SUMMARY OF PRODUCT CHARACTERISTICS (Product Data Sheet)

1. NAME OF THE MEDICINAL PRODUCT

Glaritus 100 IU/mL solution for injection in 3 mL cartridge

Glaritus 100 IU/mL solution for injection in 3 mL cartridge pre-fitted in dispopen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:

Insulin Glargine*	100 IU (Equivalent to 3.64 mg)
m-Cresol	0.27 % w/v (as preservative)
Water for injection	q.s.

Each 3 mL cartridge and 3 mL cartridge pre-fitted in dispopen of Glaritus 100 IU/mL solution for injection is equivalent to 300 international units.

*Insulin glargine is produced by recombinant DNA technology utilizing non pathogenic strain of *Escherichia coli*.

For full list of excipient, please refer section 6.1: List of excipients.

3. PHARMACEUTICAL FORM

Clear colourless solution for subcutaneous injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

4.2 Posology and Method of Administration

Posology

Glaritus contains insulin glargine, an insulin analogue, and has a prolonged duration of action.

Glaritus should be administered once daily at any time but at the same time each day.

The dose regimen (dose and timing) should be individually adjusted. In patients with type 2 diabetes mellitus, Glaritus can also be given together with orally active antidiabetic medicinal products.

The potency of this medicinal product is stated in units. These units are exclusive to Glaritus

and are not the same as IU or the units used to express the potency of other insulin analogues.

Special population

Elderly population (≥65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Paediatric population

• Adolescents and children aged 2 years and older patients

Safety and efficacy of insulin glargine have been established in adolescents and children aged 2 years and older. The dose regimen (dose and timing) should be individually adjusted.

• Children below 2 years of age

The safety and efficacy of insulin glargine have not been established. No data are available.

Switch from other insulins to Glaritus

When switching from a treatment regimen with an intermediate or long-acting insulin to a regimen with Glaritus, a change of the dose of the basal insulin may be required and the concomitant antidiabetic treatment may need to be adjusted (dose and timing of additional regular insulins or fast-acting insulin analogues or the dose of oral antidiabetic medicinal products).

Switch from twice daily NPH insulin to Glaritus

To reduce the risk of nocturnal and early morning hypoglycaemia, patients who are changing their basal insulin regimen from a twice daily NPH insulin to a once daily regimen with Glaritus should reduce their daily dose of basal insulin by 20-30% during the first weeks of treatment.

Switch from insulin glargine 300 units/ml to Glaritus(100 IU/mL)

Insulin glargine 100 units/ml and 300 units/ml are not bioequivalent and are not directly interchangeable. To reduce the risk of hypoglycemia, patients who are changing their basal insulin regimen from an insulin regimen with once daily insulin glargine 300 units/ml to a

once daily regimen with Glaritus (100 IU/mL) should reduce their dose by approximately 20%.

During the first weeks the reduction should, at least partially, be compensated by an increase in mealtime insulin, after this period the regimen should be adjusted individually.

Close metabolic monitoring is recommended during the switch and in the initial weeks thereafter.

With improved metabolic control and resulting increase in insulin sensitivity a further adjustment in dose regimen may become necessary. Dose adjustment may also be required, for example, if the patient's weight or life-style changes, change of timing of insulin dose or other circumstances arise that increase susceptibility to hypo- or hyperglycaemia.

Patients with high insulin doses because of antibodies to human insulin may experience an improved insulin response with Glaritus.

Method of administration

Glaritus is administered subcutaneously.

Glaritus should not be administered intravenously. The prolonged duration of action of Glaritus is dependent on its injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.

There are no clinically relevant differences in serum insulin or glucose levels after abdominal, deltoid or thigh administration of insulin glargine. Injection sites must be rotated within a given injection area from one injection to the next.

Glaritus must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

4.3 Contraindications

Hypersensitivity to Insulin Glargine or any of the excipients in this product.

4.4 Special warnings and special precautions for use

Glaritus is not the insulin of choice for the treatment of diabetic ketoacidosis. Instead, regular insulin administered intravenously is recommended in such cases.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transferring a patient to another type or brand of insulin should be done under strict medical

supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose.

Hypoglycaemia

The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed. Due to more sustained basal insulin supply with Glaritus, less nocturnal but more early morning hypoglycaemia can be expected.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:

- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products.

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

The prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose and dietary regimen, correct insulin administration and

awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:

- change in the injection area,
- improved insulin sensitivity (e.g., by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders, (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Intercurrent illness

Intercurrent illness requires intensified metabolic monitoring. In many cases urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Insulin antibodies

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Medication errors

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of insulin glargine. Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins.

Combination of Glaritus with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Glaritus is considered. If the combination is used, patients should be observed for signs and symptoms

of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interactions with Other Medicaments and Other Forms of Interaction

A number of substances affect glucose metabolism and may require Insulin dose adjustment. Substances that may enhance the blood glucose lowering effect and susceptibility to hypoglycaemia include: oral antidiabetic agents, ACE inhibitors, pentoxifylline, perhexiline, disopyramide, fibrates, fluoxetine, MAO inhibitors, dextropropoxyphene, salicylates, sulfonamide antibiotics.

Substances that may reduce the blood glucose lowering effect and susceptibility to hyperglycaemia include: corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oral contraceptives, phenothiazine derivatives, somatotrophin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood glucose lowering effect of Insulin. Pentamidine may cause hypoglycaemia, which may be sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

For insulin glargine no clinical data on exposed pregnancies from controlled clinical studies are available. A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicate no specific adverse effects of insulin glargine on pregnancy and no specific malformative nor feto/neonatal toxicity of insulin glargine. Animal data do not indicate reproductive toxicity.

The use of Glaritus may be considered during pregnancy, if clinically needed.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy to prevent adverse outcomes associated with hyperglycemia. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of

glucose control is essential.

Breast-feeding

It is unknown whether insulin glargine is excreted in human milk. No metabolic effects of ingested insulin glargine on the breast-fed newborn/infant are anticipated since insulin glargine as a peptide is digested into aminoacids in the human gastrointestinal tract. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility

Reported animal studies on insulin glargine do not indicate direct harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable Effects

Summary of the safety profile

Hypoglycaemia (very common), in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement (see section 4.4).

Tabulated list of adverse reactions

The following related adverse reactions from reported clinical investigations are listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**
Immune system				Allergic reactions	

disorders					
Metabolism and nutrition disorders	Hypoglycaemia				
Nervous system disorders					Dysgeusia
Eyes disorders				Visual impairment Retinopathy	
Skin and subcutaneous tissue disorders		Lipohypertrophy	Lipoatrophy		
Musculoskeletal and connective tissue disorders					Myalgia
General disorders and administration site conditions		Injection site reactions		Oedema	

Description of selected adverse reactions

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms (see section 4.4).

Immune system disorders

Immediate-type allergic reactions to insulin are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalised skin reactions, angio-oedema, bronchospasm, hypotension and shock, and may be life-threatening.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy. In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycaemic episodes may result in transient amaurosis.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions

Injection site reactions include redness, pain, itching, hives, swelling, or inflammation. Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

Rarely, insulin may cause sodium retention and oedema particularly if previously poor metabolic control is improved by intensified insulin therapy.

Paediatric population

In general, the safety profile for children and adolescents (≤18 years of age) is similar to the safety profile for adults.

The adverse reaction mentioned in reported post marketing surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in children and adolescents (≤18 years of age) than in adults.

Clinical study safety data are not available for children under 2 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.8 Overdose

Symptoms

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Anti-diabetic agent (Long acting human insulin analogue)

ATC (Anatomical Therapeutic Chemical) Classification Code: A10AE04

Mechanism of action

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 Glaritus injection solution (pH 4). After injection into the subcutaneous tissue, the acidic solution is neutralised leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action.

Insulin glargine is metabolised into 2 active metabolites M1 and M2 (see section 5.2).

Insulin receptor binding: *In vitro* studies indicate that the affinity of insulin glargine and its metabolites M1 and M2 for the human insulin receptor is similar to the one of human insulin.

IGF-1 receptor binding: The affinity of insulin glargine for the human IGF-1 receptor is approximately 5 to 8-fold greater than that of human insulin (but approximately 70 to 80-fold lower than the one of IGF-1), whereas M1 and M2 bind the IGF-1 receptor with slightly lower affinity compared to human insulin.

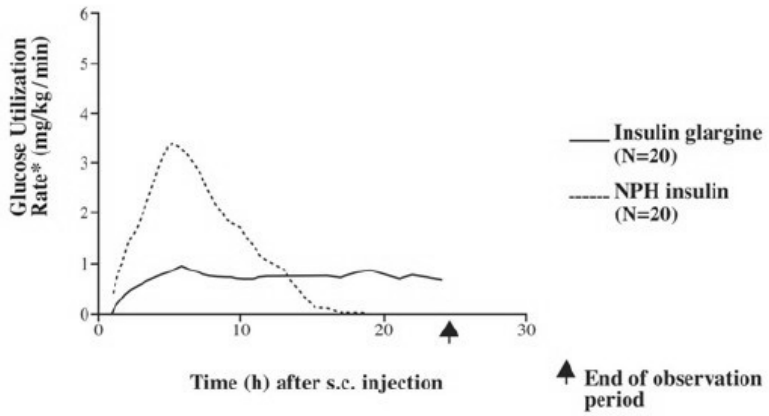
The total therapeutic insulin concentration (insulin glargine and its metabolites) found in type 1 diabetic patients was markedly lower than what would be required for a halfmaximal occupation of the IGF-1 receptor and the subsequent activation of the mitogenic-proliferative pathway initiated by the IGF-1 receptor. Physiological concentrations of endogenous IGF-1 may activate the mitogenic-proliferative pathway; however, the therapeutic concentrations found in insulin therapy, including in insulin glargine therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway.

The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. 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. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

In clinical studies, the glucose-lowering effect on a molar basis (i.e., when given at the same doses) of intravenous insulin glargine is approximately the same as human insulin. In

euglycemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than NPH human insulin. The effect profile of insulin glargine was relatively constant with no pronounced peak and the duration of its effect was prolonged compared to NPH human insulin. ***Figure 1*** shows results from a study in patients with type 1 diabetes conducted for a maximum of 24 hours after the injection. The median time between injection and the end of pharmacological effect was 14.5 hours (range: 9.5 to 19.3 hours) for NPH human insulin, and 24 hours (range: 10.8 to > 24.0 hours) (24 hours was the end of the observation period) for insulin glargine.

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); indicative of insulin activity.

†Between-patient variability (CV, coefficient of variation); insulin glargine, 84% and NPH, 78%. The longer duration of action (up to 24 hours) of insulin glargine [rDNA origin] injection is directly related to its slower rate of absorption and supports once-daily subcutaneous administration. The time course of action of insulins, including (insulin glargine [rDNA origin] injection), may vary between individuals and/or within the same individual.

The longer duration of action of subcutaneous insulin glargine is directly related to its slower rate of absorption and supports once daily administration. The time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual.

Symptoms of hypoglycaemia or counter-regulatory hormone responses were similar after intravenous insulin glargine and human insulin both in healthy volunteers and patients with type 1 diabetes in reported clinical studies.

Antibodies that cross-react with human insulin and insulin glargine have reportedly been observed with the same frequency in both NPH-insulin and insulin glargine treatment groups.

A study to compare Pharmacokinetics and Pharmacodynamics of Glaritus® with Lantus® in Healthy Subjects was conducted.

The objective of the study was to obtain estimates of mean and variability of pharmacokinetic parameters (C_{max} and AUC_{0-24h}) and pharmacodynamic parameters ($AUC_{GIR\ 0-24h}$ and GIR_{max}) and to demonstrate average bioequivalence in the pharmacokinetic (PK) endpoints of Wockhardt's long acting human recombinant insulin analogue Glargine (Glaritus® and Lantus® as well as assessing safety and local tolerability of the two insulin preparations in Healthy subjects.

Overall, of the 40 subjects enrolled in the study all of them were Asian (100%) and male (100%). The mean age for all subjects was 31.1 years (range 19 to 44 years), the mean height was 167.6 cm (range 156.0 to 183.5 cm), the mean weight was 62.08 kg (range 50.9 to 84.3 kg) and mean BMI was 22.1 (range 18.69 to 26.91). Mean fasting blood glucose levels were 72.56 mg/dL (range 63 to 89 mg/dL).

Summary statistics and bioequivalence analysis of the PK and PD of the two insulin glargine formulations are shown in the table below. Analysis of the primary PK endpoints showed that the CI 90% of the geometric LS mean ratio for Cmax and AUC_{0-24h} was entirely contained within the bioequivalence interval of 80% to 125%.

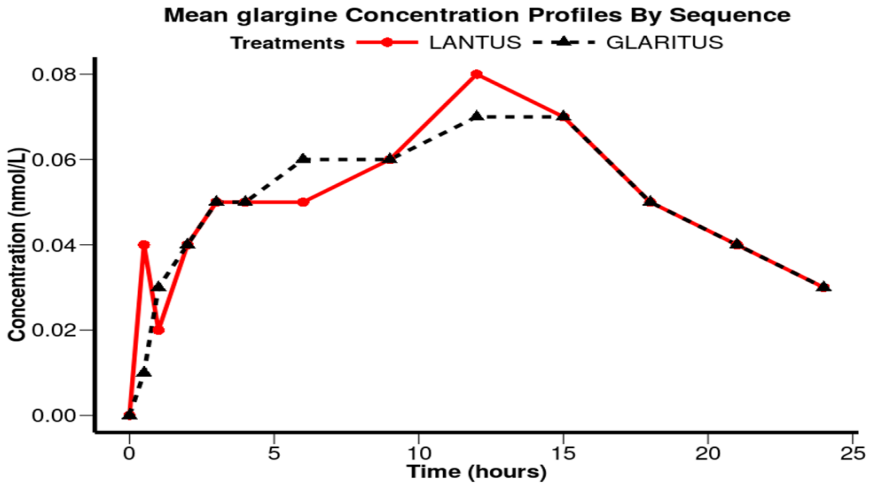
The results for the PD endpoints also support the bioequivalence for Glaritus® and Lantus®, as the CI90% of the geometric LS mean ratios for $AUC_{GIR\ 0-24h}$ and GIR_{max} were entirely contained within the bioequivalence interval of 80% to 125%.

Bioequivalence Analysis of Pharmacokinetic & Pharmacodynamic Parameters

	Geometric Least Square Mean					Between Subject Variability (%)		Within Subject Variability (%)	
Primary Pk Parameters	**Glaritus N=69**	**Lantus N=65**	**Ratio**	**90% CI Of The Ratio**		**Lantus**	**Glaritus**	**Lantus**	**Glaritus**
AUC_{0-24} (h*nmol/L)	1.09	1.05	1.04	0.91	1.18	53	50	46	38
Cmax (nmol/L)	0.08	0.08	0.96	0.86	1.08	31	31	48	25
Primary PD Parameters	**Glaritus N=71**	**Lantus N=73**	**Ratio**	**90% CI Of The Ratio**		**Lantus**	**Glaritus**	**Lantus**	**Glaritus**
$AUC_{GIR0-24}$ (h*mg/kg/ min)	20.99	21.63	0.97	0.83	1.14	58	68	57	56
GIR_{MAX}	1.82	1.85	0.98	0.87	1.11	40	48	42	44

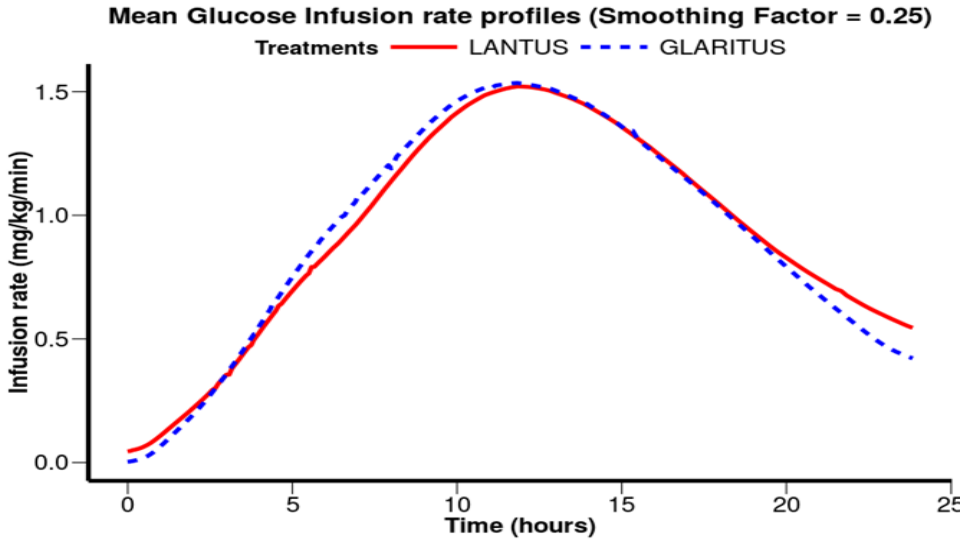
A plot of mean plasma glargine concentrations versus time since dose for Glaritus® and Lantus® is shown in ***Figure 2*** below. Visual inspection of the figure reveals comparable concentration versus time profiles for Glaritus® and Lantus®.

Figure 2: Mean Plasma Glargine Concentration vs. Time by Formulation



Glucose Infusion Rate (GIR): A plot of mean smoothed GIR versus time since dose for Glaritus® and Lantus® is shown in ***Figure 3*** below. Visual inspection of the figure reveals comparable GIR versus time profiles for Glaritus® and Lantus.

Figure 3: Mean glucose infusion rate vs. Time by Formulation



Safety Results:

In this study, a total of 8 AEs were observed in 6 subjects, of them 2 subjects had received the treatment injection Glaritus® and 4 subjects had received reference treatment injection Lantus®. All AEs in this study recovered without sequel.

Local tolerability assessments at the injection site reaction did not show any significant observations of erythema, induration, itching and oedema at 24 hours, pain on palpation and spontaneous pain post at 12 hours and 24 hours of the Glaritus and Lantus injection.

There were no clinically significant observations noted in laboratory examinations which included hematology, biochemistry, urinalysis, blood glucose and total cholesterol. The analysis of AEs, clinical laboratory evaluation and vital signs examination demonstrated that Wockhardt's Glaritus® is well tolerated and has a favorable safety profile.

Conclusion:

Glaritus® and Lantus® are bioequivalent based on the results for the primary PK and PD endpoints. The CI90% for the geometric LS mean ratio was entirely contained within the bioequivalence interval of 80% to 125% for $AUC_{0\text{-}24h}$, and C_{max}- the primary PK end points. These results indicate similar rate and extent of absorption for the two formulations. The CI90% of the geometric LS mean ratios for primary PD end points - $AUC_{GIR\ 0\text{-}24h}$ and GIR_{max} were also entirely contained within the bioequivalence interval of 80% to 125%. Based on analysis of AEs, clinical laboratory evaluation, local tolerability test and vital signs

examination it is demonstrated that Wockhardt's Glaritus® is well tolerated and has a comparable safety profile to Lantus®.

In conclusion, this study demonstrated the PK and PD bioequivalence of Glaritus® and Lantus® and both the formulations were comparably safe and well tolerated after administration of 0.4 U/kg dose.

5.2 Pharmacokinetic Properties

Absorption and Bioavailability: After subcutaneous injection of insulin glargine in healthy subjects and in patients with diabetes, the insulin serum concentrations indicated a slower, more prolonged absorption and a relatively constant concentration/time profile over 24 hours with no pronounced peak in comparison to NPH human insulin. Serum insulin concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine. After subcutaneous injection of 0.3 IU/kg insulin glargine in patients with type 1 diabetes, a relatively constant concentration/time profile has been demonstrated. The duration of action after abdominal, deltoid, or thigh subcutaneous administration was similar.

Metabolism: A metabolism study in humans indicates that insulin glargine is partly metabolized at the carboxyl terminus of the B chain in the subcutaneous depot to form two active metabolites with *in vitro* activity similar to that of insulin, M1 (21^{A}-Gly-insulin) and M2 (21^{A}-Gly-des-30^{B}- Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.

Special Populations

Age, Race and Gender: Information on the effect of age, race, and gender on the pharmacokinetics of Insulin glargine [rDNA origin] injection is not available. However, in controlled clinical trials in adults (n=3890) and a controlled clinical trial in pediatric patients (n=349), subgroup analyses based on age, race, and gender did not show differences in safety and efficacy between insulin glargine and NPH human insulin. Pharmacokinetics in children aged 2 to less than 6 years with type 1 diabetes mellitus was assessed in one clinical study. Plasma "trough" levels of insulin glargine and its main M1 and M2 metabolites were measured in children treated with insulin glargine, revealing plasma concentration patterns similar to adults, and providing no evidence for accumulation of insulin glargine or its metabolites with chronic dosing.

Smoking: The effect of smoking on the pharmacokinetics/pharmacodynamics of insulin glargine [rDNA origin] injection has not been studied.

Pregnancy: The effect of pregnancy on the pharmacokinetics and pharmacodynamics of Insulin Glargine injection has not been studied.

Obesity: Subgroup analyses based on BMI in reported studies did not show any differences in safety and efficacy between insulin glargine and NPH human insulin.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of (insulin glargine [rDNA origin] injection) has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Careful glucose monitoring and dose adjustments of insulin, including (insulin glargine [rDNA origin] injection), may be necessary in patients with renal dysfunction

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of insulin glargine [rDNA origin] injection has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including insulin glargine [rDNA origin] injection, may be necessary in patients with hepatic dysfunction.

5.3 Preclinical Safety Data

Non-clinical data on insulin glargine reveal no special hazard for humans based on reported conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:

3 mL Cartridge: Zinc Chloride, m-Cresol, Glycerol (85%), Sodium Hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment) and Water for Injection (WFI).

3 mL Dispopen: Zinc Chloride, m-Cresol, Glycerol (85%), Sodium Hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment) and Water for Injection (WFI).

6.2 Incompatibilities:

This medicinal product must not be mixed with other medicinal products.

It is important to ensure that syringes do not contain traces of any other material.

6.3 Shelf Life:

3 years

6.4 Special Precautions for Storage:

Unopened cartridges, not in-use dispopens

Store in a refrigerator (2°C - 8°C).

Do not freeze or place next to the freezer compartment or a freezer pack.

Keep the cartridge or prefilled dispopen in the outer carton in order to protect from light.

In-use cartridges or dispopens

The in-use cartridges or dispopens may be stored for a maximum of 28 days not above 30 °C and away from direct heat or direct light.

The pen cap must be put back on the pen after each injection in order to protect from light.

It is recommended that the date of the first use from the cartridge be noted on the label.

Keep all the insulin products out of reach of children.

Insulin glargine cartridge or dispopen should never be used after the expiry date.

6.5 Nature and contents of container:

A clear colourless solution.

3 mL solution filled in a glass cartridge pasted with printed sticker label. 1 or 5 filled cartridge blister packed in a printed carton with literature insert.

A labeled 3 mL solution filled cartridge, fitted in a dispopen with violet colour dose dialer. 1 or 5 dispopen packed in a tray with or without 1 or 5 pens tip and literature insert packed in a carton.

6.6 Special precautions for disposal and other handling

Inspect Glaritus before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency. Since Glaritus is a solution, it does not require resuspension before use.

Glaritus must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins.

Glaritus in a cartridge

Insulin pen

The Glaritus cartridges are to be used only in conjunction with the pen devices.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen malfunctions (see instructions for using the pen), the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 units/mL) and injected.

Cartridge

Before insertion into the pen, the cartridge must be stored at room temperature for 1 to 2 hours.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Glaritus in prefilled dispopen

Before first use, the prefilled dispopen must be stored at room temperature for 1 to 2 hours.

Empty prefilled dispopens must never be reused and must be properly discarded.

To prevent the possible transmission of disease, each dispopen must be used by one patient only.

Before using the prefilled dispopen, the instructions for use included in the package leaflet must be read carefully.

7. MARKETING AUTHORISATION HOLDER

M/s. Wockhardt Limited, Biotech Park, H-14/2, MIDC, Waluj, Aurangabad-431136, Maharashtra State, India

8. MARKETING AUTHORISATION NUMBER(S)

AD/004

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of First Authorization: **June 3, 2008**

Renewal of the Authorization: **April 8, 2013**

10. DATE OF REVISION OF THE TEXT

Date of Revision of the text: **May 2017**