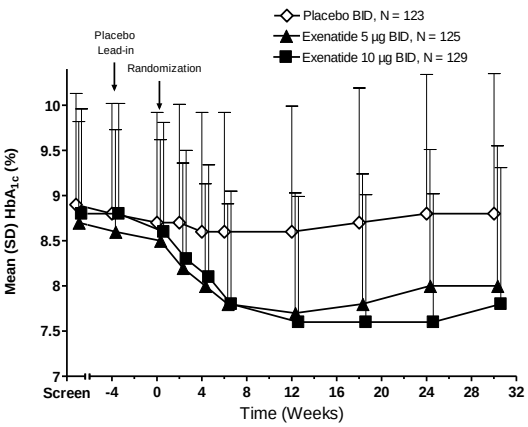
The glucose lowering effect of exenatide can be seen immediately following the first injection. The average reduction in HbA_{1c} (approximately 1%) is generally observable by 12 weeks after initiation of treatment. Figure 2 shows the mean HbA_{1c} over time in patients with type 2 diabetes using exenatide or placebo together with metformin, sulfonylurea, or a combination of both. A sustained reduction of HbA_{1c} has been shown through at least 52 weeks of therapy in a controlled study and 82 weeks in uncontrolled studies. In the 30 week placebo-controlled studies, 33.6% of patients using exenatide 10 µg BID together with metformin, sulfonylurea or a combination of both achieved HbA_{1c} ≤7.0%. The ≤7.0% HbA_{1c} goal was achieved by 46.4% of exenatide-treated versus 48% of insulin glargine-treated subjects in the 26 week study and by 31.7% of exenatide-treated and 24.1% of biphasic insulin aspart-treated subjects in the 52 weeks study (see Table 7).

Figure 2 Mean (SD) HbA_{1c} by visit in placebo-comparator controlled studies of patients also taking metformin, sulfonylurea or a combination of both

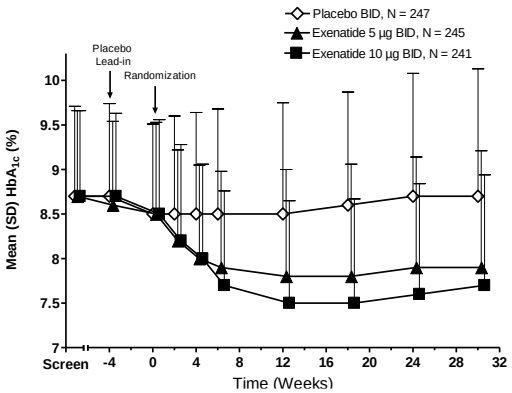
Study 2993-112 Exenatide with metformin alone (ITT population N = 336)



Study 2993-113 Exenatide with sulfonylurea alone (ITT population N = 377)



Study 2993- 115 Exenatide + metformin+ sulfonylurea (ITT population N = 733)



The LOCF method was applied to impute missing HbA_{1c} values at Week 4 through Week 30.

Patients randomised to exenatide 5 µg BID (4 weeks) followed by exenatide 5 µg BID (26 weeks) or exenatide 5 µg BID (4 weeks) followed by exenatide 10 µg BID (26 weeks).

Abbreviations: BID=twice daily before meals in the morning and evening; SD=standard deviation, ITT=intention to treat

Table 7 Number and proportion of subjects achieving HbA_{1c} of ≤7.0% (ITT subjects)

Studies 2993-112, 2993-113, 2993-115 combined (30 weeks)		Study H80-MC-GWAA (26 weeks)		Study H80-MC-GWAD (52 weeks)	
Exenatide*	Placebo	Exenatide*	Insulin Glargine	Exenatide*	Biphasic insulin aspart
152 (33.6%)	36 (7.9%)	117(46.4%)	110 (48.0%)	72 (31.7%)	57 (24.1%)

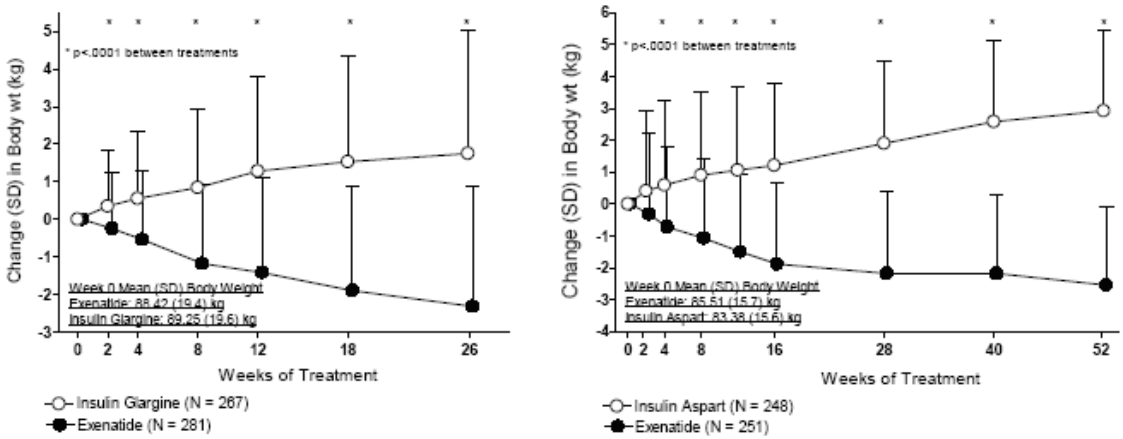
* Exenatide 10 µg, given as 5 µg BID for 4 weeks followed by 10 µg daily for remainder of study
Includes subjects whose baseline HbA_{1c} values were >7%

Body weight

Exenatide significantly reduced patient body weight in Phase 3 studies (placebo and insulin comparator controlled). Patients who continued in an uncontrolled open label extension to the placebo controlled studies continued to lose weight through 82 weeks of treatment. The long term outcomes (morbidity, mortality, or the clinical benefits) associated with these effects have not been studied.

Weight loss of 2.3 kg (2.6%, p<0.0001) was achieved in a 26-week insulin glargine comparator study and a loss of 2.5 kg (2.7%) in a 52-week biphasic insulin aspart comparator study whereas treatment with insulin was associated with weight gain (refer to Figure 3).

Figure 3 Least squares mean change in body weight in patients taking exenatide compared with insulin glargine or insulin aspart (ITT subjects)

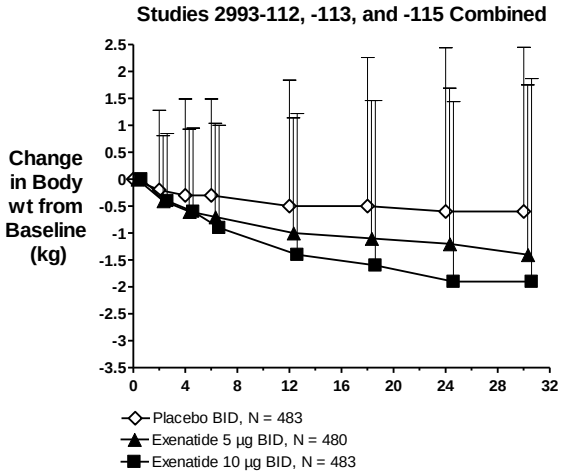


The total estimated treatment difference (exenatide minus comparator) was -4.1 kg in the 26-week study and -5.4 kg in the 52-week study.

The results of three 30 weeks randomised triple-blind, placebo controlled trials showed significantly greater reductions from baseline in bodyweight with exenatide

5 or 10 µg BID daily than with placebo in patients receiving exenatide and metformin alone (-1.3 kg and -2.6 kg versus -0.2 kg) or exenatide and metformin plus a sulfonylurea (-1.6 kg and -1.6 kg vs -0.9 kg). In patients receiving exenatide and sulfonylurea only, only patients on exenatide 10 µg BID achieved a significantly greater reduction in body weight than placebo (-1.6 kg versus -0.8 kg) (also refer to Figure 4).

Figure 4 Change in body weight over time for the placebo-controlled studies - combined (ITT subjects, N=1446)



In patients receiving exenatide and metformin alone, weight reduction was statistically significant for patients with a baseline BMI <30 kg/m^2 and ≥30kg/m^2 for exenatide 10 µg BID but not for the exenatide 5 µg BID compared with placebo. For patients receiving exenatide and sulfonylurea alone, the change in body weight was statistically significant in patients with a baseline BMI <30 kg/m^2 for exenatide 10 µg BID compared with placebo but not for exenatide 5 µg BID or patients with a BMI ≥30 kg/m^2. For the exenatide with metformin and sulfonylurea patients, a statistically significant reduction in body weight was observed for each exenatide treatment (5 µg, BID and 10 µg, BID) compared with placebo with baseline BMI ≥30 kg/m^2 but not for subjects with baseline BMI <30 kg/m^2.

The observed weight loss was not necessarily secondary to nausea and other gastrointestinal side effects, as weight loss was also observed in those subjects who did not experience these adverse events.

Effect on lipids

Exenatide has shown no adverse effects on lipid parameters. A trend for a decrease in triglycerides has been observed. An improvement in high density lipoprotein and an improvement in triglyceride levels have been correlated with greater weight loss at 82 weeks in exenatide treated patients. The long term outcomes (morbidity, mortality, or the clinical benefits) associated with these effects have not been studied.

Use in combination with a basal insulin

In a 30 week study, either exenatide (5 µg BID for 4 weeks, followed by 10 µg 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, exenatide (n=137) demonstrated a statistically significant reduction in HbA_{1c}, the primary objective of the study. In relation to the secondary objective, body weight also was significantly reduced compared to placebo in patients receiving titrated insulin glargine. Based on additional secondary objectives, the proportion of patients achieving HbA_{1c} <7% and ≤6.5% was greater in patients treated with exenatide compared to placebo. Reductions in insulin units/day, fasting serum glucose and postprandial glucose excursions after the morning and evening meal were greater with exenatide compared to placebo
(see Table 8).

Table 8 Summary of efficacy results for exenatide in combination with basal insulin compared to placebo (ITT subjects)

Variable	Least Squares Mean or Percentage of subjects		Between Treatment Difference (95% CI)
	Exenatide (N=137)	Placebo (N=122)	
Primary Objective			
Haemoglobin (A_{1c}%)			
Baseline	8.3	8.5	-0.20
Week 30	6.7	7.4	-0.71 (-0.95 to -0.47)
Change	-1.7	-1.0	p<0.001
Secondary Objectives			
Proportion reaching glycaemic target			
Haemoglobin A_{1c} <7.0%	56%	29%	--
Haemoglobin A_{1c} ≤6.5%	42%	13%	--
Body weight (kg)			
Baseline	95.4	93.8	1.6
Week 30	93.6	96.3	
Change	-1.78	+0.96	-2.74 (-3.74 to -1.74)
Change in insulin dose at Week 30			
U/day	13	20	-6.5 (-12.24 to -0.79)
U/kg	0.15	0.20	-0.05 (-0.10 to 0.00)

Variable	Least Squares Mean or Percentage of subjects		Between Treatment Difference (95% CI)
	Exenatide (N=137)	Placebo (N=122)	
Fasting serum glucose (mmol/L)			
Baseline	7.4	7.4	-0.01
Week 30	6.1	6.5	
Change	-1.28	-0.87	-0.41 (-0.99 to 0.18)
Change in glucose excursion (mmol/L)			
Morning 2-hour	-2.0	-0.2	-1.8 (-2.5 to -1.2)
Midday 2-hour	-0.5	-0.3	-0.3 (-0.8 to 0.3)
Evening 2-hour	-1.6	0.1	-1.7 (-2.3 to -1.1)

Abbreviations: CI=confidence interval.

When exenatide was added to existing basal insulin therapy (insulin glargine), the dose of basal insulin was decreased by 20% in patients with an HbA_{1c} ≤8.0%, per protocol design in order to minimise the risk of hypoglycaemia. Both treatment arms were titrated to achieve target fasting plasma glucose levels. There were no clinically significant differences in the incidence of hypoglycaemic episodes in the exenatide group compared to the placebo group (25% and 30% respectively). There were no episodes of major hypoglycaemia in the exenatide arm.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following subcutaneous administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2.1 hours. 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 µg dose of exenatide. Exenatide exposure (AUC) increased proportionally over the therapeutic dose range of 5 µg to 10 µg. The C_{max} values increased less than proportionally over the therapeutic dose range of 5 µg to 10 µg. Similar exposure is achieved with subcutaneous administration of exenatide in the abdomen, thigh, or arm. Following subcutaneous administration of a single 10 µg dose of exenatide in the abdomen, thigh and arm, mean C_{max} was 251 pg/mL, 220 pg/mL and 245 pg/mL, respectively; mean AUC was 1200 pg*h/mL, 1130 pg*h/mL and 1080 pg*h/mL, respectively.

Distribution

The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of exenatide is 28.3 L.

Metabolism

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation.

Excretion

The mean apparent clearance of exenatide in humans is 9.1 L/h and the mean terminal half-life is 2.4 hours. These pharmacokinetic characteristics of exenatide are independent of the dose. In most individuals, exenatide concentrations are measurable for approximately 10 hours post-dose.

Special populations

Patients with renal impairment

In patients with mild to moderate renal impairment (creatinine clearance 30 to 80 mL/min), exenatide clearance was only mildly reduced compared to clearance in individuals with normal renal function. Clearance was significantly reduced to 0.9 L/h in patients with end-stage renal disease receiving dialysis compared with 9.1 L/h in healthy subjects (see Sections 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.3 CONTRAINDICATIONS, and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients with hepatic insufficiency

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

Gender, race, or obesity

Gender, race or obesity has no significant influence on exenatide pharmacokinetics.

Elderly patients

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

In patients with type 2 diabetes, administration of exenatide (10 µg) 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 DOSE AND METHOD OF ADMINISTRATION).

Paediatric patients

In a single-dose pharmacokinetic study in patients with type 2 diabetes between the ages of 12 and 16, administration of exenatide (5 µg) resulted in pharmacokinetics similar to those observed in the adult population.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Exenatide was not genotoxic in bacterial reverse mutation assays, *in vitro* chromosomal aberration tests in Chinese hamster ovary cells or a mouse micronucleus assay.

Carcinogenicity

In female rats given exenatide for 2 years, an increased incidence of benign thyroid C-cell adenomas was observed at the highest dose (250 µg/kg/day), a dose that produced an exenatide plasma exposure 110 times the human clinical exposure at 20 µg/day. There was no tumorigenic response in male rats or either sex of mice at exposures 80 (mouse) and 110 (rat) times the human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients in BYETTA are metacresol, mannitol, glacial acetic acid, sodium acetate, and water for injections.

6.2 INCOMPATIBILITIES

Exenatide must not be mixed with other medicines.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2ºC to 8ºC. Refrigerate. Do not freeze. Protect from light.

Once in use the BYETTA pen should be kept below 25°C and away from direct heat and light. Shelf life for pen in use is 30 days. The pen should be discarded 30 days after use, even if some medicine remains in the pen.

The BYETTA pen should not be stored with the needle attached.

6.5 NATURE AND CONTENTS OF CONTAINER

BYETTA is supplied in a Type 1 glass cartridge that has been assembled into a disposable pen-injector (pen). Pack size of 1 BYETTA pen.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Exenatide is a 39-amino acid peptide amide. It has the empirical formula $C_{184}H_{282}N_{50}O_{60}S$ and molecular weight of 4186.6 Daltons. The amino acid sequence for exenatide is shown below.

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.

CAS number

141732-76-5.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription only medicine)

8. SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
Macquarie Park NSW 2113

Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

13 June 2007

10. DATE OF REVISION

12 September 2022

Summary table of changes

Section changed	Summary of new information
4.2	Information regarding paediatric patients updated.
4.4	Information regarding paediatric patients updated.
4.8	Information regarding paediatric study added. New adverse drug reactions – intestinal obstruction including ileus, cholelithiasis, and cholecystitis.
5.2	Information regarding paediatric patients added.