Product: Insulin Glargine (Toujeo)
Strengths: 300 Units/mL Solution for Injection (SC) [BRP-055]
Presentation: Type I colorless glass cartridge x 1.5mL closed on one end with plunger stopper (bromobutyl rubber) and on the opposite end with flanged cap (aluminum) with punch laminated sealing disk (bromobutyl rubber on the product side and synthetic Isoprene rubber on the outside). The cartridge is sealed in a disposable pen injector. (Box of 1's, 3's and 5's)
I: Treatment of diabetes mellitus in adults, adolescents and children from the age of 6 years.
D: It is a basal insulin for once-daily administration at any time of the day, preferably at the same time every day.
Flexibility n dosing time - When needed, patients can administer Insulin Glargine up to 3 hours before or after their usual time of administration.
Initiation (Patients with type 1 diabetes mellitus) - Insulin Glargine is to be used once-daily with meal-time insulin and requires individual dose adjustments.
Initiation (Patients with type 2 diabetes mellitus) - The recommended daily starting dose is 0.2 units/kg followed by individual dose adjustments.
C: Hypersensitivity to the active substance or to any of the excipients.
P: Insulin Glargine 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 hypoglycemic 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.
Int: Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycemia include anti-hyperglycemic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics. Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, estrogens and progestogens, phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, atypical antipsychotic medicinal products (e.g. clozapine and olanzapine) and protease inhibitors. Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
AE: Hypoglycemia (very common); Lipohypertrophy, Injection site reactions (common); Lipoatrophy (uncommon); Allergic reactions, Visual impairment, Retinopathy, Oedema (rare); Dysgeusia, Myalgia (very rare)
PK: Absorption and distribution - In healthy subjects and diabetic patients, insulin serum concentrations indicated a slower and more prolonged absorption resulting in a flatter time-concentration profile after subcutaneous injection of Insulin Glargine in comparison to insulin glargine 100 units/ml. Pharmacokinetic profiles were consistent with the pharmacodynamic activity of Insulin Glargine (Toujeo).
Steady state level within the therapeutic range is reached after 3-4 days of daily Insulin Glargine (Toujeo) administration.
After subcutaneous injection of Insulin Glargine (Toujeo), the intra-subject variability, defined as the coefficient of variation for the insulin exposure during 24 hours was low at steady state (17.4%).
Biotransformation - After subcutaneous injection of insulin glargine, insulin glargine is rapidly metabolized at the carboxyl terminus of the Beta chain with formation of two active metabolites M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin). In plasma, the principal circulating compound is the metabolite M1. The exposure to M1 increases with the administered dose of insulin glargine. The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with insulin glargine is principally based on exposure to M1. Insulin glargine and the metabolite M2 were not detectable in the vast majority of subjects and, when they were detectable their concentration was independent of the administered dose and formulation of insulin glargine.
Elimination - When given intravenously the elimination half-life of insulin glargine and human insulin were comparable. The half-life after subcutaneous administration of Insulin Glargine (Toujeo) is determined by the rate of absorption from the subcutaneous tissue. The half-life of Insulin Glargine (Toujeo) after subcutaneous injection is 18-19 hours independent of dose.
Pediatric population - Population pharmacokinetic analysis was conducted for Insulin Glargine (Toujeo) based on concentration data of its main metabolite M1 using data from 75 pediatric subjects (6 to <18 years of age) with type 1 diabetes. Body weight affects the clearance of Insulin Glargine (Toujeo) in a nonlinear way. As a consequence, exposure (AUC) in pediatric patients is slightly lower as compared to adult patients when receiving the same body weight adjusted dose.

PD: 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.
Pharmacodynamic effects - Insulin glargine is a human insulin analogue designed to have a low solubility at neutral pH. At pH 4, insulin glargine is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralized leading to formation of a precipitate from which small amounts of insulin glargine are continuously released.
Insulin glargine is metabolised into 2 active metabolites M1 and M2.
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.
In a clinical pharmacology study, intravenous insulin glargine and human insulin have been shown to be equipotent when given at the same doses.
As with all insulins, the time course of action of insulin glargine may be affected by physical activity and other variables.