SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Lantus. This scientific discussion has been updated until 1 September 2003. For information on changes after this date please refer to module 8B.

1. Introduction

Insulin glargine, the active ingredient in Lantus, is an insulin analogue with a prolonged duration of action after subcutaneous injection, produced by recombinant DNA technology using *Escherichia coli* (K12 strains). Structural modifications (C-terminal elongation of the B chain by two arginines and replacement of the C-terminal amino acid of the A-chain by glycine) shift the isoelectric point towards neutral pH. This results in a delay in dissociation of the hexamer complexes into monomers after subcutaneous injection, and a prolonged absorption from the injection site.

An optimal glucose regulation in type 1 and type 2 diabetic patients reduces the risk for complications resulting from diabetes such as retinopathy, nephropathy and neuropathy. Insulin preparations differing both in there time of onset and duration of action are available for insulin substitution therapy. Current regimens try to mimic physiological insulin secretion by injection of delayed action (basal) insulin for basal insulin supply and rapid-acting insulins for prandial control. The currently available intermediate or long-acting insulins do not provide a constant and reliable basal insulin supply. The duration of action is limited and a twice-daily regimen is often required. In addition a distinct insulin peak occurs a few hours after subcutaneous injection. This results in an increased risk of nocturnal hypoglycaemia and fasting hypoglycaemia. Insulin glargine is a long acting insulin analogue, which does not display a distinct insulin peak.

Insulin glargine is indicated for use in patients with type 1 or type 2 diabetes mellitus, where treatment with insulin is required and can be used in adults, adolescents and children of six years or above. Insulin glargine has a prolonged duration of action and may be administered once daily at any time but at the same time every day. The dosage should be adjusted individually. In patients with type 2 diabetes mellitus, insulin glargine can also be given together with orally active antidiabetic drugs.

Specific terminology:

Depot activity: sustained release

NPH insulin: neutral protamine Hagedorn (human insulin as isophane insulin suspension)
$HbA1_C$: glycosylated haemoglobin; the level of $HbA1_c$ allows evaluation of antecedent (2-3 month) glycaemic control (control of blood sugar levels).
AUC: area under the concentration-time curve
C_{max}: maximum concentration in plasma
FPG: fasting plasma glucose
FBG: fasting blood glucose
IGF-1: insulin-like growth factor 1
OAD: oral antidiabetic drug
t_{max}: Time to C_{max}
ITT: intention to treat
Symptomatic hypoglycaemia: event with clinical symptoms related to hypoglycaemia

Asymptomatic hypoglycaemia: blood glucose level below 2.8 mmol/l (50 mg/dl) without clinical symptoms.

Severe hypoglycaemia: event with symptoms for which the subject required the assistance of another person and which was associated with a blood glucose level below 2.8 mmol/l (50 mg/dl) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

Nocturnal hypoglycaemia: hypoglycaemia occurring while the subject was asleep, between bedtime after the evening injection and before getting up in the morning, i.e. before the morning determination of FBG and before the morning insulin injection.

2. Chemical, pharmaceutical and biological aspects

Composition

The finished product is a clear, sterile, unbuffered solution for injection with a slightly acidic pH of 4.0 presented in 5 ml colourless injection vials or 3 ml cartridges for use in pen devices. After the initial Marketing Authorisation the MAH submitted applications to add a pre-filled disposable pen and a new volume vial of 10 ml. Based on the submitted information, the CPMP recommended their granting.

The strength of 100 IU of insulin glargine per ml is equimolar to 100 IU human insulin per ml. The finished product contains the following excipients: zinc chloride, m-cresol, glycerol, hydrochloric acid, sodium hydroxide, and water for injections. The product does not contain ingredients of animal or human origin.

Active substance

Insulin glargine is a long acting analogue of the human insulin protein in which there has been an elongation of the carboxyterminus of the B chain by two arginines and a replacement of the C-terminal asparagine of the A chain by glycine. These modifications result in a shift of the isoelectric point of human insulin from pH 5.4 towards a neutral pH, making the molecule more soluble at a slightly acidic pH and less soluble at physiological pH.

Development genetics

The production process of insulin glargine uses a transformed *E.coli* K12 host strain, which has been comprehensively described in the application. This strain contains an expression plasmid encoding the modified human A and B chains of insulin, the monkey insulin C-chain, which differs from the human insulin C-chain in one position, and an artificial presequence to protect the resulting fusion protein against proteolytic destruction. This fusion protein is isolated, folded and enzymatically modified during downstream processing.

Cell bank system

A two-tiered cell bank system has been established. The master cell bank (MCB) was used to prepare the first and second working cell banks (WCB) under the same culture conditions as for the MCB. All pre-clinical and clinical work described in the dossier was performed with pharmaceutical product originating from the first WCB. The MCB and WCB were adequately tested and stability during storage was satisfactory. The protocol for the preparation of new WBCs as well as control tests and specifications will assure consistency of future WCBs with the cell bank used for development. The genetic stability, evaluated at the end of fermentation runs using a battery of tests (restriction enzyme analysis, plasmid retention, plasmid copy number, product formation), will ensure consistent production of insulin glargine.

Fermentation

The fermentation process has been adequately described in the application. In-process controls assure appropriate cell growth and the absence of microbial contamination. In addition, the correct overall performance of fermentation is verified by monitoring the production yield for which adequate limits have been set. Specifications for raw materials and a description of cell culture media (composition, preparation, sterilisation, and storage) and equipment have been provided. For the production of insulin glargine no material of human or animal origin are used. The full-scale process has been validated through compilation of operating parameters and in-process test data of 10 batches. These data indicate that the consistency of the manufacturing process of the active ingredient is within acceptable limits and that the in-process specifications and control ranges are met.

Downstream modification and purification

Usually, the harvest from one fermentation run is processed downstream to give one batch of insulin glargine. The downstream processing has been comprehensively described and purification is performed by several chromatographic steps and precipitation, which have been reasonably described. The removal of relevant impurities was examined during the development phase and was confirmed by production data. It has been shown that impurities arising from the expression system, including

residual host cell DNA, *E. coli* proteins and potential impurities arising during production are sufficiently removed.

After precipitation, the product is isolated by centrifugation and the resulting bulk of active ingredient is stored at low temperature for a period up to 24 months before further processing.

Appropriate in-process controls, mostly consisting of HPLC analysis, have been instituted to monitor downstream modification and purification and give assurance over the purification process and the quality of intermediates. Description and validation of the methods for identification of the active ingredient, purity, insulin glargine content, zinc content, and other routinely applied analytical methods have been provided. These methods are adequately validated. Insulin glargine has been well characterised using state-of-the-art methods with regard to its physicochemical characteristics and comparative investigations were performed with human insulin. Tests have demonstrated the similarity of the biological properties of insulin glargine and human insulin, which is also supported by results obtained from animal studies. Bioidentity tests are carried out routinely as release tests. The primary reference standard was prepared by further purification of a batch of insulin glargine.

Analytical test results of twenty-four batches produced on production scale indicate a consistent quality of the bulk active substance. Limits have been set for insulin glargine, relevant impurities and yield. A study conducted on three batches showed that most impurities are present in levels below 0.05% In this study no impurities larger than 0.1% were found. The impurities found in this study show structural similarity with insulin glargine. The impurity profile for each batch is monitored routinely. The acceptance criterion for the sum percentage of related proteins, currently 0.1-0.4%, will be reconsidered upon the availability of the stability study data for 24 months of storage under long term conditions. Quality of the chemicals and resins used in the purification process are adequate.

Active substance specifications

Insulin glargine is a well characterised human insulin analogue. Therefore, the active ingredient specifications have been chosen in accordance with the monograph for human insulin of the European Pharmacopoeia (3rd. ed., monograph 838), with the exception of the test for pro-insulin-like immunoreactivity, for which a non-radioactive test was established, loss on drying and sulphated ash. In addition, the product is tested for microbial contamination, bioidentity (to fulfil USP requirements) and moisture content.

Potential impurities arising from the expression system include DNA, *E .coli* proteins and endotoxins. All final batches produced are tested for the occurrence of *E. coli* proteins. Bacterial endotoxins are routinely measured in the active ingredient. The removal of *E coli* DNA and plasmid DNA has been addressed by providing adequate validation data.

In general, the active ingredient specifications are considered adequate to control the identity, purity and content of the active ingredient and to monitor batch-to-batch consistency. Specifications are sufficiently supported by the analysis of twenty-four batches of active ingredient and by the European Pharmacopoeia (Specifications of the active substance are attached).

Stability of the active ingredient at low temperature has been investigated by performing real time stability studies under normal storage conditions on three full-scale production batches for up to twelve months as well as studies under accelerated conditions. Results of these studies met the acceptance criteria. The active substance has been re-tested after 18 months and 24 months and the corresponding results have been submitted.

Other ingredients

M-cresol is added as a preservative, glycerol as tonicity agent and hydrochloric acid is used to dissolve insulin glargin and to adjust the pH during dissolution. A solution of sodium hydroxide may be used for final pH adjustment. The pH of the formulation is 4.0. Zinc chloride acts as stabilising agent promoting hexamer formation of insulin glargine. No overages are used. Excipients comply with the specifications as described in European (Ph.Eur.) or USA (USP) pharmacopoeia. Adequate descriptions, specifications and batch analysis for all packaging materials used for the bulk drug substance or the finished product were provided in the application.

Product development and finished product

The manufacturing process, which complies with Good Manufacturing Practice (GMP), has been described in sufficient detail. Briefly, insulin glargine and zinc chloride are dissolved in water for injection. The solution is sterilised by double filtration under aseptic conditions into sterilised containers. A summary of the microbiological aspects of the formulation and filling process has been provided and is adequate. In-process controls to control the manufacturing process are appropriate. Critical parameters have been validated by manufacture of three batches of each presentation. Control tests on the finished product will sufficiently guarantee the consistency of the manufacturing process of the finished product.

Stability

Based on the 18-month results from an ongoing stability study and data for 24 months of storage under the recommended storage conditions, a shelf-life of 24 months at +2 to +8 ^{o}C, protected from light, for the finished product is acceptable. The end-of-shelf life acceptance limits will be reconsidered upon availability of results from the ongoing stability study which will be carried out for up to 36 months.

The in-use stability profile was assessed in order to determine the maximum period of use after first opening as well as to determine the stability of the products during temperature fluctuations in case of adverse shipping conditions. Over a period of 28 days, the maximum intended period of use, under in-use conditions the formulation is stable at room temperature (25 °C).

Viral safety

No starting material from human or animal origin is used. Due to the usage of prokaryotic cells no viral contamination is expected. Trypsin is used in the production of the active ingredient. Trypsin is isolated from a homogenate of porcine pancreas. The process comprises treatment with organic solvents and nanofiltration or acidification of the extract. The trypsin manufacturing process ensures that no viruses are introduced into the production process by trypsin. Glycerol used as ingredient or for the preparation of the second WCB is of plant or synthetic origin. Glycerol used for the preparation of the MCB and the first WCB is of bovine origin and the processing conditions for this glycerol are in accordance with the "Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products" (CPMP/BWP/1230/98). After further investigation it was confirmed through a type II variation application that glycerol used as ingredient for the preparation of the MCB of synthetic origin.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The information provided in the application demonstrated consistent production of insulin glargine achieving a well-defined quality for the active substance and the finished product. The fermentation, down-stream processes and purification of the active substance are adequately controlled. Insulin glargine has been well characterised using state-of the-art methods with regard to its physicochemical characteristics. The manufacturing process of the finished product, which complies with Good Manufacturing Practice (GMP), has been described in sufficient detail and product specifications are adequate. In general, methods to control the quality of the product are adequate. The submitted documentation assured viral safety of insulin glargine. Stability data support a shelf-life of 24 months for the finished product.

Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of Lantus is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral safety and batch-to-batch consistency has been documented and the relevant test will be performed according to the agreed specifications (specifications are attached).

3. Toxico-pharmacological aspects

Insulin glargine is a human insulin analogue designed to have a low solubility at neutral pH. It is completely soluble at the acidic pH of the insulin glargine injection solution (pH 4). It is proposed that subcutaneous injection of the slightly acidic solution of insulin glargine will result in precipitation of the substance in the subcutaneous tissues. Small amounts of insulin glargine are continuously released from the precipitate giving a longer duration of absorption which in turn results in a prolonged duration of action and supports the dose regimen of one daily administration.

Pharmacodynamics

Insulin receptor binding studies have shown that insulin glargine has an about two-fold lower affinity for the insulin receptor with a similar association rate and a two-fold faster dissociation rate than human insulin. Further, nearly all *in vitro* metabolic studies have shown a relative *in vitro* potency for insulin glargine of about 50% and similar maximal responsiveness as compared to human insulin. The latter indicates that insulin glargine acts as a full agonist of human insulin. In comparison with human insulin, insulin glargine had a 1.4 (assay with mycocytes) to 12-fold (assay with osteosarcoma cells) higher affinity to the IGF-1 receptor when tested *in vitro*. The results from IGF-1 mitogenicity assays on osteosarcoma cells suggested that insulin glargine might have a mitogen potential through binding to the IGF-1 receptor. This was a particular point of concern and was addressed in an oral explanation at CPMP and is discussed below.

After intravenous injection of insulin glargine in dogs and rats, the glucose lowering activity of insulin glargine did not markedly differ from human insulin. There is evidence that higher plasma levels *in vivo* compensate for the 50% *in vitro* potency found for insulin glargine as compared to human insulin.

Studies performed in different animal species have shown that the depot activity as well as the effect of zinc concentration on the depot activity strongly depended upon the animal species tested. Given the homology between the insulin receptor in dog and human, results obtained in dogs were most informative. After subcutaneous injection in dogs, a higher depot activity (i.e. *sustained release*) than for NPH (neutral protamine Hagedorn) insulin was demonstrated for insulin glargine. In contrast to NPH insulin, insulin glargine displayed a depot activity, which was dependent upon its concentration and the concentration of zinc. Trials in dogs allowed selection of the insulin glargine formulation to be used in clinical studies.

Pre-clinical studies showed that the general pharmacodynamic profile of insulin glargine is related to its glucose lowering activity and at high dose to its catecholamine releasing properties and does not differ from the profile displayed by other insulins. From insulin glargine's general pharmacodynamic profile there is no concern about its safety.

Studies have demonstrated that the effects of insulin glargine and human insulin are additive. Firstly, in an adipocyte cell assay using equipotent mixtures of insulin glargine and human insulin, the effects of these products on lipogenesis and glucose transport were additive. Secondly, after intravenous treatment in dogs, a 1:1 mixture of insulin glargine and human insulin exhibited additive activity for both insulins. There is no pre-clinical evidence for interference of insulin glargine with the effects of human insulin.

In summary, the pre-clinical *in vivo* studies, especially those in dogs, provided sufficient evidence for clinical efficacy of insulin glargine in the treatment of diabetes.

Pharmacokinetics

Absorption

Autoradiographic data in rats and toxicokinetic data showed that the release of the active compound from the site of injection in laboratory animals was relatively slow as compared to human insulin. In a metabolism study in rats, 24 hours after injection, parent compound could still be detected at the subcutaneous injection site. The toxicokinetic studies in rats, mice and dogs showed that the period during which the compound was released from the injection site increased with increasing dose.

Plasma protein binding

Human insulin is not expected to be bound to plasma proteins. Insulin glargine and human insulin are structurally similar, and so are their respective active biodegradation products. Therefore the binding of insulin glargine to plasma proteins is likely to be similar to human insulin. The same applies to insulin glargine's metabolites.

Distribution

Studies using auto-radiography have shown that the distribution of radio-labelled insulin glargine and human insulin after single subcutaneous or intravenous administration to male rats were very similar, the only difference being that after subcutaneous administration, distribution and elimination of the label were slower than after intravenous administration. High radioactivity was found in kidney, urinary bladder, liver, thyroid gland and stomach content. Little to no radioactivity was found in the central nervous system. Given the intrinsic instability of the radio-labelled compounds used in these studies, the distribution of the label in the body at different time points after administration were not considered to give a representative picture of the distribution of the active compound and its metabolites. However, based on the similarity of insulin glargine to human insulin, it is unlikely that the distribution of insulin glargine will differ significantly from that of human insulin. The same applies to their respective metabolites, which share a high degree of similarity.

Metabolic pathway and metabolites

The biodegradation of insulin glargine has been studied *in vitro* in human and rat tissues and *in vivo* in the rat, the dog as well as in man. These studies indicated that the main metabolic pathway consists in successive removal of three amino acids at the carboxy-end of the B-chain of insulin glargine. Given the structural similarity of insulin glargine with human insulin, it can be assumed that the resulting molecule is further degraded following the metabolic pathway for human insulin. Following subcutaneous injection in man, insulin glargine is already partially degraded at the injection site so that not only insulin glargine but also its metabolites are released in the circulation.

Excretion

The compound is assumed to be recycled as amino acids. No metabolites were detected in rat urine. In dog urine, less than 1% from a given dose could be recovered in the form of insulin glargine metabolites.

Results from single-dose kinetics

The pharmacokinetics following single-dose intravenous and subcutaneous administration of insulin glargine was evaluated in male rats and dogs. Following intravenous administration, insulin glargine is eliminated from the circulation with terminal half-lives of 1.2 and 1.8 hours in rats and dogs, respectively. Following subcutaneous administration, maximum concentrations are reached 2 or 4 hours post dosing, and elimination from plasma takes place with half-lives of 4.3 or 5.4 hours in rats and dogs, respectively. In man, insulin glargine had a slightly shorter terminal half-life of 0.8 h, the same half-life as for insulin, but the effective half-life from depots of 13 hours was considerably slower than in the rat or the dog.

Toxicology

Single dose toxicity

High doses of insulin glargine resulted in death due to excessive hypoglycaemia.

Repeated dose toxicity

Repeated dose toxicity studies were performed by subcutaneous administration of insulin glargine in mice rats and dogs. The animals suffered from dose dependent hypoglycaemia, hypoglycaemic shock and coma. These effects are due to the excessive pharmacodynamic action of the product. Haemorrhage, inflammation and fibrosis were observed at the injection site. Pancreatic beta-cell degranulation was observed in both dogs and rats. This reversible beta-cell degranulation was probably due to the down regulation of insulin synthesis due to a compound over-stimulation, and would therefore also occur during long-term treatment with human NPH insulin as well.

Reproduction studies

Effects on reproduction occurred at high doses inducing hypoglycaemia and maternal toxicity. At low doses reproduction was not affected.

Mutagenic potential

The mutagenic potential of insulin glargine was investigated using three bacterial assays, one *in vitro* point mutation assay in mammalian cells, one *in vitro* V79 Chinese hamster chromosome aberration assay, all with and without metabolic activation. In addition, an *in vivo* bone marrow chromosome aberration assay in Chinese hamsters following single subcutaneous doses of 0 and 750 IU insulin glargine/kg was performed. These studies demonstrated that insulin glargine is not mutagenic.

Oncogenic and carcinogenic potential

The carcinogenic potential was studied in mice and rats. Malignant Fibrous Histiocytomas at the injection site were the predominant findings in both mice and rats. This effect was not related to the dose but correlated to the low pH of the insulin glargine solution. Malignant Fibrous Histiocytomas is a type of tumour commonly found in subcutaneous tissues of laboratory rats and mice when solutions with non-neutral pH are used. In both mice and rats, there was no evidence for treatment related neoplastic findings other than Malignant Fibrous Histiocytomas. However, the affinity of insulin glargine for the IGF-1 receptor was a particular concern, especially because of the fact that published results for the B10-Asp insulin analogue, a fast-acting bolus insulin, have raised concern about the mitogenicity of insulins. This point is discussed below.

Insulin glargine Non-neoplastic changes including subcutaneous fibrosis, sclerosis and inflammation, squamous cell hyperplasia, epidermitis and haemorrhage were observed at the injection site.

Local tolerance

Local tolerance in a number of rabbit studies was good for single intravenous, paravenous and subcutaneous injections of doses similar to those intended to be used in humans and moderate to good for single intramuscular injection. The formulations used in the repeated dose toxicity studies in mice and rats elicited tissue damage caused by the low pH of these formulations (see above).

Antigenic potential

The antigenicity of insulin glargine was evaluated in rats and dogs. Antibody formation was observed in rats. However, due to the differences in structure between rat and human insulin, this finding is not relevant for humans. In dogs, antibody formation against insulin glargine was not observed. Since human and dog insulin share high structural homology it is likely that insulin glargine has low antigenic potential in humans.

Ecotoxicity/Environmental risk assessment

Ecotoxicity and environmental risk are not to be expected with this compound.

Compliance to Good Laboratory Practice (GLP)

All pivotal studies were in compliance with GLP.

Discussion on toxico-pharmacological aspects

Overall, pharmacodynamic and pharmacokinetic studies provided adequate evidence for efficacy of insulin glargine in the treatment of diabetes and demonstrated the slow release of the active ingredient from the injection site, which is the rationale for its depot activity.

The major safety concern related to the risk associated with the long and constant exposure to insulin glargine when compared to slow release formulations of native human insulin already in clinical use. The published findings with the B10-Asp insulin analogue has raised concern, especially with regard to the mitogenicity of insulins. This was all the more a concern since an IGF-1 mitogenicity assay on osteosarcoma cells suggested that insulin glargine might have a mitogenic potential through binding to the IGF-1 receptor. This point of concern was addressed in an oral explanation at CPMP where the company highlighted that insulin glargine has a lower mitogenic activity than the comparator B10-Asp insulin or IGF-1 in 3 out of 4 cell assays. The company discussed the clinical safety implications raised by binding to the IGF-1 receptor in light of carcinogenicity studies in rats and mitogenicity estimates provided in the application dossier. The company emphasised that the long term rodent

studies did not show any increase in mammary tumours as would be expected had the compound a mitogenic potential. The clarification provided by the company was acceptable and it was concluded that the carcinogenic potential of insulin glargine was small.

Overall, results from the toxicology programme did not raise particular concerns for the safe use of insulin glargine.

4. Clinical aspects

Clinical pharmacology

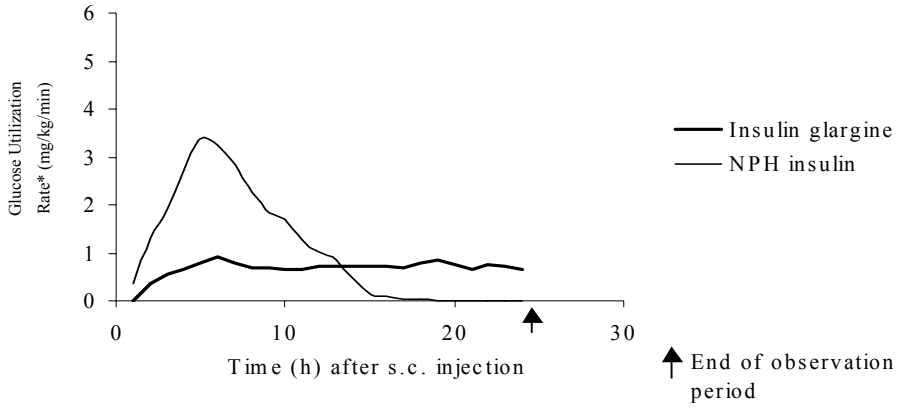
Pharmacodynamics

The primary activity of insulins, including insulin glargine, is regulation of glucose metabolism by binding to a specific cell receptor. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis in the adipocyte, inhibit proteolysis and enhance protein synthesis.

Insulin glargine is classified in the pharmacotherapeutic group "Antidiabetic agent" (ATC Code: A10AE04 Insulin and analogues, long-acting).

To evaluate the pharmacodynamic behaviour of insulin glargine, a total of 15 studies including 10 euglycaemic clamp studies and 1 hypoglycaemic clamp study in healthy volunteers or in patients with type 1 diabetes were performed. Intravenous administration in healthy volunteers of equimolar doses of insulin glargine and human insulin yielded comparable time-action profiles and showed that insulin glargine had similar effects on hepatic glucose production and glucose turnover. This indicated that insulin glargine and human insulin have equal efficacy on target tissues when given in equimolar doses. After subcutaneous injection in healthy volunteers, the onset of action of insulin glargine was slower than with human NPH insulin and insulin glargine had a longer duration of action (Figure 1). After repeated subcutaneous injection in healthy subjects, the median time-action profile of insulin glargine had a lower intra-subject variability than Ultralong (human ultralente insulin), a long acting insulin. The median time-action profile after subcutaneous injection of insulin glargine in subjects with type 1 diabetes mellitus also indicated that insulin glargine displays a moderate sustained glucose lowering activity over 24 hours, compared to a distinct peak in activity with NPH insulin.

Figure 1. Activity Profile in Patients with Type 1 Diabetes



*determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values)
s.c.: subcutaneous

During intentionally induced profound hypoglycaemia by intravenous infusion to healthy subjects and subjects with type 1 diabetes mellitus, insulin glargine or human insulin had similar neurogenic,

neuroglycopenic and counter-regulatory hormone responses. This result indicated that insulin glargine and human insulin provoke similar physiological and biochemical responses to hypoglycaemia.

Conclusion

In clinical pharmacology studies, intravenous insulin glargine and human insulin have been shown to be equipotent when given at the same doses. In patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than with human NPH insulin, its effect profile was smooth and peakless, and the duration of its effect was prolonged. The longer duration of action of insulin glargine is directly related to its slower rate of absorption and supports once daily administration.

Pharmacokinetics

A limited amount of pharmacokinetic data on insulin glargine was presented in the application. The human pharmacokinetics of insulin glargine was investigated in 11 different studies (listed in the table below).

Pharmacokinetic studies

Study	N*	Subjects	Scope
1001, 1002	9	Healthy male volunteers	comparison of pharmacodynamics and pharmacokinetics following injection at different injection sites
1003	14	Healthy male volunteers	comparison of pharmacodynamics and pharmacokinetics in euglycaemic clamp
1004		healthy volunteers	investigation of absorption rate with formulations not intended to be marketed
1006	14	Healthy male volunteers	investigation of the effect of zinc content on the pharmacodynamics and pharmacokinetics in euglycaemic clamp
1007	12	Healthy male volunteers	comparison between insulin glargine, HOE 36H and Ultratard HM®
1008	20	Healthy subjects	determination of the equimolar potency of insulin glargine compared with regular insulin following intravenous infusion on glucose lowering effect and pharmacokinetics in euglycaemic clamp
1010	12	Healthy male volunteers	study in which the absorption from different injection sites was compared with the formulation to be marketed
1015	20	type 1 diabetic subjects	characterisation of time-action profiles of insulin glargine in comparison with NPH insulin after a single dose
1016	5	Healthy male volunteers	determination of metabolic degradation products
1017	14	type 2 diabetic subjects	comparison of the subcutaneous absorption of insulin glargine and NPH insulin

*N is the number of subjects involved in the study

In healthy subjects and diabetic patients, insulin serum concentrations indicated a slower and much more prolonged absorption and showed a lack of a peak after subcutaneous injection of insulin glargine in comparison to human NPH insulin. Concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine (Figure 1).

There were no clinically relevant differences in serum insulin levels after abdominal, deltoid or thigh administration of insulin glargine. Insulin absorption was similar in type 2 diabetic subjects as compared to healthy volunteers.

Insulin glargine is partly degraded at the site of injection, i.e. in the subcutaneous tissue. The first metabolite is formed by loss of both arginines at the carboxyl-terminus of the B chain. Additional loss of the next amino acid, threonine, generates the second metabolite. The same metabolites were found

in animal studies. The biological activity of these metabolites was investigated *in vitro* in rat adipocytes and *in vivo* in rats. Both metabolites were found to exhibit similar hypoglycaemic activity to insulin glargine. Since the two metabolites found in humans are identical to the metabolites found in animal studies, it is expected that they also have similar biological activity to insulin glargine in humans. Unchanged insulin glargine and degradation products are present in the plasma in similar quantities. Further degradation is assumed to be similar to endogenous insulin. Data indicated that degradation of the two major metabolites occurred only minimally during sample collection and storage.

After an intravenous infusion the elimination half-lives were comparable for insulin glargine and regular insulin.

Absorption studies performed following subcutaneous injection of insulin glargine indicated that after 24 h approximately 50 % of the dose still remained at the site of injection. After 48 h the amount of insulin glargine at the injection site was still about 20 %. Given the method used for the quantification of insulin glargine, these amounts do not reflect the exact amount of active substance present at the injection site. This is supported by findings that injected insulin may be metabolised locally, resulting in a disproportional relationship between the measured amount and the actual amount remaining at the site of injection. No pharmacokinetic study involving repeated dosing of insulin glargine was performed to address the question of possible accumulation of active substance and its metabolites at the injection site.

The lack of pharmacokinetic data on repeated dosing was a point of concern. In response the company explained that experience with subcutaneous administration of NPH insulin indicated that extensive accumulation upon multiple dosing of insulin glargine is not expected. The company performed supportive simulation calculations. Simulated mean multiple-dose concentration-time profiles of exogenous insulin based on individual subject data obtained after single subcutaneous injections of insulin glargine indicated that steady-state may be reached after 2 to 4 days of treatment, and C_{max} values may be 1.8-fold higher than after the first dose of insulin glargine. This was supported by interim results from an ongoing pharmacokinetic study presented at the oral explanation at CPMP. Results from this study also suggest that accumulation is not expected. The SPC indicates that insulin glargine injected once daily will reach steady state levels in 2-4 days after the first dose. This has to be confirmed upon completion of the ongoing pharmacokinetic study as part of a follow-up commitment.

As part of this follow-up commitment, the pharmacokinetic profile on repeated dosing of insulin glargine has been investigated further. In subjects with type 1 diabetes, 11-day repeated subcutaneous administration of insulin glargine revealed that steady state was reached by day 2. There were no statistically significant differences in the point estimates and in the 90% confidence intervals for the mean ratios of Cmax and AUC(0-24h) between day 5 and day 2 or day 12 and day 2. The plateau reached does not show relevant peaks or nadirs. No accumulation or peak absorption was observed in repeated subcutaneous administration of insulin glargine.

The pharmacokinetics of insulin glargine were not evaluated in special populations (e.g. patients with impaired renal or liver function), nor was the influence of gender, age or race. In long-term clinical studies in patients, subgroup analyses based on age and gender did not indicate any difference in safety and efficacy between patients treated with insulin glargine and the entire study population. It is also expected that modifications to pharmacokinetics and pharmacodynamics occurring with insulin glargine in subjects with impaired renal and hepatic function will be similar to modifications observed with human insulin. A warning for diminished insulin requirements in renal impairment, and a steady decrease in insulin requirements in the elderly has been included in the SPC. In the light of these warnings and since the dose must be individually adjusted to each patient, the lack of pharmacokinetic data in sub-populations was considered acceptable.

Clinical efficacy

Insulin glargine is indicated for use in patients with type 1 or type 2 diabetes mellitus, where treatment with insulin is required. To support efficacy and safety of insulin glargine in the treatment of type 1 and type 2 diabetes, a total of 10 clinical trials were performed. Five studies were of a short duration (4 weeks) and 5 studies were of a longer duration of 16-52 weeks.

The table below provides an overview of all clinical studies.

Study	Duration	Number of subjects screened	Number of subjects randomised and treated		
			insulin glargine	NPH insulin	Total
Short Duration					
Type 1 diabetes					
Study # 2002	4 weeks	315	168	88	256
Study # 2003	4 weeks	372	223	110	333
Subtotal, type 1		687	391	198	589
Type 2 diabetes					
Study # 2004	4 weeks	256	136	68	204
Study # 2005	4 weeks	188	108	49	157
Study # 2006	4 weeks	131	57	57	114
Subtotal, type 2		575	301	174	475
Subtotal Short Duration		1262	692	372	1064
Long Duration					
Type 1 diabetes					
Study # 3001	28 weeks	655	292	293	585
Study # 3004	28 weeks	677	264	270	534
Study # 3005	16 weeks	689	310	309	619
Subtotal, type 1		2021	866	872	1738
Type 2 diabetes					
Study # 3002	52 weeks	687	289	281	570
Study # 3006	28 weeks	846	259	259	518
Subtotal, type 2		1533	548	540	1088
Subtotal Long Duration		3554	1414	1412	2826
TOTAL		4816	2106	1784	3890

All studies were multicentre, randomised, open studies comparing insulin glargine with human NPH insulin (except study 2006), the standard insulin used to provide basal insulin supply. Centralised, computerised, telephone randomisation was used in all studies to avoid imbalances in the treatment groups potentially caused by investigator bias due to the open study design. The basal insulin dosing regimen for subjects receiving insulin glargine was once daily (at bedtime) regardless of their prior regimen. The regimen for subjects receiving NPH insulin was either once daily (at bedtime) or twice daily (in the morning and at bedtime), based on their regimen prior to the treatment phase. In the studies in type 1 diabetes mellitus, the daily insulin dose was adjusted to maintain fasting blood glucose (FBG) between 80 and 120 mg/dl (4.4 and 6.7 mmol/l). In the studies in type 2 diabetes, target fasting plasma glucose (FPG) levels were between 80 and 140 mg/dl [4.4 – 7.8 mmol/l] with an optimum FPG < 126 mg/dl [7.0 mmol/l]) while avoiding hypoglycaemia. Human regular insulin (except study 3005 where insulin lispro was used) was injected before meals according to common practice in all studies in type 1 diabetes and studies 2005, 2006 and 3006 in type 2 diabetes mellitus. In study 3006 additional antidiabetic treatments was provided by oral antidiabetic drugs.

Short duration studies (4 weeks)

Short duration studies were used to compare the efficacy and safety of insulin glargine with that of human NPH insulin as well as to select the insulin glargine formulation to be investigated in the longer duration studies. Primary efficacy parameters were FPG at endpoint (adjusted for baseline) in the intention to treat (ITT) population. Secondary efficacy variables in most studies were hypoglycaemic episodes, FBG, blood glucose profile, nocturnal blood glucose, stability of FPG and FBG, treatment response, serial overnight plasma glucose, fasting serum insulin, insulin doses, HbA_{1c} and fructosamine.

Long duration studies (16-52 weeks)

Long duration studies were used to compare the efficacy and safety of insulin glargine and human NPH insulin. The primary efficacy parameter was the change in $_c$ HbA_{1c} from baseline to endpoint in the ITT population. Hypoglycaemia was analysed as a secondary efficacy variable. Other secondary efficacy parameters were FPG, FBG, variability of FBG, nocturnal blood glucose, 24-hour average blood glucose, 24-hour average plasma glucose, fasting serum C-peptide, fasting serum insulin. Quality of life (QoL) was investigated in studies 3001, 3002, 3004, 3006 using the Diabetes Treatment Satisfaction Questionnaire and the Well-Being Questionnaire. Studies were planned to provide a 90% power to detect an average difference of 0.5% HbA_{1c} between treatment groups.

Paediatric studies

Based on the results of 3 clinical trials in paediatric populations, the MAH submitted a type II variation application to include the use of Lantus in children of 6 years or above.

Study 3003 is the pivotal study. It was an open-label, randomised, parallel-group study, comparing Lantus to NPH insulin in type 1 diabetic children. Duration of the trial was 28 weeks and the number of subjects (children between 5 and 16 years) included was 174 on Lantus and 175 on NPH insulin.
Study 3013 was an extension study of study 3003 in which all subjects received Lantus and which provided further long-term safety data in these subjects. Inclusion criteria for study 3013 were subjects who had successfully completed study 3003 and whose glycaemia was well controlled with Lantus. The median duration of the trial from the start of study 3003 was 2.6 years (201 to 1159 days). 143 subjects have been included in the study.
Study 4005 was done in 26 adolescents (12-18 years) who had type 1 diabetes mellitus for more than 1 year, or were C-peptide negative at start of the study. This was an open, randomised, active controlled, 2-way crossover study to compare the effects of a regimen with Lantus+Lispro to those of a regimen with NPH+regular human insulin. Duration of the trial was 32 weeks (2 treatment sequences of 16 weeks).
In all studies Lantus was given in the evening.

Efficacy in type I diabetes

With respect to GHb, insulin glargine appeared to be equally effective as NPH insulin. No changes were found in GHb at endpoint as compared to baseline. Patients had already a rather well controlled blood sugar level at baseline. The blood glucose lowering potential of insulin glargine was demonstrated in all three studies (3001,3004 and 3005). Comparable decreases of FBG and FPG were found for insulin glargine and for NPH insulin administered once daily (study 3001), where similar basal insulin doses were given. FBG and FPG decreased more in the insulin glargine than in the group receiving NPH insulin twice a day (studies 3004 and 3005), where the insulin glargine bedtime dose was 70% higher than the NPH bedtime dose.

A responder analysis, according to a target FBG of 120 mg/dl (6.66 mmol/l) revealed variable results when insulin glargine was compared to NPH insulin administered once daily. When compared to NPH insulin administered twice a day, insulin glargine scored slightly better. However, the majority of patients in both treatment groups still had FBG values above the target.

Special attention was paid to nocturnal hypoglycaemia. When comparing insulin glargine and subjects receiving NPH insulin once daily, significantly fewer subjects receiving insulin glargine reported severe or nocturnal hypoglycaemia, while the decreases in FBG and FPG for the two treatment groups were comparable (3001/3004 combined). When comparing the insulin glargine to the group receiving NPH insulin twice a day, where the NPH dose given at bedtime was lower than that of insulin

glargine, FBG decreased significantly more in the insulin glargine than the NPH group, while the percentage of subjects reporting nocturnal hypoglycaemia was similar. Asymptomatic hypoglycaemia based on fasting self-monitored blood glucose determinations and visit fasting glucoses, with BG < 50 mg/dl or 36 mg/dl, was seen more frequently in patients receiving insulin glargine in studies 3004 and 3005, especially from month 2 till the end of the study, in subjects that had a prior more than once daily basal insulin regimen; the frequency of asymptomatic hypoglycemia in subjects that had a prior once daily basal insulin regimen was similar with insulin glargine and NPH. A similar number of insulin glargine and NPH patients had asymptomatic hypoglycemia in study 3001. The issue of hypoglycaemia is discussed in the section devoted to *Clinical Safety*.

From the clinical studies performed to demonstrate efficacy it can be inferred that patients receiving a treatment with a single dose of NPH insulin per day could be directly transferred to the same dose of insulin glargine. A reduction of the total starting dose of basal insulin dose by 20% or more (efficacy and safety issue, which are discussed further in the safety section) could be recommended when a twice daily NPH regimen is changed to a once daily insulin glargine regimen.

Efficacy in type 2 diabetes

Results from clinical studies were unclear as to the efficacy of insulin glargine in patients with Type 2 diabetes. Glycaemic control as measured by HbA_{1c} was better with NPH insulin than with insulin glargine in study 3006. Study 3002, however, demonstrated similar efficacy for insulin glargine and NPH insulin. Upon request for further clarification the company presented the results of a meta-analysis of studies 3002 and 3006 at the oral explanation at the CPMP. Results from this analysis provided evidence that both NPH insulin and insulin glargine have a substantial lowering effect on GHb in subjects with Type 2 diabetes mellitus.

Insulin glargine treated subjects reported less nocturnal hypoglycaemia. However, 24-hour registration of hypoglycaemias showed that there were more hypoglycaemias in the period between 6:00 and 8:00 a.m in patients treated with insulin glargine than in patients treated with NPH insulin (safety concerns related to hypoglycaemia are discussed in the section devoted to *Clinical Safety*).

Efficacy in children

Study 3003 was designed as a superiority trial with a 90% power to detect an average difference of 0.5% Glycated Haemoglobin (HbA_{1c}) in favour of Lantus versus NPH insulin. Mean changes from baseline to endpoint in HbA_{1c} were comparable in the Lantus (0.28%) and NPH (0.27%). Since superiority was not demonstrated, the MAH performed a post-hoc analysis of equivalence. This analysis showed that the the 95% confidence interval of the mean difference in change from baseline in HbA_{1c} between Lantus and NPH ranged from –0.24 to 0.26 in the intent to treat population and from –0.27 to 0.23 in the per protocol population. Therefore Lantus was demonstrated to be non-inferior to NPH.

The effects of treatment on HbA_{1c} was also analysed in the subgroups of children ≤11 years and >11 years. No difference was seen between the effects of Lantus and NPH in the 2 subgroups.

Reductions in fasting blood glucose (FBG) were observed in both treatment groups throughout study 3003 but there was a greater average decrease in FBG in the Lantus group compared to the NPH group at all timepoints. This difference was statistically significant at weeks 4, 16 and endpoint.

No significant differences were seen between Lantus and NPH with respect to the incidence of hypoglycaemia.

The primary objective of study 4005 was to compare the proportion of subjects with at least one nocturnal hypoglycemic episode occurring during an overnight metabolic profile carried out at the end of each 16-weeks treatment period. The percentage of subjects with at least one nocturnal hypoglycemic episode was 32% in the Lantus + Lispro group as compared to 52% in the NPH + regular human insulin. As the study was powered to detect a difference of 37% in the percentage of subjects with nocturnal hypoglycemia between Lantus + Lispro and NPH + regular human insulin the observed difference of 20% did not reach statistical significance (p=0.17).

Conclusion

In type 1 diabetic patients, insulin glargine appeared to be equally effective as NPH insulin with respect to glycaemic control. The blood glucose lowering potential of insulin glargine was demonstrated in all studies.

In type 2 diabetic patients glycaemic control was similarly good with insulin glargine and NPH, both in combination with oral antidiabetic drugs and insulin.

Clinical safety

The safety of insulin glargine was evaluated on the basis of 10 clinical trials designed for the evaluation of clinical efficacy and safety by comparing insulin glargine to NPH insulin (see section *Clinical efficacy* for the description of the trials). While five of these trials where only of short duration (4 weeks), five trials had a longer duration of 16 to 52 weeks. Overall, 1104 patients have been exposed to the product for at least 6 months and 289 patients have been exposed to the product over a period of one year. Overall, the studies showed that the safety profile of insulin glargine is similar to that of NPH insulin. However a number of major safety issues have been identified. These are hypoglycaemia, local reactions/toxicity, immunological reactions/antibody formation and ocular safety.

Hypoglycaemia

Less nocturnal hypoglycaemia occurred when patients were transferred from once daily NPH insulin to an equivalent dose of once daily insulin glargine. However, an initial increase in the incidence of nocturnal hypoglycaemia was observed with insulin glargine when patients were transferred from more than once daily NPH insulin to once daily insulin glargine. More nocturnal hypoglycaemia occurred even with a 20-25% reduction of the total insulin glargine dose during the initial treatment phase.

It should be noted that during clinical trials dose-titration of insulin glargine was done at the discretion of the treating physician. This explains inconsistency of observations made in relation to the occurrence of hypoglycaemia. Nevertheless, it can be concluded that insulin glargine may give less nocturnal hypoglycaemia if careful initial dose titration is performed and that the recommended starting dose of insulin glargine should be reduced by more than 20-25% for patients who were previously treated with twice daily NPH insulin.

Studies indicated that after the initial titration phase, the frequency of symptomatic hypoglycaemia induced by insulin glargine and NPH were comparable. The incidence of serious and severe hypoglycaemia was also comparable. A higher incidence of asymptomatic hypoglycaemia was observed in patients treated with insulin glargine. However the studies suggest that there is no increased risk for the development of severe hypoglycaemia with insulin glargine in patients with asymptomatic hypoglycaemia. The incidence of nocturnal hypoglycaemia was lower during the later study period in study 3002 and 3006 (3002: months 2-5 and months 6-12; 3006: months 2-6) for insulin glargine than for NPH insulin. This result was confirmed by the meta-analysis of studies 3002 and 3006.

Overall, studies suggest that following the initial titration phase, insulin glargine is as safe as NPH insulin with respect to hypoglycaemia.

Local reactions

Insulin glargine provoked pain at the injection site at a higher frequency than NPH insulin. The pain was generally tolerated, since patients were not withdrawn from studies. One serious local reaction that required hospital care was reported.

Pharmacology studies indicated that absorption of insulin glargine from the injection site is very slow and that some product (insulin glargine and/or its metabolites) is still present at the injection site after 24 hours. Since insulin glargine is intended for continued treatment over a long period of time and even if injection sites are frequently changed, the prolonged exposure of relatively small areas of subcutaneous tissue to the product may result in local toxicity.

From safety data collected there is no evidence that insulin glargine may have caused any of the observed injection site reactions (including injection site mass and inflammation) that cannot be

considered a common side effect of insulin injections. There is no evidence for local cancers in humans. However, on the basis of the collected safety data, which cover a period of a maximum of 52 weeks, the effect of long-term exposure to insulin glargine cannot be fully evaluated. Therefore careful post- marketing surveillance will be required in order to monitor the appearance of more serious local reactions.

Immunological reactions and antibody formation

There was no significant difference in the incidence of local or systemic hypersensitivity reactions reported in the clinical studies between patients receiving insulin glargine and patients receiving NPH insulin. Systemic hypersensitivity reactions were rare and they were rarely accompanied by an increase in antibody formation. Increase in insulin glargine antibody formation was accompanied by an increase in human insulin antibody formation due to a considerable cross-reactivity between these antibodies. For patients experiencing an increase in antibody formation, defined as clinically important in the study design, there was generally no loss of glycaemic control. In some patients, the total insulin dose was increased by 2-35 IU but the increase was also often accompanied by a better glycaemic control. In few patients a worsening of glycaemic control occurred, even if the insulin dose was increased. Given the specificity and sensitivity of the method used for antibody determination, it is unlikely that this deterioration in glycaemic control was due to clinically meaningful antibody formation that remained undetected. This deterioration was more likely due to inadequate insulin dose adjustment necessary to maintain optimal glycaemic control.

In view of the safety data collected in clinical trials, the issue of antibody formation and immunological reactions and loss of glycaemic control is not a major concern.

Ocular safety

Retinal adverse events were reported with a similar incidence in patients treated with insulin glargine or with NPH insulin. To evaluate retinopathy, fundus photographs were taken at study start and at study end in studies 3001, 3002, 3004 and 3006. For some patients a third examination was performed. In one study (3006) a statistically significant increase in the incidence of retinopathy (≥3 step progression) was observed in patients treated with insulin glargine. The increase does not appear to be related to the glycaemic control (i.e. HbA1c and FPG) or to the insulin dose. A similar negative trend was observed in study 3001.

Results of a meta-analysis performed for studies 3001, 3002, 3004 and 3006 did not demonstrate a meaningful difference in the number of subjects who had a ≥3-step progression in retinopathy between insulin glargine and NPH. Subjects with a ≥3-step progression generally demonstrated greater improvement of glycaemic control than subjects without such a progression. There were no clinically relevant differences for insulin dose and insulin antibodies between insulin glargine and NPH subjects either with or without ≥3-step progression.

Even if insulin glargine displays a higher affinity to the IGF-1 receptor than human insulin, its affinity is still very low as compared to IGF-1. Therefore it is unlikely that IGF-1 is involved in the progression of retinopathy in patients treated with insulin glargine. This is also supported by the fact that optic disc swelling, the most commonly associated retinopathy symptom resulting from IGF-1 treatment, was not observed in any of the clinical trials.

In light of the safety data collected during clinical trials the influence of insulin glargine on ocular safety is unclear. Results from different studies are not consistent. Since the observed increase of retinopathies could be indicative of a less well-controlled blood sugar level in patients treated with insulin glargine compared to patients treated with NPH insulin the company was asked to provide further clarification. In response to this concern the company consulted several experts in the field of ophthalmology. Their conclusion was that there is no reason to suspect that there is an increased incidence in adverse ocular reactions associated with insulin glargine treatment.

Clinical Safety in Children

The results of the paediatric studies showed that there were no significant differences between Lantus and NPH insulin with respect to Treatment Emergent Adverse Events (TEAE). The most common TEAEs in all 3 studies were infection, upper respiratory tract infections, gastro-enteritis, rhinitis, and pharyngitis. There were no clinically significant findings with laboratory parameters.
In study 3003, mean Lantus and human insulin antibody titers decreased from baseline to endpoint in the Lantus group whereas they slightly increased in the NPH group. The decrease in antibody titers in the Lantus group continued in study 3013.
Post-marketing experience coming mainly from the US where Lantus is approved for use in children of 6 years and older did not reveal unexpected safety concerns.

Dosing scheme

The MAH submitted a type II variation application to change the initially approved dosing scheme for Lantus (i.e. once daily in the evening). The submission provided data to support a more flexible dosing regimen such that Lantus may be administered once daily, at any time of the day, provided it is the same time every day.

The application was based on clinical data derived from a total of 1392 subjects with type 1 and type 2 diabetes mellitus, randomised and treated in 3 randomised, parallel-group, open-label clinical trials.
The first study (study 4007) compared the effects of Lantus administered once daily at breakfast, at dinner or at bedtime in addition to insulin lispro before meals in 378 type 1 diabetic patients. The two other studies (4001 and 3102) were performed in type 2 diabetic patients and compared Lantus administered at breakfast or at bedtime (study 4001 only) with NPH.

Mean endpoint HbA1c (study 4007) or change in HbA1c from baseline to endpoint (studies 4001 and 3102) was the primary efficacy criteria used. Equivalence (study 4007) or non inferiority (studies 4001 and 3102) was demonstrated for HbA1c either between the different times of Lantus administration (studies 4001 and 4007) or between Lantus (at each time of administration) and NPH (studies 4001 and 3102). In addition, in study 4001, the decrease in HbA1c seen in the Lantus breakfast group was shown to be superior to that seen in the Lantus and NPH bedtime groups.

In study 4007, significantly fewer patients reported nocturnal hypoglycemia in the Lantus breakfast group (59.55%) compared to the Lantus dinner or bedtime groups (71.9 and 77.5% respectively) ($p=0.0050$). In study 4001, significantly fewer patients in the Lantus breakfast and bedtime groups (16.5 and 22.9 % respectively) reported nocturnal hypoglycemia compared to NPH bedtime patients (38.2%)($p=0.001$).
In the three clinical studies, Lantus was well tolerated at all injection times and in studies 4001 and 3102 had a safety profile similar to that of NPH. There were no relevant differences between treatment groups in any of the study with respect to Treatment Emergent Adverse Events or laboratory safety data.

In conclusion, the results shown that the efficacy and safety of Lantus appear to be comparable regardless the time of administration

The CPMP agreed that the timing of administration should be individualised so that Lantus may be administered once daily at any time but at the same time every day. This is reflected in section 4.2 of the SPC.

5. Overall conclusions and benefit/risk assessment

Quality

Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of Lantus is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral

safety and batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications (specifications are attached).

Preclinical pharmacology and toxicology

Overall, pharmacodynamic and pharmacokinetic studies provided adequate evidence for efficacy of insulin glargine in the treatment of diabetes and demonstrated the slow release of the active ingredient from the injection site, which is the rationale for its depot activity. The major safety concern relates to the risk associated with the long and constant exposure to insulin glargine when compared to slow release formulations of native human insulin already in clinical use.

The major point for concern revealed by toxicology studies was the affinity for the IGF-1 receptor. However, after careful evaluation of the clinical relevance of these findings, it was concluded that the occurrence of Malignant Fibrous Histiocytomas in rats was not of particular concern as to the clinical safety of insulin glargine. Overall, results from the toxicology program did not raise particular concerns for the safe use of insulin glargine.

Clinical efficacy

The results from clinical studies support the use of insulin glargine in diabetes mellitus adults, adolescents and children of 6 years, where treatment with insulin is required.

Efficacy has been demonstrated for type 1 and type 2 diabetes.

Although it was not evaluated in special risk patients, it is expected that modifications to pharmacokinetics and pharmacodynamics occurring with insulin glargine in subjects with impaired renal and hepatic function will be similar to modifications observed with human insulin. A warning on dose adjustment in renal impairment and in the elderly has been included in the SPC.

Clinical safety

The major safety issues are hypoglycaemia, local reactions/toxicity, immunological reactions/antibody formation and ocular safety. Clinical experience indicated that following the initial titration phase, i.e. upon correct dose adjustment, insulin glargine is as safe as NPH insulin with respect to hypoglycaemia. Clinical experience also indicated that the issue of antibody formation is not a major concern and that the incidence in adverse ocular reactions is not increased with insulin glargine as compared to NPH insulin.

The occurrence of injection site reactions is a common side effect of treatment by insulin injection. However on the basis of the collected safety data the effect of long-term exposure to insulin glargine could not be fully assessed. Therefore careful post-marketing surveillance will be required in order to monitor the appearance of more serious local reactions.

Benefit/risk assessment

Except for a limited number of points, which will be addressed as part of post-authorisation commitments, the quality of Lantus is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral safety and batch-to-batch consistency has been documented and the relevant test will be performed according to the agreed specifications.

Benefit

The results from clinical studies support the use of insulin glargine in diabetes mellitus, where treatment with insulin is required. The efficacy for insulin glargine is comparable to other long acting insulins and has been demonstrated for type 1 and type 2 diabetes.

The main benefit expected from insulin glargine as compared to other existing long acting insulins is a prolonged duration of action, which supports administration only once a day. The prolonged action is due to the low solubility of insulin glargine at neutral pH. After injection, insulin glargine precipitates in the subcutaneous tissue and small amounts of active substance are continuously released from the precipitate, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action.

Risk

The major safety issues were hypoglycaemia, local reactions/toxicity, immunological reactions/antibody formation and ocular safety. Clinical experience indicated that following the initial titration phase, i.e. upon correct dose adjustment, insulin glargine is as safe as NPH insulin with respect to hypoglycaemia. Clinical experience also indicated that the issue of antibody formation is not a major concern and that the incidence in adverse ocular reactions is not increased with insulin glargine as compared to NPH insulin.

The occurrence of injection site reactions is a common side effect of treatment by insulin injection. However the occurrence of Malignant Fibrous Histiocytomas in rats in pre-clinical studies raised concerns as to the carcinogenic potential of insulin glargine. Following careful evaluation of the clinical relevance of these findings, it was concluded that at present the carcinogenic potential is not a point for particular concern. However, in view of the lack of clinical experience following long-term exposure to insulin glargine careful post-marketing surveillance will be required in order to monitor the appearance of more serious local reactions.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Lantus was favourable in the treatment of diabetes mellitus, where treatment with insulin is required.

The Committee for Proprietary Medicinal Products recommends the granting of a marketing authorisation for Lantus, subject to the chemical, pharmaceutical and biological as well as clinical follow-up measures undertaken by the company.

Based on the CPMP review of available data of a paediatric variation application, the CPMP considered that the benefit/risk profile of Lantus was favourable in the treatment of children of 6 years or above and recommended therefore the extension of indication.