NATIONAL PHARMACEUTICAL REGULATORY DIVISION MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

PRODUCT NAME:
1. Glaritus 100 IU/mL Solution for injection (MAL20126005AZ)
2. Glaritus 100 IU/mL Solution for injection in Pre-filled Pen (MAL20126006AZ)

ACTIVE INGREDIENT:
Recombinant Insulin Glargine 100 IU/ml

PRODUCT REGISTRATION HOLDER:
SM Pharmaceuticals Sdn. Bhd.

PRODUCT MANUFACTURER:
Wockhardt Limited (Biotech Park), Aurangabad, India

APPROVAL DATE:
03 December 2020 (DCA 351)

1.0 BACKGROUND INFORMATION

Glaritus is developed as a biosimilar product to the reference product Lantus. The evaluation for this product is based on the biosimilar pathway according to *Malaysia Guideline for Registration of Biosimilars (2008)* and *EMEA Guideline on Non-Clinical And Clinical Development Of Similar Biological Medical Products Containing Recombinant Human Insulin And Insulin Analogues (2015)*.

1.1 Approved Indication

GLARITUS is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

1.2 Approved Posology

Dosage

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 glargine has 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 glargine has 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
GLARITUS and insulin glargine 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 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.

1.3 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 GLARITUS. 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.

1.4 Pharmacological Aspects

Pharmacodynamic Properties

Mechanism of Action
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.

Pharmacokinetic Properties

Absorption and Bioavailability
After subcutaneous injection of Insulin Glargine, the Insulin serum concentrations indicate a slower, more prolonged absorption and a lack of a peak in comparison to NPH human Insulin. Concentrations are thus consistent with the time profile of the pharmacodynamics activity of Insulin Glargine.

Metabolism and Elimination
A reported 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 human insulin, M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thrinsulin). Unchanged drug and these degradation products are also present in the circulation.

Special Populations

Age, Race and Gender
Effect of age, race, and gender on the pharmacokinetics of Glaritus has not been evaluated. However, in reported clinical studies in adults and pediatric patients, subgroup analyses based on age, race, and gender did not show differences in safety and efficacy between insulin glargine and NPH insulin.

Obesity
Effect of Body Mass Index (BMI) on the pharmacokinetics of Glaritus has not been evaluated.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

- Insulin glargine, an insulin analogue produced by recombinant DNA technology through the expression of *Escherichia coli* (*E. coli*) is composed of two amino acid chains (A & B)

covalently linked by disulfide bond. It weighs 6063 Da and differs from human insulin at which the amino acid asparagine (Asn) at position 21 of chain A was replaced by glycine (Gly) whereas two arginine [(Arg)(B31) and (Arg)(B32)] were added to the C-terminus of the B-chain threonine. This structural modifications shift an isoelectric point towards neutral pH which leads to delayed dissociation of hexamer complexes into monomers after subcutaneous injection, thus prolonged absorption from the injection site.

- The manufacturing process using four consecutive batches has been validated following the *EMA/CHMP/BWP/187338/2014* guideline and the results fulfilled the expected acceptance criteria proving that the manufacturing processes of active substance are robust and reproducible.
- The accelerated (5±3^{o}C) and long-term (-20±3^{o}C) stability studies conducted using three batches was in line with *ICH Q5C* and *ICH Q1A(R2)* guidelines and the obtained data support the proposed shelf life of 48 months when stored at -20±3^{o}C.
- Certificate of Good Manufacturing Practice (GMP) for the drug substance manufacturer (Wockhardt Limited (Biotech Park), Aurangabad, India) was issued by Turkish Medicines and Medical Devices Agency, Ministry of Health, Republic of Turkey.

2.1.2 Finished Product

- The manufacturing process has been validated using three consecutive batches following *EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1* guideline and the results fulfilled the expected acceptance criteria proving that the finished product manufacturing processes are robust and reproducible.
- The proposed shelf life of 24 months when stored at 5 ± 3^{o}C is justified as supported by the available 24 months long-term stability data at 5 ± 3^{o}C and 6 months accelerated stability data at 25 ± 2^{o}C/ 60% ± 5% RH conducted in line with *ICH Q5C* and *ICH Q1A(R2)* guidelines using three consecutive commercial batches.
- The finished product is presented as clear, sterile solution contained either within a 3 ml USP type I glass cartridge closed with bromobutyl rubber stopper and sealed with aluminium/ rubber disc (Cartridges: 1's x 3ml & 5's x 3ml) or in a pen with a lid and cap (PFP [Dispopen]: 1's x 3ml & 5's x 3ml).
- The analytical protocol and method validation data for the product has been evaluated and found to be satisfactory based on the documentation submitted.
- Certificate of Good Manufacturing Practice (GMP) for the drug product manufacturer (Wockhardt Limited (Biotech Park), Aurangabad, India) was issued by Turkish Medicines and Medical Devices Agency, Ministry of Health, Republic of Turkey.

2.1.3 Quality Comparability for Biosimilar Product

- Insulin glargine of Glaritus is produced in *Escherichia coli* cells which is the same as used in the reference product, Lantus.
- The analytical similarity of Glaritus to Lantus was assessed side-by-side at multiple levels beginning with primary structure, secondary structure, higher order structure, purity and general properties. The orthogonal analytical techniques were used during the comparability assessment.
- The full set of biosimilarity data at quality level presented was considered appropriate and sufficient thus concluded the biosimilarity between Glaritus to Lantus.

2.2 Non-Clinical Study Comparability for Biosimilar Product

- The efficacy and safety of Glaritus were further compared side-by-side to Lantus in total of six non-clinical comparability studies.
- All functional activities of both products were assessed and compared mainly via in-vitro studies particularly on metabolic assay, mitogenic assay, and receptor auto-phosphorylation assay using orthogonal analytical methods. Based on the studies, it can be concluded that Glaritus has equivalent potency and binding affinity to Lantus.
- No in-vivo pharmacodynamic studies were conducted because as outlined in the *EMEA/CHMP/BMWP/32775/2005_Rev. 1* guideline, comparative in-vivo studies of pharmacodynamics effects would not be anticipated to be sensitive enough to detect differences not identified by in-vitro assays, and are not required as part of the comparability exercise.
- For toxicity assessment, one pivotal *comparative side-by-side 28-day repeat-dose [8 IU/kg, 24 IU/kg, and 72 IU/kg] subcutaneous toxicity and toxicokinetic study of Glaritus and Lantus in Wistar rats with a 14-day recovery period* was conducted as per OECD Principles of GLP and concluded that Glaritus and Lantus respond similarly and exhibit comparable toxicity, toxicokinetic and immunogenicity at 24 IU/kg dose.
- Overall, the completed non-clinical studies comparing Glaritus and Lantus were considered adequate to support a positive benefit risk profile as well as sufficient to establish comparability between Glaritus and Lantus.

2.3 Efficacy

- Demonstration of similar pharmacokinetic (PK) and pharmacodynamic (PD) profiles have been conducted in healthy adults male and type 1 diabetes mellitus subjects. The information on the studies is as tabulated below:

<table>
<tr><th>Study Type & Design</th><th>Objective of the study</th><th>Results</th></tr>
<tr><td>A phase 1, double-blind, randomized, single centre, two sequence, four period, two single doses crossover 24 hour euglycemic clamp.

N= 40 healthy adult male subjects

Bhatia, A., Tawade, S., Mastim, M., Kitabi, E. N., Gopalakrishnan,</td><td>To compare the pharmacokinetic (PK) and pharmacodynamic (PD) properties of an insulin glargine formulation, Glaritus (test) with the innovator's formulation Lantus (reference) using the euglycemic clamp technique</td><td>Similarity is demonstrated if the 90% and 95% confidence interval (PK and PD respectively) of the primary endpoint parameters are within the predefined acceptance limit of 80 – 125%.

Table 1: Statistical assessment of PK & PD parameters
<table>
<tr><th></th><th colspan="4">Geometric least-square mean</th></tr>
<tr><th></th><th>Glaritus n=69</th><th>Lantus n= 65</th><th>Ratio</th><th>90% CI of ratio</th></tr>
<tr><td colspan="5">Primary PK parameters</td></tr>
<tr><td>AUC $_{0-24}$ (h.nmol/L)</td><td>1.09</td><td>1.05</td><td>1.04</td><td>0.91, 1.18</td></tr>
<tr><td>C_{max} (nmol/L)</td><td>0.078</td><td>0.081</td><td>0.96</td><td>0.86, 1.08</td></tr>
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</td></tr>
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<table>
<tr>
<td>M., Shah, M., Yeshamaina, S. & Kumar, K. P. (2018). Comparative evaluation of pharmacokinetics and pharmacodynamics of insulin glargine (Glaritus) and Lantus in healthy subjects: a double-blind, randomized clamp study. Acta diabetologica, 55(5), 461-468.</td>
<td></td>
<td>
<table>
<tr><th></th><th>Glaritus n=71</th><th>Lantus n= 73</th><th>Ratio</th><th>95% CI of ratio</th></tr>
<tr><td colspan="5">Primary PD parameters</td></tr>
<tr><td>AUC GIR (0-24h)(h.mg/kg/min)</td><td>20.99</td><td>21.63</td><td>0.97</td><td>0.83, 1.14</td></tr>
<tr><td>GIR max (mg/kg/min)</td><td>1.82</td><td>1.85</td><td>0.98</td><td>0.87, 1.11</td></tr>
</table>
AUC 0-24h: Area under the glargine concentration versus time curve
Cmax: Peak glargine concentration
AUCGIR (0-24h): Area under the glucose infusion rate versus time curve
GIRmax: Peak of glucose infusion rate

Conclusion:
The confidence interval (CI) were contained within the equivalence margin for both PK and PD endpoints. Hence, the study demonstrated similarity between Glaritus and the reference product, Lantus.
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<tr>
<td>A phase 1, randomized, double-blind, two-period, crossover glucose clamp study

N= 94 Type 1 diabetes subjects</td>
<td>To test for bioequivalence based on the pharmacokinetic (PK) parameters of the area under the serum insulin glargine concentration-time curve from 0 to 24 hours (AUC INS GLR 0-24h) and the maximum insulin glargine concentration ($C_{max\ INS\text{-}GLR}$), as well as on the pharmacodynamic (PD) parameter of the area under the glucose infusion rate (GIR)-time smoothed curve from 0 to 24 hours ($AUC_{GIR\ 0\text{-}24h}$) between Wockhardt's Glaritus and</td>
<td>
Similarity is demonstrated if the 90% and 95% confidence interval (PK and PD respectively) of the primary endpoint parameters are within the predefined acceptance limit of 80 – 125%.

Table 1: Statistical assessment of PK & PD endpoints
<table>
<tr><th></th><th colspan="4">Geometric least-square mean</th></tr>
<tr><th></th><th>Glaritus n=94</th><th>Lantus n= 94</th><th>Ratio</th><th>90% CI of ratio</th></tr>
<tr><td colspan="5">Primary PK parameters</td></tr>
<tr><td>AUC 0-24 (h.mU/L)</td><td>181.95</td><td>185.74</td><td>98.0</td><td>92.9, 103.3</td></tr>
<tr><td>Cmax (mU/L)</td><td>11.98</td><td>12.33</td><td>97.2</td><td>90.1, 104.9</td></tr>
<tr><th></th><th>Glaritus n=93</th><th>Lantus n= 93</th><th>Ratio</th><th>95% CI of ratio</th></tr>
<tr><td colspan="5">Primary PD parameters</td></tr>
<tr><td>AUC GIR (0-24h)(h.mg/min)</td><td>1275.55</td><td>1376.97</td><td>92.63</td><td>80.92, 106.05</td></tr>
<tr><td>GIR max (mg/min)</td><td>109.30</td><td>112.84</td><td>96.86</td><td>88.60, 105.89</td></tr>
</table>
AUC 0-24h: Area under the glargine concentration versus time curve
Cmax: Peak glargine concentration
AUCGIR (0-24h): Area under the glucose infusion rate versus time curve
GIRmax: Peak of glucose infusion rate
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</table>

	Lantus.	Conclusion: The confidence interval (CI) were contained within the equivalence margin for both PK and PD endpoints. Hence, the study demonstrated similarity between Glaritus and the reference product, Lantus.

2.4 Safety

- A phase IV, prospective, open label, randomized, active controlled, parallel group, comparative, multi-center study was conducted to evaluate the change in immunogenic response to glargine in Glaritus and Lantus treatment arms from baseline to 6 months in type 2 diabetes mellitus subjects. Based on the study, a total of 10 hypoglycemic episodes were reported, with 7 hypoglycemic episodes in comparative phase and 3 hypoglycemic episodes over next 6 months single arm period of Glaritus. Overall, the incidence of hypoglycemia events was similar in both the groups.
- There was no statistically significant difference in change in the anti-insulin antibody (AIA) titer between Glaritus and Lantus treatment groups at the end of 6 months.
- The safety profile of Glaritus was comparable between the groups with intensity being mild and outcome resolved for most patients. There were no new or unexpected safety findings observed in the study.
- Overall, the safety and immunogenicity of Glaritus is well tolerated with similar safety profiles of Lantus.
- Based on periodic safety update report (PSUR) covering the period from April 2015 to July 2020, no new relevant safety findings were identified. The safety data remain in accord with the previous experience and the safety information presented in the package insert.

3.0 CONCLUSION

- Glaritus was developed as a biosimilar to the reference product Lantus. An extensive stepwise approach to demonstrate biosimilarity in terms of structure, function, animal toxicology and human PK and safety studies has been conducted.

- Comparability data was generated from stepwise approach from comparison of quality (functional and analytical), nonclinical (pharmacologic and toxicology) and clinical (pharmacokinetic, pharmacodynamic and safety) between Glaritus and Lantus. Glaritus has demonstrated similarity to Lantus from aspect of the totality of evidence.

- Drug Control Authority (DCA) on the 351st meeting on 3rd December 2020 has decided to approve the registration of this product with the following indication:

  Glaritus is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above