SCIENTIFIC DISCUSSION

Introduction

The hallmark of diabetes mellitus is hyperglycaemia resulting from impaired carbohydrate metabolism.
Type 2 diabetes has a complex pathophysiology characterised by deficient insulin activity arising from decreased insulin secretion secondary to beta-cell failure, compromised insulin action in peripheral target tissues (insulin resistance), or a combination of the two abnormalities. This abnormal metabolic state is exacerbated by excess hepatic glucose production and altered metabolism of proteins and lipids, which along with hyperglycaemia, contribute to microvascular and macrovascular complications.
Type 2 diabetes accounts for approximately 85% to 95% of diabetes cases in developed regions like the European Union. Age and weight are established risk factors for type 2 diabetes. The majority of patients with type 2 diabetes are overweight or obese.
Diet modification and exercise is the first line treatment for type 2 diabetes. Pharmacologic intervention with one oral antidiabetic agent (OAD) such as metformin or sulphonylureas or several OADs in combination is usually the next step in treatment. Other second line oral treatment alternatives include alpha-glucosidase inhibitors, meglitinides and thiazolidinediones.
Currently, insulin is the remaining treatment option for patients who are no longer achieving good glycaemic control on OADs. Different insulin regimens are used in type 2 diabetes; basal insulin or an insulin mixture is often added to existing OAD therapy. Appropriate insulin doses require self-monitoring of blood glucose and insulin use is often associated with weight gain.
For patients with type 2 diabetes who are no longer achieving good glycaemic control on OADs, an effective and safe alternative to insulin could be beneficial.
BYETTA contains exenatide which is an incretin mimetic. Endogenous incretins, such as glucagon-like peptide 1 (GLP-1), facilitate insulin secretion following their release from the gut into the circulation in response to food intake.
Incretin mimetics have multiple anti-hyperglycaemic actions that mimic some of the effects of GLP-1. These actions are different from the actions of any other currently approved therapeutic agent, and together these actions cannot be duplicated by existing therapeutics.

The therapeutic indication for exenatide is:

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

The proposed dosing recommendation is as follows:

- Exenatide therapy should be initiated at 5 µg per dose administered twice daily (BID) for at least 1 month. The dose of exenatide can then be increased to 10 µg BID .

Exenatide solution for injection is a clear parenteral solution intended for subcutaneous (SC) injection. The product is supplied in two multiple-dose cartridge presentations (1.2 ml and 2.4 ml) containing sterile preserved solutions with the same concentration, which are assembled into disposable pen-injector devices.
Each pen contains 60 doses allowing one month treatment since the product has to be administered twice a day subcutaneously.

Quality aspects

Introduction

BYETTA solution for injection is a parenteral drug product for subcutaneous administration. The formulation contains 250 µg/ml exenatide as the active substance.

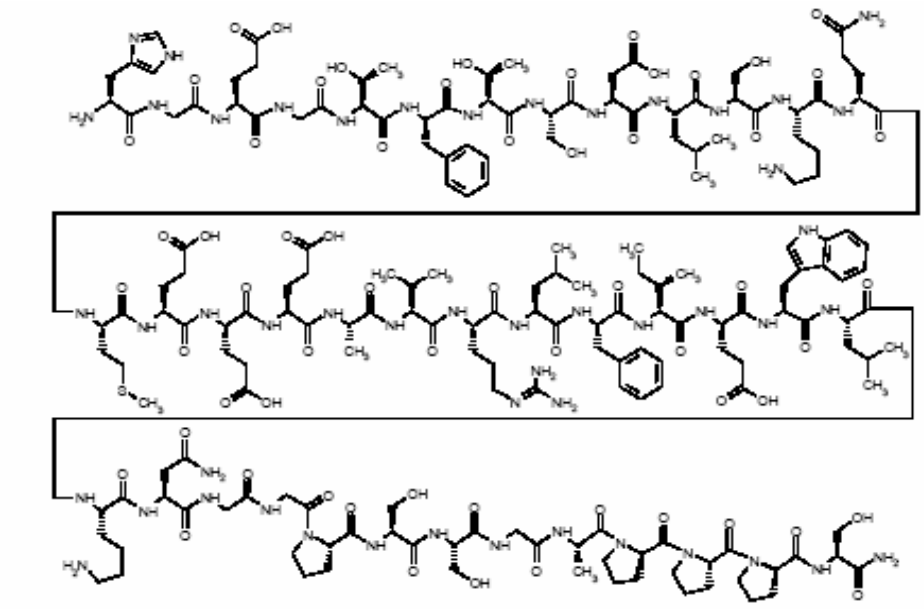
The other ingredients include water for injections, acetic acid and sodium acetate, metacresol and mannitol.

The product is supplied in two multiple-dose cartridge presentations (1.2 ml and 2.4 ml) containing sterile preserved solutions with the same concentration, which are assembled into disposable pen-injector devices.

The 5µg pen (1.2 ml) delivers 5 µg of exenatide per dose and the 10µg pen (2.4 ml) delivers 10 µg. Each pen contains 60 doses allowing one month treatment before disposal since the product has to be administered twice a day subcutaneously.

Active Substance

Exenatide is a chemically synthesized peptide:



- Manufacture

Exenatide is synthesised by two manufacturers using 9-fluorenyl-methoxycarbonyl (Fmoc) solid-phase peptide chemistry. The synthesis using protected L-amino acids has been stereochemically controlled.
Satisfactory specifications and associated methods have been provided for raw materials, starting materials, solvents and reagents used in the preparation of exenatide. Adequate process flow diagrams and overviews of the manufacturing processes were provided.
After synthesis, the resin-bound peptide is cleaved from the resin and the crude peptide undergoes a series of processing steps, including purification (by reversed-phase chromatography), and isolation to produce exenatide drug substance.
Exenatide is freely soluble in water and in various solvents. Exenatide is hygroscopic and has to be protected from humidity during storage. Process-related impurities associated with exenatide from each manufacturer and potential degradation products generated from exenatide have been extensively discussed.
The structure of exenatide is confirmed by chemical and spectroscopic data supporting the composition, the primary sequence, the secondary and higher order structure.
Techniques used involve amino acid analysis, mass spectrometry, High-Pressure Liquid Chromatography (HPLC), proteolytic mapping, and peptide sequencing.,circular dichroism, Nuclear Magnetic Resonance (NMR), analytical ultracentrifugation, and light scattering studies.
Results of the testing have shown that chemical, physical and biological properties of exenatide produced by the two manufacturers are comparable. The impurity profiles of exenatide differ slightly

for both suppliers however this should have no impact on the risk/benefit balance. For the future, the impurity profiles will be monitored.

- Specification

Appropriate specifications for exenatide have been set including parameters such as appearance, identification, assay, product-related impurities, residual solvents, acetate content, and microbial limit.
Impurity limits have been adequately justified by batch analysis, stability studies, toxicological and clinical studies.
Analytical Methods to control the active substance including methods such as Strong Cation-exchange chromatography (SCX-HPLC), Amino Acid Analysis, Tryptic Peptide Map, Mass Spectrometry, Assay, Reversed-Phase Chromatography (RP-HPLC), Ion Chromatography (for acetate), and Gas Chromatography (for residual solvents) have been suitably described and validated according to ICH guidelines. Methods from both manufacturers are considered equivalent.

Batch analyses for six validation lots and seven commercial lots of exenatide manufactured at the two manufacturing sites have been provided. Results comply with the specification and are consistent with batch results used in the toxicological and clinical studies.

- Stability

Results of pilot-scale batches stored in the commercial packaging under ICH conditions (-20°C up to 36 months, 5ºC for 12 months, and 25°C/60% RH 6 months) have been provided. Additional results have been presented on production batches and confirm results with primary batches.
Photostability studies have been carried out on 3 batches in accordance with ICH guideline. Exenatide is light-sensitive and therefore a protective packaging is justified.
Results showed that properly packaged exenatide is stable under the tested conditions. No significant degradation could be observed apart from a slight increase in total impurities at 25°C.
Based on the stability data, a re-test period of 2 years can be granted providing that exenatide is kept - ≤ -15 °C, protected from light and packaged under low humidity.

Medicinal Product

- Pharmaceutical Development

Adequate formulation studies have been conducted to develop a parenteral drug product for subcutaneous administration. Important formulation parameters such as solution pH, buffer species, buffer concentration, tonicity-modifying agent, and preservative have been studied and adjusted. Compendial excipients have been selected and their quantities are usual for solutions for injections and can be found in already marketed drug products. Compatibility between excipients and the active substance has been demonstrated by formulation and stability studies.
The formulation consists of 250 µg/ml exenatide in pH 4.5 acetate buffer. It contains metacresol as an antimicrobial preservative and mannitol as a tonicity modifying agent.
Adequate information on physicochemical and biological properties which are key points for the manufacturing process such as hygroscopicity, solubility, and solid-state properties has been provided.
Extensive and sufficient information on the manufacturing process development has been provided in particular regarding the standard aseptic processing techniques, the excipients, the container and the sterilizing filtration.
Since the product is a sterile product for multiple dosing, a preservative is required. The amount of preservative has been justified.

- Adventitious Agents

None of the manufacturing process used by the active substance manufacturers involves recombinant DNA technology, fermentation, or extraction of biological matrices.
Exenatide is obtained by solid phase peptide chemistry from chemically protected amino acids which are the only potential sources of transmittable spongiform encephalitis (TSE). However, the amino

acid derivatives are sourced from non-human/non-ruminant animal materials. Therefore no TSE risk can be anticipated.

- Manufacture of the Product

The manufacturing process is a standard process and can be summarized in 3 steps :
- compounding with dissolution of all components
- sterile filtration
- aseptic filling into pre-sterilised glass cartridges. Sterile filtration has been chosen since exenatide is heat sensitive.

The manufacturing process has been fully described.
Adequate in-process controls have been set during the manufacturing process.
All the excipients are described in Ph.Eur and USP and a certificate of analysis in compliance with the specification is presented for each excipient.
None of the excipients is of human or animal origin. Therefore no TSE issue is expected.

- Product Specification

Appropriate specifications have been set for the finished product and include tests such as appearance tests, identification (HPLC and mass spectrometry), assay (SE-HPLC), potency, impurities (SCX-HPLC), oligomer (SE-HPLC), subvisible particles, pH control, osmolality, preservative content (HPLC), bacterial endotoxins, and sterility. Proposed release specifications for the finished product include acceptable specification for the cartridges and for the pen-injector.
Analytical methods are appropriate and have been sufficiently described. Summaries of validations have been provided for non-compendial analytical procedures.
Batch analysis data are provided for six validation lots and three commercial lots of drug product using exenatide obtained from both manufacturers.
All results comply with the set specifications.
Additional results of production scale batches manufactured at BPS will be submitted when available.

Container Closure System

Exenatide solution for injection is a kept in a Type I clear glass cartridge of 1.5 or 2.7 ml, sealed with a rubber disc with an aluminum over-seal and a rubber plunger.
The two cartridge presentations are assembled into pen-injectors designed to deliver 60 doses. The pen-injectors deliver 5 µg (20 µl) or 10 µg (40 µl) doses of exenatide.
Specifications have been provided. Materials used comply with the Ph. Eur. requirements.
Compatibility of the container closure system with exenatide solution for injection has been demonstrated by stability studies.
The medical device, consisting of pre-filled, disposable pen-injector has been adequately described. Information on the pen-injector and its ability with regard to dose accuracy has been provided. The cartridge assembled in the pen-injector is protected for light since exenatide is sensitive to light-exposure.

- Stability of the Product

Primary stability studies were carried out with a total of 11 batches (pilot-scale and commercial batches) under the following conditions: up to 30 months at 5°C/ambient RH, 12 months at 15°C/75%RH, 6 months at 25°C/60%RH, and photostability.
Parameters tested include physical appearance, assay, potency, product-related impurities, pH, metacresol, subvisible particles, sterility, bacterial endotoxins, and anti-microbial preservative effectiveness.
The product remained rather stable and the only trend observed was an increase in product-related impurities.
Photostability studies performed, in line with ICH Q1B Guideline, indicate that the drug product should be protected from light exposure.
In-use stability studies reflecting the condition of use have been performed. Results remained within the proposed specifications and support the in-use period of 30 days when it is stored at 5°C protected from light and in-use storage for 7 days at room temperature.

Stability data support the proposed shelf-life (before opening and in-use) and storage conditions as defined in the Summary of Product Characteristics.

Discussion on chemical, pharmaceutical and biological aspects

Generally satisfactory documentation has been provided. The active substance is well-characterised and the retained specification including the impurities level are acceptable taking into consideration the type of active substance (peptide) and the various guidelines.
Results showed that exenatide is stable and stability data support the proposed re-test period providing that exenatide is kept -≤ -15 °C, protected from light and packaged under low humidity.
Regarding the finished product, the manufacturing process is adequately described and controlled. It should ensure a consistent quality for the product. Appropriate specification has been selected for this parenteral solution.
Stability studies under ICH conditions have demonstrated the good stability of the finished product. Stability data support the proposed shelf-life (before opening and in-use) and storage conditions as defined in the Summary of Product Characteristics.
At the time of the CHMP opinion, there were some outstanding quality issues with no impact on the benefit/risk. The applicant undertook to provide with the necessary information as follow-up measures within an agreed timeframe and to submit variations if required following the evaluation of this additional information.

Non-clinical aspects

Introduction

Pivotal toxicology and toxicokinetic studies were performed in accordance with GLP regulations. Cardiovascular safety pharmacology studies were GLP compliant.

Pharmacology

- Primary pharmacodynamics

In vitro studies
Exenatide and GLP-1 (glucagon-like peptide 1) bind and stimulate GLP receptors equipotently in both human- and rat-based receptor systems. Exenatide showed no binding to a number of other members of the glucagon-secretin G protein-coupled receptor super family, including the receptors for VIP and secretin. Distribution of exenatide binding sites within mouse tissue overlaps with that observed with GLP, with predominant binding in the lateral septum and basal forebrain, as well as within circumventricular organs including the area postrema. CNS mediated effects are likely to be of importance for the overall pharmacology of exenatide, through effects on food intake and gastric emptying, and are believed to be mediated through GLP-1 receptors. Significant binding was also observed in the pancreas and the outer cortex of the mouse kidney.

In vitro studies demonstrated that exenatide enhances insulin production in presence of increased glucose concentration, with no or minimal effect at basal glucose levels. Exenatide was also shown to suppress glucagon release induced by arginine. Literature studies demonstrating a GLP-1 effect on peripheral glucose utilization via receptors in various tissues such as skeletal muscle, liver and adipose tissue could not be reproduced. Several studies have demonstrated the absence of GLP-1 receptor mRNA in these tissues, hence the literature findings on effects in these tissues are considered controversial.

In vivo studies
Exenatide has been studied extensively in animal models to examine its acute and chronic effects on blood glucose control. In nondiabetic mice and rabbits, exenatide reduced plasma glucose with a maximum effect of about 30-35%. Nondiabetic rats showed an acute, paradoxical, hyperglycaemic and hyperlactemic response not demonstrated in other species. These effects were not observed in adrenalectomized rats. In diabetic mice and rats, exenatide markedly improved glucose control. Both

acute effects (reduction in fasting glucose associated with acute increases in insulin secretion) and chronic effects (decrease in plasma HbA1c and increased insulin sensitivity) were demonstrated.

The following activities of exenatide were demonstrated in the animal models:

- Increased insulin secretion
- Suppressed basal and postprandial glucagon secretion
- Slowed gastric emptying
- Reduced food intake and body weight
- Improved insulin sensitivity
- Stimulation of islet neogenesis

These effects may all contribute to the pharmacological activity of exenatide in the targeted patient population.

Since hypoglycaemia is a common safety problem during treatment of diabetes, some aspects of the exenatide pharmacology deserve further attention. The applicant has discussed the potential negative consequences of reduced glucagon secretion and slowed gastric emptying under hypoglycaemic conditions. Glucagon-stimulated release of glucose from the liver is an important part of the counterregulatory response to hypoglycaemia, and self-administration of oral carbohydrate is an important means to raise plasma glucose for patients experiencing hypoglycaemia. It was demonstrated that the slowing of gastric emptying was abrogated in animals with low blood glucose. It was not convincingly demonstrated that the effect on glucagon secretion was similarly abrogated by low glucose. However, clinical studies have shown that the glucagon response is not impeded by exenatide in hypoglycaemic situations.

- Secondary pharmacodynamics

Several reports have indicated that GLP-1 can significantly reduce pancreatic exocrine secretion, inhibit gastric emptying and gastric acid secretion. However, exenatide showed no effect on cholecystokin (CCK-8)-stimulated secretion of amylase and lipase in rat, nor did single s.c. doses of exenatide had a significant effect on pentagastrin-stimulated gastric acid secretion in cannulated rats.

Acute administration of exenatide did not affect basal plasma levels of follicle stimulating hormone, luteinising hormone, testosterone, or thyroid hormones T3 and T4 in nondiabetic rats. Exenatide has been shown to reduce plasma levels of thyroid stimulating hormone in rats. The paradoxical increase in plasma levels in response to exenatide observed in nondiabetic rats (but not in other species) appears to be mediated by catecholamines. Exenatide-related effects on cortisol serum concentration have been evaluated as part of the clinical program.

- Safety pharmacology programme

In a CNS safety pharmacology study in mice, grip strength and limb tone were transiently slightly reduced, and there was a dose-dependent decrease in spontaneous motor activity. A reduction in general activity was also observed in a cardiovascular safety pharmacology in monkeys, but the effect was not dose-related. The CNS effects which occurred at doses and C_{max} levels substantially higher than in the clinic, are likely to be due to activity on GLP-1 receptors within the CNS.

A single iv dose of exenatide produced a dose-dependent increase in mean arterial blood pressure and heart rate in rats. No hypertensive effects were observed in mice or in monkeys. No effects on ECG, arterial pressure or heart rate were observed in monkeys.

Exenatide produced an acute, profound diuresis and natriuresis in rats following iv dosing. Similar but less potent effects were observed in mice. There was no evidence of a renal pathology in any of the repeat-dose toxicity studies in mice, rats or monkeys.

- Pharmacodynamic drug interactions

No specific non-clinical pharmacology studies to evaluate drug interactions have been performed, which was found to be acceptable by the CHMP.

Pharmacokinetics

A series of non-clinical studies were conducted in mice, rats, female rabbits and monkeys to determine the PK parameters for exenatide. There were no sex differences for mice, rats and monkeys. In general, for sc administration, C_{max} and AUC increased dose-linearly. Terminal half-life varied from 18 minutes in mice up to 114 minutes in rats.

Whole-animal distribution studies were not done, since exenatide is composed of natural amino acids. Exenatide was shown to be transported across the placenta only to a low degree with a maximal foetal to maternal ratio of 0.035 in mice and rabbits.

As expected for a peptide, the kidney is the main organ for clearance of exenatide. No significant fragments of exenatide could be identified in vivo. Analysis of post-administration urine samples from rats failed to reveal significant concentrations of intact exenatide suggesting that proteolytic degradation may occur in the renal tubule after filtration. Exenatide, unlike GLP-1, has been shown in in-vitro studies not to be a substrate for dipeptidyl peptidase-IV (DPP-IV), being thought to be the cause for the longer plasma half-life of exenatide compared to GLP-1.

Clearance of exenatide was not changed in animals with induced liver injury. Clearance of exenatide was significantly decreased in a renal-ligation model in rats.
The transport to milk has not been adequately studied. Exenatide should therefore not be used during lactation, as mentioned in the SPC, section 4.6.

No specific non-clinical pharmacokinetic studies to evaluate drug interactions have been conducted. Because exenatide slows gastric emptying, it is likely to alter the rate of intestinal absorption of concomitant oral drugs, when administered within a certain timeframe relative to an exenatide dose. Such effects have been studied as part of the clinical program.

Toxicology

- Single dose toxicity

Single dose toxicity of exenatide was assessed in mice (iv route), rats (sc route) and monkeys (sc route). No lethality or serious toxicity was observed.

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicity studies were performed in mice (28-182 days), rats (14-91 days), and monkeys (5-273 days). Since exenatide was shown to produce paradoxical pharmacological effects in non-diabetic rats (increased blood glucose levels), the mouse was selected for pivotal chronic toxicity testing as well as for reproductive and developmental toxicity studies. No important toxicity was observed in the repeat-dose toxicity studies. Exposure at NOAEL levels were generally >100-fold higher than the human systemic exposure.

- Genotoxicity

Exenatide was negative for genotoxicity in a standard package of in vitro and in vivo genotoxicity assays in bacteria, mammalian cells, and rodents.

- Carcinogenicity

There was no evidence for carcinogenicity in the mouse. At the highest dose in female rats (250 µg/kg/day, 130 times human exposure), an increased incidence of benign thyroid C-cell adenomas was observed. The numerical increase in tumours was not statistically significant when adjusting for survival. There was no increased incidence in C-cell carcinomas. The exposure margin at the NOEL (70 µg/kg) was 22. The findings were found to not raise concerns for human safety.

- Reproduction Toxicity

Exenatide showed no effect on fertility and early embryonic development in mice. In the embryo-foetal toxicity studies in mice and rabbits, maternal food consumption and body weights were reduced. In both species, developmental toxicity occurred in conjunction with maternal toxicity. Pregnant

rabbits exhibited a particularly high sensitivity to the anorexogenic activity of exenatide. In mice, foetal growth was slowed, and there were skeletal variations associated with slowed foetal growth, including changes in number of rib pairs or vertebral ossification sites and wavy ribs. The NOEL for developmental toxicity in mice was 6 μg/kg/day (3 times the human exposure). In rabbits, developmental toxicity was manifested as morphologic markers of foetal growth retardation (umbilical hernias and skeletal variations). In a second rabbit study, additional groups were pair-fed (fed the same average daily amount of food) to match the three exenatide-dosed groups. In the pair-fed animals, skeletal variations occurred at similar incidences in exenatide and pair-fed animals. Umbilical hernias were not observed in pair-fed animals. However, the pair-fed animals did not demonstrate maternal toxicity to the same extent as exenatide-dosed animals. In exenatide-treated animals but not in pair-fed animals, water consumption and body weights were decreased. The NOEL for developmental toxicity in rabbits was 2 μg/kg/day (12 times human exposure).
In the perinatal and postnatal developmental toxicity study in mice, developmental effects occurred in the F1 offspring in conjunction with maternal toxicity. Developmental toxicity was indicated by increased perinatal and neonatal mortality in the F1 offspring of the high-dose group (760 μg/kg/day), and by reduced growth in the F1 offspring of the mid-dose group (68 μg/kg/day). The NOEL for developmental toxicity was 6 μg/kg/day (3 times human exposure).

It thus has been concluded, that exenatide is not considered teratogenic.The control of blood glucose is of great importance during pregnancy and this is best achieved by insulin treatment. Exenatide should therefore not be used during pregnancy, which is reflected in the SPC section 4.6.

- Local Tolerance

Local tolerability of exenatide was evaluated as clinical observations and morphologic pathology of injection sites in mice, rats and monkeys. Microscopic changes of minimal to moderate severity were common to both vehicle and exenatide-treated animals.

- Studies on Antigenicity

Exenatide was weakly antigenic or non-antigenic in rodents and weakly antigenic in monkeys. The formation of anti-exenatide antibodies in monkeys was not dose-dependent. The antibodies were not neutralizing, but they did result in altered pharmacokinetics. There were no apparent adverse effects of anti-exenatide antibody formation.

- Immunotoxicity

Exenatide-related effects on the immune system were evaluated as part of the 9-months repeat-dose toxicity study in monkeys, where no effect on the antibody response to keyhole limpet hemocyanin (KLH) was seen.

Ecotoxicity/environmental risk assessment

No risk to the environment from the use of exenatide is expected.

Clinical aspects

Introduction

The application was submitted as a complete dossier for a new chemical entity. Exenatide is the first of a class of agents known as incretin mimetics.

The proposed therapeutic indication for exenatide was:
Treatment of type 2 diabetes in combination with metformin, a sulphonylurea, or a combination of metformin and a sulphonylurea.

The approved indication is:

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

The posology proposed and approved was for two strengths: 5 µg exenatide per dose administered twice daily (BID) for at least one month in order to improve tolerability. 10 µg BID subsequently to further improve glycaemic control.

As of the data cut off date (15 June 2005) for the submission, the exenatide clinical development programme consisted of 31 completed studies. Approximately two-thirds of these studies were designed for the primary purpose of assessing clinical pharmacology. The programme also included 3 short-term (28-day exposure) and 5 long-term (26-week to 52-week exposure) controlled studies as well as 3 uncontrolled studies. The 5 long-term controlled studies consisted of 2 active-comparator trials and 3 placebo-controlled trials. Additional safety data were provided during the review Two clinical studies will be conducted as post marketing commitments.

The sponsor sought scientific advice from the CHMP in 2003 and in 2004 regarding the clinical development of exenatide as adjunctive therapy to sulphonylurea, metformin, or combination therapy. The questions focused mostly on the appropriateness of non-inferiority margins, treatment durations, appropriateness of comparators, and pre-study OAD doses required in the design of long-term active-comparator controlled studies and on clinical pharmacology.

GCP

The applicant claimed that all clinical trials were performed in accordance with GCP. The applicant had provided a statement declaring that clinical trials were conducted according to GCP, and in accordance with the Helsinki Declaration and that clinical trials carried out outside EU met ethical requirements of Directive 2001/20/EC. It was noted that one investigational site involving 68 subjects was excluded from the primary results due to GCP violations.

Pharmacokinetics

The pharmacokinetics of exenatide has been evaluated in 21 clinical pharmacology studies mainly in type 2 diabetic patients. Pharmacokinetic information was also collected in several clinical efficacy studies and evaluated using population pharmacokinetics. Exenatide plasma concentrations were determined using an immunoenzymetric assay (IEMA). Data to support stability have been provided. It has been shown that the presence of antibodies interferes with the analysis of exenatide at least at high antibody titres. PK data in patients with high antibody titre should be interpreted with caution.

- Absorption

Following sc administration, exenatide is rapidly absorbed reaching peak concentrations in approximately 2 h. Upon sc administration of 10 µg exenatide, C_{max} is approximately 250 pg/ml and AUC 1200 pg.h/ml. Relative bioavailability of exenatide in the arm or thigh, as compared to the abdomen, was 93% and 97%, respectively. Therefore, exenatide can be administered either in the abdomen, arm or thigh, which is reflected in the SPC. The mean absolute bioavailability was estimated to >100%, likely caused by an underestimation of the AUC after iv. administration. The final formulation has been used in the phase3 studies. Cross-study comparison revealed no major differences between formulations used in early studies and the final formulation.

- Distribution

The mean apparent volume of distribution Vz/F for exenatide is 28 l. The potential for exenatide to cross the placental barrier is considered low.

- Metabolism and Excretion

Exenatide has a mean apparent clearance (CL/F) of 9.1 L/h and has a mean terminal half-life of 2.4 h. Exenatide is primarily renally cleared (by filtration and subsequent reabsorption and degradation in the renal tubules). Exenatide displays dose-proportional and time independent pharmacokinetics.

- Variability

In a combined meta-analysis of six phase 1 and 2 studies, the intrasubject variability in C_{max} and AUC were 28% and 22% respectively. Inter-individual variability for the fixed 5 or 10 µg dose ranged from approximately 20 to 60% for AUC and 30-60% for C_{max}, which is considered moderate to high. The relatively high variability is likely to be caused by the weight-dependent pharmacokinetics. When exenatide exposure was dose-weight normalised across studies, the inter-individual variability was 27% for AUC and 31% for C_{max}.

Exenatide pharmacokinetics is similar in healthy volunteers and subjects with type 2 diabetes.

Antibody status Based on the available data it is not possible to evaluate if or how exenatide PK is influenced by formation of antibodies or differences in antibody titre.

- Special populations

Renal impairment. A combined analysis of phase 1-2 data showed a reduced exenatide clearance with reduced renal function, as expected for a renally eliminated drug. In mild renal impairment CL/F was decreased by 13%, in moderate renal impairment by 36% and in ESRD by 84%. Simulations demonstrated that the exposure in patients with mild to moderate renal impairment after administration of 5 µ g bid would be within a well tolerated range, supporting that no dosage adjustment is needed in these subjects. Given the large decrease in CL/F in ESRD, use is not recommended in patients with severe renal impairment or ESRD. A warning is included in section 4.4 of the SPC. In moderate renal impairment, AUC is expected to increase on average by 50%. A cautious titration of the dose from 5 to 10 µg is therefore advised in the SPC.
Hepatic impairment. The influence of reduced hepatic function on exenatide pharmacokinetics has not been evaluated. This is acceptable given that exenatide is eliminated renally.
Weight. Based on population pharmacokinetic analysis, mean clearance and volume of distribution increased with body weight. Clearance increased approximately 2-fold and apparent volume of distribution about 4.8-fold as body weight increased from 50 kg to 160 kg. Additionally, in a meta-analysis of pooled data from Phase 1 and 2 studies, the influence of obesity (BMI) $\geq$ 30 kg/m^2 was evaluated. No statistically significant difference was observed in Vz/F in patients with BMI<30 kg/m^2 and patients with BMI $\geq$ 30 kg/m^2. Although clearance was 22% higher (statistically significant) in patients with BMI $\geq$ 30 kg/m^2, this increase is considered not clinically relevant.
Age, gender and race No specific studies have been conducted evaluating the effect of age, gender or race on the pharmacokinetics of exenatide. The influence of these (and other) demographic factors was evaluated in the population pharmacokinetic analysis. The population analysis suggests that absorption rate is more rapid in females than in males resulting in higher C_{max}. There is no difference in total exposure. This is unlikely to be of clinical relevance and does not warrant any precautions. Age (mean age 54 years, range 22-73 years) and race were not identified as covariates with significant influence on exenatide pharmacokinetics. The number of subjects >65 years was limited and there were no subjects >75 years, which is mentioned in the SPC in section 5.2. A cross-study comparison suggested no difference in exposure between Japanese and non-Japanese subjects. Additional studies in Asian subjects are ongoing.

Exenatide has not been investigated in adolescents and children. A study in adolescents is ongoing, results from which will be provided as a follow-up measure.

- Pharmacokinetic interaction studies

No in vitro data with regard to interactions were submitted. In vivo interaction studies suggest that exenatide has no effect on CYP2C9 or CYP3A4. The risk for inhibition of other CYP isoenzymes is considered to be low. Available pre-clinical data do not suggest any significant risk for induction, however an effect in humans cannot be completely excluded. Data from an ongoing interaction study with oral contraceptives (study H8O-EW-GWBC) might provide some information on the potential for induction. This study will be provided as a follow-up measure.

Exenatide delays gastric emptying, and can therefore delay the absorption, decrease the absorption rate and to some extent decrease the extent of absorption of concomitantly administered drugs. A

scintigraphy study in type 2 diabetes patients showed that exenatide displays a concentration dependent delay in gastric emptying. Data are variable, but suggest a maximum delay of 3 h and an EC_{50} (AUC resulting in a delay of 1.5 h) of about 418 pg·h/ml. At a dose of 10 µg bid, a large part of the patients will have an exposure approaching the flat part of the concentration effect curve and consequently a delay in gastric emptying of 2-3 h. The effect on gastric emptying was also evaluated using paracetamol as a marker substrate. The effect on paracetamol was most marked when paracetamol was administered 1-2 h after exenatide; C_{max} was decreased by 56%, t_{max} increased by 4 h and AUC decreased by 23%. The effect was decreasing at 4 h after exenatide dosing (41% decrease in C_{max} and 1 h delay in t_{max}). No effect was observed when paracetamol was administered one h before exenatide.
The effect on digoxin, warfarin, lisinopril and lovastatin administered about 30 min after exenatide was evaluated. For digoxin, warfarin and lisinopril there was a delay in t_{max} of about 2 h and usually a slight decrease in C_{max} but no significant effect on AUC. For lovastatin, t_{max} was increased 4 h, and AUC and C_{max} decreased by 40 and 28% respectively. Retrospective analysis of statin users from the Phase 3 studies showed no clinically relevant change in lipid parameters or dosage between exenatide or placebo arms. However, as a precaution it is mentioned in the SPC section 4.5 that lovastatin exposure may be lowered and that one should be aware of possible changes in LDL-C or total cholesterol and that lipid profiles should be monitored regularly.
The effect on C_{max} and t_{max} may be significant for drugs taken 1-2 h after exenatide and could also result in a clinically relevant reduction in AUC for drugs with narrow therapeutic index. A cautionary statement for medicinal products of either a narrow therapeutic ratio or medicinal products that require careful clinical monitoring is included in the SPC. For these drugs a reduction of C_{max} (and a potential small reduction in AUC) could be important and consequently it may be important to take these drugs in a standardised way in relation to BYETTA, so that the potential effect of BYETTA on the coadministered drug is kept constant. If such medicinal products are to be administered with food, patients should be advised to, if possible, take them with a meal when BYETTA is not administered.
Additional concern is the potential effect of exenatide on the absorption of gastroresistant formulations. The SPC, section 4.5, advises therefore that gastroresistant formulations containing substances sensitive for degradation in the stomach, such as proton pump inhibitors, should be taken at least 1 h before or more than 4 h after BYETTA injections.
Overall, exenatide pharmacokinetics has been investigated to a fair extent. Results from ongoing PK studies (two in Japanese and Chinese subjects, respectively, one interaction study with oral contraceptives, and one PK/PD study in adolescents) will be submitted as follow up measures.

Pharmacodynamics

- Mechanism of action

See also the preclinical section of this document.
Incretin hormones, such as gastric inhibitory polypeptide and glucagon like peptide 1(GLP-1), are released from the gut after food intake and are reportedly responsible for 50% to 70% of postprandial insulin release. GLP-1 administration has been shown to reduce food-intake in humans and inhibit gastric emptying. It is rapidly degraded by the protease dipeptidyl peptidase IV (DPP-IV) leading to an extremely short half-life (1 to 2 minutes). Exenatide, a 39-amino-acid peptide amide, exhibits partial amino acid sequence overlap (53%) with that of GLP-1 and mimics some glucoregulatory effects of GLP-1. In diabetic mice, exenatide is approximately 3 orders of magnitude more potent than GLP-1 in reducing plasma glucose concentrations.
The proposed glucose lowering mechanisms of exenatide include:

- beta-cell effects
  - -enhancement of glucose-dependent insulin secretion
  - -restoration of first-phase insulin secretion
  - -other beta-cell effects, including enhanced insulin synthesis and increased beta-cell mass
- glucose-dependent suppression of glucagon secretion
- slowing of gastric emptying, resulting in slowed absorption of meal-derived glucose.
- reduction of food intake

Beta-cell effects
Studies in subjects with type 2 diabetes (n=12) and healthy volunteers (n=11) showed that exenatide promoted insulin secretion under hyper-and euglycaemic conditions. This action was diminished or absent under hypoglycaemic conditions. In one study the first-phase insulin response was restored in 13 diabetic subjects. This may be an indication of improved beta-cell function.

Suppression of glucagon secretion
In studies of subjects with type 2 diabetes (n=20) and healthy volunteers (n=11) exenatide suppressed glucagon secretion after a meal compared to placebo. The glucagon response to hypoglycaemia was preserved during exenatide treatment.

Slowing of gastric emptying
Several studies of subjects with type 2 diabetes and healthy volunteers have shown that exenatide has dose-dependent gastric emptying effects. These effects manifested most prominently 1 to 2 h after administration of exenatide with a declining trend by 4 h and leads to a regulation of the inflow of nutrients into the circulation, which may lead to reduced postprandial glucose concentrations.

Food intake effects
Reductions in food intake following exenatide administration have previously been reported in a study of healthy volunteers. This may theoretically affect glucose concentrations.
The most plausible pharmacodynamic mechanism behind the reduction in weight is reductions in food intake following exenatide administration that have been documented in preclinical studies. To some extent nausea contributed to the decrease in body weight seen during treatment with exenatide, but is clearly not the sole explanation since weight reduction was seen also in patients without nausea.

PK/PD
PK/PD analyses of postprandial glucose exposure as the pharmacodynamic response variable was used to support the switch from weight-based dosing to fixed dosing before phase 3, and to support that the selected doses, 5 and 10 µg are appropriate both in antibody negative and positive patients. The PK/PD analysis and simulations support the use of a fixed dose regimen. Although weight-based dosing could result in more patients obtaining exenatide exposure within the target range, this seems to have limited impact on reduction of glucose. Hence, the decision to select a fixed dose of 10 µg for the phase 3 clinical studies seems appropriate.
A PK/PD analysis of Phase 3 data predicted a larger maximum mean effect in antibody negative subjects than in antibody positive subjects (36% and 28%, respectively). The results suggest that in patients without antibodies the proposed doses will result in exposure close to or at the top of the concentration effect curve, i.e. close to maximum efficacy. With some uncertainty this can probably be extrapolated to patients with low antibody titre. The data also suggest that a lower efficacy might be expected in high-titre anti-body positive patients. It should be noted that the variability between patients is large in relation to the quite small estimated differences in maximum effect between antibody positive and negative patients, limiting the predictability in the individual patient. Given limited and inadequate PK data in patients with high antibody titre, no conclusions can be made regarding appropriateness of the doses 5 and 10 µg in high-titer antibody positive patients.

Clinical efficacy

The clinical efficacy studies of exenatide consisted of:
●Three Phase 2, short-term placebo-controlled studies designed to evaluate the efficacy and safety of exenatide treatment. (Study 107, 116, 120).
●Three Phase 3, long-term placebo-controlled studies designed to determine the magnitude of response to adding exenatide (5 µg or 10 µg BID) to concomitant OAD therapy (Metformin [Met], a sulfonylurea [SU], or Met + SU). After completion of the placebo controlled phase these studies continued into 3 long-term uncontrolled extension studies designed to demonstrate the durability of the efficacy of exenatide treatment. (Study 112, 113, 115).
●Two Phase 3, long-term active-comparator controlled studies designed to establish the non-inferiority of exenatide treatment (10 µg BID) to insulin treatment (insulin glargine, QD or biphasic insulin aspart, BID), (Study H80-MC-GWAA, H80-MC-GWAD).

- Dose response studies

The studies showed little incremental benefit in postprandial glucose reduction at doses greater than 0.1µg/kg. Doses exceeding 0.2 µg/kg resulted in increased incidence of gastrointestinal side effects. Simulations based on population pharmacokinetic and pharmacodynamic modelling based on data from 4 studies supported the transition from weight-normalised dosing to a fixed-dosing paradigm. One study demonstrated that a scheduled, gradual escalation to a target dose reduced the incidence of gastrointestinal side effects to some extent compared with direct administration of the final target dose.
The clinical studies also contributed to the dose-finding (see below): Study 107 examined the effect of the addition of a third dose at bedtime. Study 116 examined the dose response at doses of 2.5 µg to 10 µg BID for one month. The Phase 3 placebo-controlled studies compared the efficacy of 5 µg and 10 µg BID for 30 weeks.

- Main studies

Short-term placebo-controlled studies

Study 107 was designed to evaluate the efficacy and safety of exenatide in subjects failing to achieve adequate glucose control with Met and/or SU therapy. Subjects subcutaneously (sc) injected exenatide (0.08 µg/kg) or placebo for 28 days defined by one of four regimens: 1) exenatide BID before breakfast and dinner, 2) exenatide BID before breakfast and bedtime, 3) exenatide three times daily (TID) before breakfast, dinner, and bedtime, or 4) placebo TID before breakfast, dinner, and bedtime. Each BID regimen had an additional SC placebo injection at the third time point, dinner or bedtime, to maintain blinding. The primary efficacy measures in Study 107 were postprandial plasma glucose and serum fructosamine. Exenatide at the dose regimens tested led to clinically and statistically significant reductions in postprandial plasma glucose and fructosamine concentrations. The regimen (BID versus TID) did not appear to differentially impact clinical outcome, although the study was not designed to detect small differences in dose regimens.

Study 116 was designed to evaluate the efficacy and safety of exenatide in subjects treated with diet modification and exercise, or Met. Subjects subcutaneously injected exenatide (2.5 µg, 5.0 µg, 7.5 µg, or 10.0 µg BID), or placebo for 28 days. The primary efficacy measure was change in HbA_{1c}. Results showed a statistically significant, dose-dependent (2.5 µg to 7.5 µg exenatide) reduction in HbA_{1c}.

Study 120 was designed to evaluate the efficacy and safety of exenatide, compared with placebo, in subjects who had their OAD withdrawn at least 2 weeks prior to the triple-blind portion of the study; 1) 10 µg, BID 2) 10 µg QD or 3) 20 µg QD, over 28 days. The primary efficacy measure was change in HbA_{1c}. There was a statistically significant reduction in HbA_{1c} in subjects treated with 10 µg BID exenatide compared to placebo. The decrease in HbA_{1c} in subjects treated with 10 and 20 µg QD exenatide when compared to placebo was not statistically significant. The dose 20µg QD was not well tolerable because of gastrointestinal side effects.

In these studies 81 % (107), 88% (116), and 65% (120) of the subjects were using >50% of the maximally effective dose of OAD. Even though the percentage in study 120 was rather low, patients in the other two studies were representative of the target population.

Long-term placebo-controlled studies

The 3 long-term placebo-controlled Studies 112, 113, and 115 were randomised, triple-blind, 3-arm parallel group, multicentre studies designed to examine the efficacy and safety of exenatide 5 µg or 10 µg injected SC, BID for 30 weeks in subjects with type 2 diabetes with BMI 27-45 kg/m2, treated with maximally effective doses of Met (Study 112), SU (Study 113), or Met + SU (Study 115). Subjects in Studies 112 and 115 were required to be on a maximum effective regimen of Met at study entry (≥1500 mg daily dose). Maximally effective doses (MaxED) of SU were required at study entry in Studies 113 and 115, although the SU dose could be reduced in response to hypoglycemia. A key aspect of Study 115 was to evaluate exenatide treatment and the use of a MaxED of SU, versus a minimally recommended dose (MinRD) of SU, on efficacy and the occurrence of hypoglycemia.

In all these studies the primary efficacy measure was the change in HbA_{1c} from baseline to endpoint. Additional efficacy measures included the change in HbA_{1c} from baseline to each intermediate visit; the proportion of subjects achieving HbA_{1c} values ≤7.0%, change from baseline in fasting glucose concentrations, change in postprandial glucose concentrations in the test meal cohort, and change in body weight from baseline to each of the intermediate visits and to endpoint. Pancreatic beta-cell functioning was assessed using the homeostasis model assessment for beta-cell function (HOMA-B) and the fasting proinsulin to insulin ratio. Baseline characteristics were similar in the different treatment groups and were representative for the target population. The withdrawal was larger in the placebo group compared to the exenatide groups (27% versus 20%). This was mainly because of loss of glucose control and withdrawal of consent. The incidence of adverse events was highest in the exenatide 10 µg BID group.

Treatment with 5 µg or 10 µg exenatide demonstrated improved glucose control by mean reductions in $HbA_{1c}$and fasting glucose conentrations. Subjects showed significant mean reductions in body weight (see table 1). HbA1c below 7% and 6.5% was reached by 38.5% and 20.7 % of the subjects respectively on the highest dose. A dose effect was seen where the proportion of subjects achieving either HbA_{1c} ≤7% or ≤6.5% at endpoint was greater for the exenatide 10 µg group than the exenatide 5 µg group. The effect was larger in study 112 and 113 compared to study 115 as evaluated by subjects achieving HbA1c ≤7%.There was a tendency to a diminishing effect towards the end of the studies in all treatment groups. There was a clinically and statistically significant reduction of postprandial glucose associated with exenatide when analysed in a subset of the total population. There were improvements in surrogate measures of beta cell function such as HOMA-B and the fasting proinsulin to insulin ratio, but these changes are difficult to translate into clinical terms. In the ITT populations there were no consistent, clinically relevant, changes in fasting total cholesterol, LDL-C, HDL-C, LDL/HDL ratio, triglyceride or apolipoprotein B concentrations in the 5 µg or 10 µg exenatide-treatment groups when compared with placebo.

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

Long-term active comparator-controlled studies
Studies GWAA and GWAD were randomized, open-label, 2-arm parallel group, multicentre studies. These studies enrolled subjects with type 2 diabetes with BMI >25 and <40/45 kg/m2, who had inadequately controlled blood glucose using a combination therapy of SU+ Met. Subjects continued taking OAD during the studies and added either insulin or exenatide (SC injected 10 µg BID).

The primary objective of Studies GWAA and GWAD was to test the hypothesis that the glycaemic control achieved with exenatide 10 µg BID was non-inferior to that of insulin glargine (Study GWAA, Lantus®, Aventis Pharmaceuticals, QD bedtime) or biphasic insulin aspart (Study GWAD, NovoMix® 30/NovoLog 30®, BID) with respect to the change in HbA_{1c} after 26 (GWAA) or 52 (GWAD) weeks of treatment. Non-inferiority was demonstrated if the upper limit of a two-sided 95% confidence interval for the difference in the change in HbA_{1c} between exenatide and insulin was less than 0.4%.

The primary efficacy measure in Studies GWAA and GWAD was the change in HbA_{1c} from baseline to endpoint. Additional efficacy measures included the proportion of subjects achieving HbA_{1c} ≤7%, body weight, fasting and postprandial glucose, 7-point self-monitored blood glucose (SMBG) profiles and fasting serum lipids. In Study GWAD, improvement in beta-cell function was evaluated in the exenatide-treatment group using HOMA-B analysis. There were larger withdrawals in the exenatide-groups compared to those treated with insulin. This was mainly caused by increased incidence of adverse events. The proportions of subjects who were lost to follow-up were relatively low throughout the studies.

There were no clinically significant differences in baseline data between the insulin and exenatide groups. Subjects in study GWAD had higher baseline HbA1c compared to subjects in study GWAA.

In both long-term active-comparator controlled studies, the change in HbA_{1c} in the exenatide treated group was statistically non-inferior to that of insulin glargine or biphasic insulin aspart. The mean insulin doses were 24.9 IU/day, (range 4-95 IU/day), at the end of study GWAA with insulin glargine and mean insulin dose 24.4 IU /day, (range 3-78 IU/day), at the end of study GWAD with biphasic insulin aspart. In study GWAD the biphasic insulin aspart group had a reduction of HbA1c with 0.86 %, and 8.5 % of the subjects reached HbA1c below 6.5 %. Based on the non-blinded nature of the insulin-comparator studies, a potential bias towards lower insulin doses cannot be fully excluded; however, the Applicant has tried to minimise this potential bias.

At endpoint, subjects demonstrated improved glucose control by mean reductions in HbA_{1c} and fasting glucose concentrations in both treatment groups (see table). Exenatide-treated subjects showed significant reductions in mean body weight. The proportions of evaluable subjects achieving HbA_{1c} ≤7% at endpoint were approximately equal for the exenatide and insulin glargine (almost 50 %) in study GWAA. In study GWAD 33% (exenatide) and 24 %(biphasic insulin aspart) achieved an HbA_{1c} ≤7%. One reason for the differing results between the comparator controlled studies could be the difference in baseline HbA1c.

There was a tendency to a diminishing effect towards the end of the studies in all treatment groups. However, a further loss of effect was not seen among those who remained in the extension studies. Exenatide lowered postprandial glucose concentrations more than insulin, and was associated with a more flat blood glucose profile. Insulin was associated with lower premeal concentrations. In study GWAD there was an increase in HOMA-B, but as in the long-term placebo studies this is difficult to translate into clinical terms.

Table 1: Summary of Efficacy Results for Exenatide Long-Term Placebo- and Active-Comparator Controlled Studies (Intent-to-Treat Subjects)

Study	N	Change From Baseline to Endpoint (LOCF) (Least Squares Mean ± Standard Error)		
		Haemoglobin A_{1c} (%)	Fasting Glucose (mmol/L)	Body Weight (kg)
H8O-MC-GWAA (Metformin + Sulphonylurea) – 26 Weeks of Treatment				
Insulin glargine	[1]	-1.10 ± 0.07	-2.86 ± 0.19	1.85 ± 0.23
Exenatide 10 µg	[1]	-1.13 ± 0.07	-1.22 ± 0.19***	-1.92 ± 0.22***
H8O-MC-GWAD (Metformin + Sulphonylurea) – 52 Weeks of Treatment				
Biphasic insulin aspart	[1]	-0.86 ± 0.08	-1.64 ± 0.19	2.92 ± 0.17
Exenatide 10 µg	[1]	-1.01 ± 0.08	-1.75 ± 0.19	-2.54 ± 0.17***
112 (Metformin) – 30 Weeks of Treatment				
Placebo	113	-0.00 ± 0.106	0.79 ± 0.26	-0.2 ± 0.42
Exenatide 5 µg	110	-0.46 ± 0.112**	-0.29 ± 0.28*	-1.3 ± 0.45*
Exenatide 10 µg	113	-0.86 ± 0.110**	-0.56 ± 0.27*	-2.6 ± 0.44*
113 (Sulphonylurea) – 30 Weeks of Treatment				
Placebo	123	0.06 ± 0.115	0.32 ± 0.29	-0.8 ± 0.32
Exenatide 5 µg	125	-0.51 ± 0.111**	-0.29 ± 0.28	-1.1 ± 0.30
Exenatide 10 µg	129	-0.91 ± 0.110**	-0.60 ± 0.28*	-1.6 ± 0.30*
115 (Metformin + Sulphonylurea) – 30 Weeks of Treatment				
Placebo	247	0.12 ± 0.079	0.72 ± 0.20	-0.9 ± 0.21
Exenatide 5 µg	245	-0.66 ± 0.079**	-0.60 ± 0.20*	-1.6 ± 0.21*
Exenatide 10 µg	241	-0.88 ± 0.080**	-0.68 ± 0.20*	-1.6 ± 0.21*

[1] The primary endpoint, change in haemoglobin A1c, is presented for the Per-Protocol Subjects (GWAA: exenatide N=228, insulin glargine N=228; GWAD: exenatide N=243, biphasic insulin aspart N=240);

fasting glucose and body weight presented for the Intent-to-Treat Subjects (GWAA: exenatide N=282, insulin glargine N=267; GWAD: exenatide N=253, biphasic insulin aspart N=248).
Statistical significance of difference compared to placebo or insulin: *p<0.05, **p<0.01,***p<0.0001.

Clinical studies in special populations

The proportion of men and women in the long term controlled studies was 56% / 44%.
There were no clinically meaningful differences in change in HbA1c depending on gender. One hundred -sixty-five patients ≥ 70 years have been treated with exenatide in the clinical studies. These patients were thinner, had a somewhat lower HbA1c and a higher prevalence of mild renal impairment compared to patients < 70 years. SU was used by more than 80 % of the older population. The number of patients is in line with The International Conference on Harmonisation (ICH) guidance on studies in support of geriatrics. The older population had a greater decrease in HbA1c and, even more so, in weight compared to the younger patients. The increased prevalence of renal impairment in the older population may be of importance for these differences. However, when looking at patients with normal and mildly impaired renal function, there was little difference in the efficacy of 10 µg BID exenatide based on renal function. There were few patients ≥75 years.
In the long-term placebo-controlled studies subjects with mild renal impairment had greater reductions in mean HbA1c at each dose, although not statistically different, from subjects with normal renal function. In the active-comparator controlled studies no such differences were seen. Very few patients with moderate renal impairment were included in the studies.
No statistically significant interaction was observed between subject baseline BMI (<30 or ≥30 kg/m2) and change in HbA1c, although greater, not statistically significant, mean reductions in HbA1c were observed in the subgroups with baseline BMI <30 kg/m2 in the long-term placebo-controlled studies. Due to the inclusion criteria in the clinical studies, the experience in subjects with BMI≤ 25 must be considered as limited (only 36 patients have been exposed to the recommended dose of 10µg BID). Normal weighted subjects tend to lose less weight compared to those with higher BMI. The limited data presented does not indicate any risks associated with this weight loss.
Patients that did not lose weight had a reduction in HbA1c although smaller compared to those who lost weight. The correlation between weight loss and change in HbA1c was statistically significant, but rather weak. Weight loss seems to explain parts of the reduction in HbA1c associated with exenatide treatment, but is not the sole explanation.

Uncontrolled extension studies

The long-term uncontrolled extension Studies 112E, 113E, and 115E were open-label, multi-centre extension studies designed to assess long-term glucose control (as measured by $HbA_{1c)}$ and long-term safety and tolerability of treatment with 10 µg exenatide in subjects concomitantly treated with Met (112E), SU (113E) or Met + SU (115E).
Efficacy measure in Studies 112E, 113E and 115E included the change in HbA_{1c} from baseline to Week 82, change in fasting glucose concentrations, body weight, lipids, and in Studies 112E and 113E, insulin, and proinsulin concentrations.

At Week 82 of the 3 long-term uncontrolled extension studies, subjects demonstrated improvements in glucose control by mean reductions in HbA_{1c} values and fasting glucose concentrations, and sustained mean reduction in body weight. There was also a trend towards larger changes in triglycerides and HDL-cholesterol in those who lost most weight.

Table 2:

		Change From Baseline to Week 82 (Mean [SD])		
	N	HbA_{1c} (%)	Fasting Glucose (mmol/L)	Body Weight (kg)
Studies 112E, 113E, and 115E				
Cohort I	265	-1.2 (1.32)	-0.94	-4.6 (5.74)
Cohort II	128	-1.2 (1.03)	-1.70	-3.3 (4.27)

• Cohort I subjects received 5 µg or 10 µg exenatide for 26 weeks during the placebo-controlled study, followed by 10 µg exenatide during the uncontrolled extension study maintenance period.

• Cohort II subjects received placebo for 30 weeks during the placebo-controlled study, followed by exenatide 10 µg during the uncontrolled extension study maintenance period.

The results from the extension studies must be interpreted with caution, since more than 80% of the subjects either withdrew or discontinued due to administrative reasons after week 52. A bias for subjects with good treatment responses to continue through 82 weeks of treatment cannot be excluded.

- Discussion on clinical efficacy

In the scenario for the possible add-on use of exenatide to OAD, the alternative treatment for the patient is add-on therapy with insulin, and therefore the crucial issues are whether exenatide has an add-on effect and whether its ´risk/benefit profile is comparable to insulin in the treatment of patients considered as OAD failures.

When evaluating efficacy, the most important issue concerning the study population is that it reflects the target population, in this case patients with type 2 diabetes who fail to reach glycaemic control despite maximal tolerable dose of OAD. Among the long term placebo controlled studies, study 115 best reflected this population. The study populations in the long-term active-comparator-controlled studies had treatment with both Met and SU and were representative of the target population.

In the long-term placebo controlled studies the reduction of HbA1c was almost 1 % with a tendency to a diminishing effect towards the end of the studies. The reduction of HbA1c was somewhat larger in the comparator-controlled study GWAA. The results were poorer for the exenatide and insulin treated subjects in study GWAD. The main reason for the differing results between the comparator controlled studies probably was the difference in baseline HbA1c with higher concentrations in study GWAD. According to the non-inferiority margin of 0.4 %, exenatide was non-inferior to insulin. However, the mean daily insulin doses at the end of the studies were low. To claim clinical non-inferiority to insulin, it must be proven that the insulin treated subjects had maximally tolerated doses of insulin. This is doubtful, especially in study GWAD in which the biphasic insulin aspart - group only had a reduction of HbA1c with 0.86 % and only 8.5 % of the subjects reached HbA1c below 6.5 %. Based on the non-blinded nature of the insulin-comparator studies, a potential bias towards lower insulin doses cannot be fully excluded; however, the Applicant has tried to minimise this potential bias.
The decrease in body weight associated with treatment with exenatide was consistent and persistent throughout all studies. This is an advantage especially in the comparison with insulin. Due to the inclusion criteria in the clinical studies, the experience in subjects with BMI≤ 25 must be considered as limited. Normal weighted subjects tended to lose less weight compared to those with higher BMI. The limited data presented does not indicate any risks associated with this weight loss.
Patients that did not lose weight had a reduction in HbA1c although smaller compared to those who lost weight.

There were no statistically significant interactions between age, gender or BMI on the effect of exenatide. One-hundred -sixty-five patients ≥ 70 years have been treated with exenatide in the clinical studies. These patients were thinner, had a somewhat lower HbA1c and a higher prevalence of mild renal impairment compared to patients < 70 years. The older population had a greater decrease in HbA1c and, even more so, in weight compared to the younger patients. There were few patients ≥75 years and efficacy and safety in these subjects can not be considered as fully evaluated.

In the long term placebo controlled studies subjects with mild renal impairment had greater reductions in mean HbA1c at each dose, although not statistically different from subjects with normal renal function. In the active-comparator controlled studies no such differences were seen. Very few patients with moderate renal impairment were included in the studies. Patients with severe renal dysfunction were not included in the studies.
Towards the end of the placebo-controlled studies there seemed to be a reduction in efficacy with a tendency to an increase of HbA1c, however during the extension studies, there were no such trends. At week 82 about 50 % of the subjects had achieved HbA1c ≤ 7% which is a better result compared to the original studies. The reduction in body weight continued during the studies.
The results from the extension studies must be interpreted with caution, since more than 80% of the subjects either withdrew or discontinued due to administrative reasons after week 52.

In conclusion, exenatide has a moderate add-on effect when combined with OAD in patients who are considered as OAD failures. Exenatide was non-inferior to insulin in the referred studies as evaluated by the pre-specified non-inferiority margin. Based on the non-blinded nature of the insulin-comparator studies, a potential bias towards lower insulin doses cannot be fully excluded. The decrease in body weight associated with treatment with exenatide was consistent and persistent throughout all studies. This is an advantage especially in the comparison with insulin.

Clinical safety

- Patient exposure

Exenatide is a new substance not previously used in clinical circumstances and therefore safety issues are of great importance. The safety database is sufficiently large, but is notable that the mean exposure per subject is less than a year in the efficacy and safety studies. This is not long considering that the treatment of patients with type 2 DM often continues for decades. The submission consists of 36 completed studies and 9 ongoing studies supporting the safety and efficacy of exenatide in the treatment of type 2 diabetes in combination with Met, a SU, or both Met and a SU. As of 15. June 2005, safety data from 35 of the 36 completed studies were integrated in the Completed Studies database. The updated database included 122 patients treated with exenatide and thiazolidinediones with or without metformin. No new safety signals were recorded but the mean duration of exposure was no more than 13.7 weeks. The safety of exenatide has been evaluated in 3945 subjects (2997 received exenatide. Approximately 825 patients in the controlled and uncontrolled clinical studies have been exposed to exenatide for more than one year. In the long term controlled studies database the mean exposure per subject was 0.84 years

- Adverse events

The most common adverse events are hypoglycaemia and nausea/vomiting.

Table 3: Adverse events reported by at least 5% of exenatide-treated subjects (ITT subjects[1])

	Efficacy and Safety							Total	
	Controlled								
	Short-Term		Long-Term		Long-term Comparator		Uncon-trolled		
	Exenatide (N=278)	Placebo (N=86)	Exenatide (N=963)	Placebo (N=483)	Exenatide (N=535)	Insulin (N=515)	Exenatide (N=974) [2]	Exenatide (N=2535)	Placebo (N=846) [3]
Gastrointestinal disorders									
Nausea	123(44)	5(6)	419(44)	87(18)	245(46)	24(5)	441(45)	1303(51)	225(27)
Vomiting	35(13)	2(2)	123(13)	18(4)	87(16)	18(3)	116(12)	481(19)	107(13)
Diarrhoea	11(4)	0(0)	132(14)	33(7)	48(9)	13(3)	130(13)	336(13)	57(7)
Dyspepsia	2(1)	0(0)	54(6)	10(2)	17(3)	2(<1)	43(4)	138(5)	25(3)
General disorders and administration site conditions									
Feeling jittery	4(1)	0(0)	90(9)	20(4)	0(0)	1(<1)	106(11)	174(7)	20(2)
Infections and infestations									
Upper respiratory tract infection	9(3)	5(6)	122(13)	72(15)	18(3)	17(3)	173(18)	290(11)	81(10)
Nasopharyngitis	3(1)	2(2)	64(7)	39(8)	50(9)	48(9)	97(10)	203(8)	41(5)
Urinary tract infection	4(1)	1(1)	26(3)	12(2)	12(2)	8(2)	85(9)	126(5)	15(2)
Influenza	6(2)	1(1)	38(4)	21(4)	25(5)	31(6)	57(6)	124(5)	22(3)
Sinusitis	5(2)	0(0)	56(6)	28(6)	9(2)	7(1)	58(6)	117(5)	28(3)
Metabolism and nutrition disorders									
Hypoglycaemia	18(6)	0(0)	189(20)	41(8)	290(54)	288(56)	253(26)	697(27)	53(6)
Musculoskeletal and connective tissue disorders									
Back pain	1(<1)	1(1)	32(3)	16(3)	28(5)	18(3)	48(5)	116(5)	20(2)
Nervous system disorders									

	Efficacy and Safety Controlled							Total	
	Short-Term		Long-Term		Long-term Comparator		Uncon-trolled		
	Exenatide (N=278)	Placebo (N=86)	Exenatide (N=963)	Placebo (N=483)	Exenatide (N=535)	Insulin (N=515)	Exenatide (N=974) [2]	Exenatide (N=2535)	Placebo (N=846) [3]
Headache	16(6)	1(1)	82(9)	30(6)	37(7)	36(7)	67(7)	299(12)	90(11)
Dizziness	15(5)	2(2)	84(9)	30(6)	19(4)	8(2)	80(8)	235(9)	62(7)

(Percentage in brackets) [1]As of 15 June 2005

Hypoglycaemia

The incidence of hypoglycaemia associated with exenatide was mainly dependent on the concomitant use of SU. This is not surprising since both exenatide and SU stimulate the beta cells to produce more insulin. A special warning on this is included in section 4.4 of the SPC. In the 16 week placebo-controlled study with a thiazolidinedione, with or without metformin, no significant increase of symptomatic mild to moderate hypoglycaemia was reported compared to placebo.

The incidence of severe hypoglycaemia was low. In the active comparator controlled studies the incidence of hypoglycaemia was similar in exenatide and insulin treated subjects.
In study 115 two regimens of SU was examined (maximal effective dose and minimal recommended dose).

Incidence of hypoglycaemia by sulphonylurea use

Table 4:

	Sulphonylurea Use				**Non-Sulphonylurea Use**	
	113 and 115 Max SU Regimen		**115 Min SU Regimen**		**112**	
Hypoglycaemic Episodes	Exenatide (N=496)	Placebo (N=243)	Exenatide (N=244)	Placebo (N=127)	Exenatide (N=223)	Placebo (N=113)
Incidence n (%)	132 (26.6)	22 (9.1)	46 (18.9)	13 (10.2)	11 (4.9)	6 (5.3)
Total Number of Episodes	355	52	98	23	14	7

Nausea

Nausea and vomiting were common side effects in the clinical studies. Nausea affected 50% of the patients that were treated with exenatide, but with continued therapy, the frequency and severity decreased in most patients who initially experienced nausea. Nausea contributed in some extent to the reduction of body weight, but was clearly not the sole explanation. 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. Although the mechanisms for nausea with exenatide treatment are not well understood, it is likely that the events are centrally mediated. Furthermore, it is known that exenatide slows gastric emptying which also may contribute to the nausea.

Anti-exenatide antibodies

Antibody development is not unexpected as exenatide is a synthetic version of a peptide that is derived from a non-mammalian source and therefore may be recognised as an antigen by the immune system. Patients who developed anti-exenatide antibodies had similar rates and types of adverse events as those with no anti-exenatide antibodies. In the three placebo-controlled trials (n=963) 38 % of patients had low titre anti-exenatide antibodies at 30 weeks. For this group, the level of glycaemic control (HbA_{1c}) was generally comparable to that observed in those without antibody titres. An additional 6 % of patients had higher titre antibodies at 30 weeks. About half of this 6 % (3 % of the total patients given BYETTA in the controlled studies), had no apparent glycaemic response to BYETTA. In two

insulin-comparator controlled trials (n=475) comparable efficacy and adverse events were observed in BYETTA-treated patients regardless of antibody titre.
Few patients have been subject to retreatment with exenatide. The Applicant therefore committed to enrol a separate retreatment study.

Antibody Assay
The company has developed an enzyme-linked immunosorbent assay (ELISA) to detect antibodies against AC2993(=Exenatide). The method has been validated to detect antibodies in human, cynomologus monkey and mouse plasmas. The method has been properly validated.
Cross-reactivity between anti-exenatide antibodies and glucagon and GLP-1 has been examined in one study in which no cross-reactivity was shown. The Applicant has commited to further study the issue of cross-reactivity in other studies.

To address immune response related questionst the Applicant has committed to develop an assay for determining the isotypes of the antibodies, since certain isotypes are more likely to yield neutralizing antibodies than other isotypes. The applicant will provide the data as a follow-up measure. The Applicant has also committed to try to further develop an existing assay to detect neutralizing antibodies with higher sensitivity than currently possible. Such an assay would make also isotyping of antibodies irrelevant. Furthermore, the Applicant has committed to study anti-exenatide antibodies and HbA1c in 2 planned studies to provide information on immunogenicity of the products obtained from the 2 exenatide suppliers, since there have been indications that there may be differences in the immune response to the two products. Overall, the issue of the influence of anti-exenatide antibodies is considered only an efficacy effect and not a safety issue.

- Serious adverse event/deaths/other significant events

Coronary artery disease
Among all exenatide-treated subjects, the system organ class of cardiac disorders had the highest percentage (2%) of subjects experiencing serious adverse events (SAE). The most common (1%) SAE within this system organ class was coronary artery disease (CAD). More exenatide- (17 of 2997 [1%]) than placebo-treated (1 of 975 [<1%]) subjects experienced serious CAD events in the safety update of the placebo-controlled studies. However, the subject-rate of TE CAD and TE CAD-related disorders (serious and non-serious) in the total exenatide-treated population of both the original and updated safety summaries was less than that observed in the total placebo-treated population.

Neoplasms
Safety data from the long term placebo-controlled studies were integrated for the first time in the last quarter of 2003 and showed that a disproportionate number of malignancies had occurred among exenatide- (11 of 963, 1.1%) compared with placebo-treated subjects (2 of 483, 0.4%) in these studies. In the active-comparator studies both the exenatide- (1%) and insulin-treatment (1%) groups had comparable incidences of neoplasms. Exenatide-treated subjects in the uncontrolled studies had a 2% incidence of neoplasms.
A group of experts in cancer epidemiology, histopathology, and clinical oncology concluded that a causal relationship between exenatide treatment and cancer is unlikely, although the relatively small number of subjects and short duration of follow-up precluded a definitive conclusion. The lack of a causal relationship was supported by:

- no observed cancer signal in non-clinical genotoxicity studies
- no observed cancer signals in lifetime carcinogenicity studies in two species
- heterogeneity of the types of malignancies observed
- relatively short interval between initial exenatide exposure and diagnosis time for many cancers reported in the controlled studies
- decreased malignancy event rate with increasing exenatide exposure time.

In the rat studies a numerical increase in benign thyroid C-cell adenomas was observed in female rats at all exenatide doses, however, when adjusted for survival, the numerical increase was not significant. Five exenatide-treated subjects in the completed or ongoing studies of the exenatide clinical programme were identified by the MedDRA preferred terms as neoplasm of the thyroid gland (3 thyroid neoplasm, 1 thyroid cyst and 1 benign neoplasm). In all cases, the TEAEs were recorded as non-serious events and assessed as unrelated or probably not related to study medication.

After an update of the clinical studies database (December 2005) no significant difference in the incidence of malignant neoplasms between exenatide and insulin-and placebo-treated subjects was observed.

- Laboratory findings (including analyses of ECG)

There were no clinically meaningful changes from baseline to endpoint in haematology, chemistry, or urine analysis assessments for exenatide-, insulin-, or placebo-treatment groups in any of the efficacy and safety studies. There were no indications that exenatide has the potential to induce clinically significant ECG changes.

Other adverse events

There was an increased incidence of the general disorder "feeling jittery" in exenatide subjects compared to placebo. The increased incidence may be related to the incidence of hypoglycaemia since 92 % of the patients were taking SU and "feeling jittery" is a recognised symptom of hypoglycaemia. Significantly more exenatide- (5.1%) than insulin- and placebo- (3.0%) treated subjects in these studies reported injection site and injection-site reaction related events.
The incidence of pedal oedema was not increased in patients treated with exenatide and thiazolidinediones with or without metformin compared to placebo.

- Safety in special populations

There was not a statistically significant increase in overall incidence of adverse events in patients with mild renal impairment except for an increased incidence of hypoglycaemia.
There is no clinical data concerning subjects with moderate or severe renal impairment.
Among exenatide-treated subjects, a higher incidence of hypoglycaemia episodes occurred among subjects ≥ 65 years of age compared to those < 65years. However, when hypoglycaemia incidence was presented as the yearly rate there was no difference between age groups. In this analyses hypoglycaemia incidence increased with reduced renal function but not with increasing age.
There were only 36 subjects older than 75 years treated with exenatide. To explore exenatide PK in subjects >75 years of age with varying degrees of renal impairment, a pharmacokinetic/pharmacodynamic (PK/PD) study in the very elderly is proposed as part of the Risk Management Plan.
The clinical experience of the combination of exenatide and thiazolidinediones in patients with renal impairment and in patients >65 years is very limited.

For frequent AEs (> 5%), more exenatide-treated females than males reported nausea, vomiting, feeling jittery, and headache. However, also among insulin- and placebo treated subjects, more females than males reported similar adverse events. There was no difference concerning hypoglycaemias between males and females.

- Safety related to drug-drug interactions and other interactions

There were no adverse events in the long-term studies associated with concomitant medications.

- Discontinuation due to adverse events

Overall, 9% of exenatide-, 1% of insulin-, and 3% of placebo-treated subjects withdrew early from controlled and uncontrolled studies because of AEs. Of 2997 exenatide-treated subjects, 168 (6%) discontinued because of gastrointestinal disorders, mostly nausea. Few exenatide-treated subjects (<1%; 5 of 2997 subjects) discontinued because of hypoglycaemia. More exenatide- (11 of 2997, <1%) than insulin- (1 of 658) or placebo-treated (0 of 975) subjects withdrew from studies because of neoplasms.

Post marketing experience

Pancreatitis

Concerning post-marketing data until 28 July 2006, 40 spontaneous cases of pancreatitis(37 health care professional confirmed) have been reported. This is reflected in section 4.8 of the SPC under the heading *Spontaneous reports*, where the following wording is included: Since market introduction of BYETTA, the following additional adverse reactions have been reported: Gastrointestinal disorders: Pancreatitis, cases have been reported.

Concerning a case report published in Diabetes Care, this case of acute pancreatitis is possibly related to exenatide use, however the data fall far short of demonstrating a definite association.
Safety data from the exenatide clinical trial programme did not suggest that exenatide induces pancreatitis.
The Applicant has commissioned an epidemiological database study through United HealthCare (UHC) to estimate the annual incidence and prevalence of acute pancreatitis among patients with type2 diabetes. The UHC study data showed an estimated 3.74-fold greater incidence of acute pancreatitis in the cohort with type 2 diabetes compared with the age-and gender-matched cohort without type 2 diabetes. The estimated annualised incidence in the cohort with diabetes was 107.8/100,000 patient-years versus 28.8/100,000 patient-years for the cohort without diabetes, thus strongly suggesting that patients with type 2 diabetes have a higher background incidence of pancreatitis.
The Applicant is committed to investigate this further and plans to commission an additional epidemiological database study through UHC to estimate the annual incidence and prevalence of acute pancreatitis among patients treated with BYETTA versus those treated with other antidiabetic agents.

Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan (see the table below)

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

Summary of Risk Management Plan for BYETTA – Potential Risks

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Anti-exenatide Antibodies	• Routine pharmacovigilance and targeted surveillance of allergic/immunologic events(angioodema/anaphylaxis). • Antibody analysis of serum samples in LT studies following reports of serious allergic/immunologic events. • Further clinical study to investigate antibody formation on the retreatment of exenatide	SPC 4.3: Contraindication regarding hypersensitivity to exenatide or any of the product's excipients SPC 4.8: Added spontaneous AE reports of allergy/hypersensitivity reactions such as generalised pruritus and/or urticaria, macular or papular rash, angiooedema, and anaphylactic reaction.
Cardiovascular Events	• Routine pharmacovigilance. • Meta-analyses of CAD AEs from LT studies 2007 & 2009.	Not applicable.
Risk(s) of Elevated Pulse Rate	• Further evaluation in a clinical study	Not applicable.
Malignant Neoplasms	• Routine pharmacovigilance. • Targeted surveillance of malignant AEs • Meta-analyses of malignant AEs from LT studies in 2007 & 2009.	Not applicable.
Dehydration and Acute Renal Impairment	• Routine pharmacovigilance. • Targeted surveillance of dehydration, hypovolaemia, and acute renal impairment.	SPC 4.2: Precautionary language in patients with moderate renal impairment and BYETTA is not recommended for use in patients with ESRD or severe renal impairment. SPC 4.8: Includes spontaneous AEs, "Dehydration /increased serum creatinine: dehydration, generally associated with nausea, vomiting, and/or diarrhoea, some reports associated with an elevation of serum creatinine."
Pancreatitis	• Routine pharmacovigilance. • Targeted surveillance of reports of pancreatitis. • Database study to assess incidence rates of pancreatitis among exenatide- versus other antidiabetic agents.	SPC 4.8: Includes spontaneously reported AEs, Pancreatitis, cases have been reported.
Increased INR with Concomitant Warfarin	• Routine pharmacovigilance. • Targeted surveillance of reports of events of increased INR with concomitant warfarin.	SPC 4.5: discusses concomitant use of exenatide with warfarin. SPC 4.8: spontaneously reported AEs, "INR increased with concomitant warfarin use, some reports associated with bleeding."

Summary of Risk Management Plan for BYETTA – Information to be completed

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Adolescents	• Further PK/PD study	SPC 4.2: states "There is no experience in children and adolescents below 18 years."
Pregnant women	• Pregnancy registry	SPC 4.6: Use in pregnancy and lactation is not recommended.
Very elderly (≥75 years of age)	• Further PK/PD study	SPC 4.2: "BYETTA 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."

Abbreviations: AE= adverse event, CAD =coronary artery disease, ESRD = end-stage renal disease, INR = international normalised ratio; LT = long-term clinical; PK = pharmacokinetic, PD = pharmacodynamic; SPC = Summary of Product Characteristics

Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this medicinal product is considered satisfactory when used with the conditions defined in the SPC.
The documentation provided for the active substance (synthetic peptide exenatide) is comprehensive and adequately detailed.
The pharmaceutical development is adequate and took into consideration the properties and the stability of the active substance. The excipients used are common excipients for a parenteral solution. Similarly, the packaging material is well documented and no incompatibility has been noticed.
The validation of the manufacturing process ensures consistency and reproducibility of the finished product.
The finished product has been satisfactorily controlled and stability studies conducted under ICH conditions showed that the product is stable throughout the proposed shelf-life.
At the time of the CHMP opinion, there were some outstanding quality issues with no impact on the benefit/risk. The applicant undertook to provide the necessary information as follow-up measures within an agreed timeframe and to submit variations if required following the evaluation of this additional information.

Non-clinical pharmacology and toxicology

Exenatide binds to and stimulates the glucagon-like peptide 1 receptor in both human- and rat-based receptor systems in vitro and enhances insulin production in presence of increased glucose concentration in vivo.
The primary pharmacodynamic studies provided adequate evidence, that exenatide markedly improves glucose control in diabetic mice and rats via various mechanisms.
A series of pharmacokinetic studies was conducted in mice, rats, rabbits, and monkeys. The kidney was the main organ for clearance. Clearance was not effected in a liver injury model.
In single and repeat dose toxicity studies in mice and in rats, no important toxicity was observed.
Carcinogenicity studies did not raise any concern for human safety.
Exenatide showed no effect on fertility and early embryonic development in mice. In the embryo-foetal toxicity studies in mice and rabbits, maternal food consumption and body weights were reduced. In both species, developmental toxicity occurred in conjunction with maternal toxicity but there were no evidence for teratogencity. The control of blood glucose is of great importance during pregnancy and this is best achieved by insulin treatment. Therefore, exenatide should not be used during pregnancy, which is reflected in the SPC section 4.6.
Overall, the non-clinical safety studies have not identified any important safety concerns which affect the benefit risk assessment.

Efficacy

Exenatide is an incretin mimetic and is thought to act by mimicking some of the effects of glucagon-like peptide 1 (GLP-1). GLP-1, an endogenous incretin, facilitates insulin secretion following its release from the gut into the circulation in response to food intake. Exenatide therefore acts differently from any other currently approved therapeutic agent.

Studies considered to be pivotal for the evaluation of exenatide included 3 long-term placebo-controlled studies, where the magnitude of response of adding exenatide (5 µg or 10 µg BID) to a concomitant therapy with oral antidiabetics (OAD; Metformin [Met], a sulfonylurea [SU], or Met + SU) was investigated. In these long-term placebo-controlled studies the reduction of HbA1c, as the primary outcome parameter suggested by CHMP guidelines, was almost 1 %, this was considered to be an effect of a relevant magnitude. There was a tendency to a diminishing effect towards the end of the studies. The reduction of HbA1c differed in comparator-controlled studies, with a likely explanation being different baseline HbA1c values. Towards the end of the placebo-controlled studies there seemed to be a reduction in efficacy with a tendency to an increase of HbA1c, but during the extension of these studies, this trend was reversed, with a higher percentage of subjects having achieved an HbA1c ≤ 7% at week 82. The results from the extension studies must be interpreted with caution, since more than 80% of the subjects either withdrew or discontinued due to administrative reasons after week 52. The studies showed also improvements in secondary endpoints, e.g. in fasting and postprandial glucose concentrations at endpoint compared to baseline.

The indication for exenatide is the "Treatment of type 2 diabetes mellitus in combination with metformin and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies."
In this scenario, the alternative treatment for the patient is an add-on therapy with insulin, requiring active-comparator controlled studies to compare the risk/benefit profile of exenatide to insulin in the treatment of patients considered as OAD failures. Two such long-term active-comparator controlled studies were therefore considered to be pivotal and investigated the non-inferiority of exenatide treatment (10 µg BID) to insulin treatment (insulin glargine, QD, and biphasic insulin aspart, BID, repectively) within an add-on study design. In these active-comparator-controlled studies, exenatide was noninferior to insulin, as judged by a predefined non-inferiority margin of 0.4 %. The mean daily insulin dose at the end of the studies was 24.9 IU/day, (range 4-95 IU/day), at the end of study GWAA with insulin glargine and mean insulin dose 24.4 IU /day, (range 3-78 IU/day), at the end of study GWAD with biphasic insulin aspart). The patients may not have reached maximally tolerated doses of insulin, although study protocols required the physicians to use best clinical practise to achieve blood glucose target control without increasing the risk of hypoglycaemia.
Based on the non-blinded nature of the insulin-comparator studies, a potential bias towards lower insulin doses cannot be fully excluded; however, the Applicant has tried to minimise this potential bias. In study GWAD the biphasic insulin aspart-group had a reduction of HbA1c of 0.86 % and only 8.5 % of the subjects reached HbA1c below 6.5 % and this was considered to be a limitation of the result.

The study population in the long-term placebo-controlled studies did reasonably well reflect the target population, which is a crucial issue for evaluating efficacy. The target population was in this case patients with type 2 diabetes who failed to reach glycaemic control despite maximal tolerable dose of OAD. The study population in the long-term active-comparator-controlled studies had treatment with both Met and SU and were also representative of the target population.

There was a decrease in body weight associated with treatment with exenatide, which was consistent and persistent throughout all studies. This was considered to be a distinct advantage especially in the comparison with insulin. Due to the inclusion criteria in the clinical studies, the experience in subjects with BMI ≤ 25 is considered as limited. Subjects with a normal weight tended to lose less weight compared to those with higher BMI. The limited data presented did not indicate any risks associated with this weight loss. Patients that did not lose weight had a reduction in HbA1c although smaller compared to those who lost weight.

There were no statistically significant interactions between age, gender or BMI on the effect of exenatide. One-hundred -sixty-five patients ≥ 70 years have been treated with exenatide in the clinical studies. These patients were thinner, had a somewhat lower HbA1c and a higher prevalence of mild renal impairment compared to patients < 70 years. The older population had a greater decrease in HbA1c and, even more so, in weight compared to the younger patients. There were few patients ≥75 years and experience with efficacy and safety in these subjects is thus very limited.

Subjects with mild renal impairment had a trend to greater reductions in mean HbA1c at each dose in the long-term placebo-controlled studies, which, however, was not seen in the active-comparator controlled studies. Very few patients with moderate renal impairment, and no patients with severe renal dysfunction were included in the studies. Knowledge about exenatide action in various stages of renal insufficiency is therefore very limited.

Safety

Exenatide is a new substance not previously used in clinical circumstances and therefore safety issues are of great importance. The safety database is sufficiently large, however the mean exposure per subject is less than a year in the efficacy and safety studies. This is not long considering that the treatment of patients with type 2 diabetes often continues for decades. The updated database included 122 patients treated with exenatide and thiazolidinediones with or without metformin. No new safety signals were recorded but the mean duration of exposure was no more than 13.7 weeks. The safety of exenatide has been evaluated in about 3000 subjects.

The most common adverse events are hypoglycaemia and nausea/vomiting. Hypoglycaemia is primarily a risk in the co-treatment with sulfonylureas (SU). This is not surprising since both medicinal products stimulate the beta cells to produce more insulin. Warnings concerning this combination are included in the SPC.

Nausea and vomiting were common side effects in the clinical studies. Nausea affected 50% of the patients that were treated with exenatide, but with continued therapy, the frequency and severity decreased in most patients who initially experienced nausea. Nausea contributed to some extent to the reduction of body weight, but was clearly not the sole explanation. 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. Although the mechanisms for nausea with exenatide treatment are not well understood, it is likely that the events are centrally mediated. Furthermore, it is known that exenatide slows gastric emptying which also may contribute to the nausea.

There was an observed slightly increased incidence of neoplasms in patients treated with exenatide in the placebo controlled studies. Clinical experts have considered this association to be unlikely, and an update of the clinical studies database (December 2005) showed no significant difference in the incidence of malignant neoplasms between exenatide and insulin-and placebo-treated subjects. However, continued surveillance of the incidence of neoplasms will be carried out and is implemented as a follow-up measure.

There does not seem to be any clinically relevant differences in adverse events associated with age or gender. However, there are some indications that subjects older than 65 years of age may have an increased incidence of hypoglycaemia. The number of subjects older than 70 years was sufficient according to ICH guidelines, however, only 36 patients older than 75 years were treated with exenatide. This limited experience is mentioned in the SPC and further studies in this patient group rea planned and implemented as a follow-up measure.

Patients with mild renal dysfunction had an increased risk of hypoglycaemia. Patients with moderate renal dysfunction were few, and no clinical data were presented for these subjects. The titration from 5 to 10 µ BID should be performed cautiously in patients over 70 years and patients with moderate renal dysfunction. The clinical experience of the combination of exenatide and thiazolidinediones in patients with renal impairment and in patients >65 years is very limited. These issues are considered in the SPC.

Exenatide has not been associated with ECG-changes or clinically relevant changes in laboratory parameters. About 45 % of the patients developed anti-exenatide antibodies in the controlled studies. There was no consistent pattern of increased incidence or a different pattern of AE in subjects with anti-bodies compared to those without immunologic response. For further information, see section of efficacy.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics
Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

User testing has been performed satisfactorily on the Product Information and the User Manual.

Risk-benefit assessment

Efficacy and safety of exenatide has been investigated in about 3000 patients with type 2 diabetes. Exenatide had an add-on effect when combined with OAD in patients who are considered as OAD failures. The reduction of HbA1c in the long term controlled studies was approximately 1% and this was considered as a clinically relevant effect by the CHMP. Treatment with exenatide was associated with a decrease in body weight. A main risk associated with exenatide is hypoglycaemia, in particular in the combination treatment with a sulfonylurea. Overall, the benefit/risk ratio for exenatide was considered as positive by the CHMP, provided that it is used as an add-on therapy within the limits described in the SPC.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns
- no additional risk minimisation activities were required beyond those included in the product information

Similarity with authorised orphan medicinal products

Not applicable

Market exclusivity

Not applicable

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of BYETTA in the treatment of type 2 diabetes mellitus in combination with metformin, and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies was favourable and therefore recommended the granting of the marketing authorisation.