ADIS NEW DRUG PROFILE

Drugs 2000 Feb; 59 (2): 253-260
0012-6667/00/0002-0253/$25.00/0

Insulin Glargine

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Contents

Abstract

▲ Insulin glargine is an extended-action biosynthetic human insulin. It precipitates in the neutral environment of subcutaneous tissue and is thus gradually absorbed into the bloodstream. The addition of small amounts of zinc to the formulation further delays absorption.

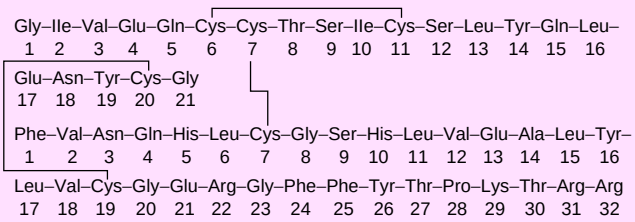
▲ In small euglycaemic clamp studies, the onset of action of insulin glargine was shown to be later, the duration of action longer and the time-action profile flatter than that of Neutral Protamine Hagedorn (NPH) insulin in patients with type 1 diabetes mellitus and healthy volunteers.

▲ Four large clinical trials of up to 28 weeks' duration have shown that a single bedtime dose of insulin glargine, in combination with preprandial short-acting insulin, is as effective or more effective than once or twice daily NPH plus short-acting insulin in improving glycaemic control in patients with type 1 diabetes mellitus.

▲ In 3 large comparative trials, insulin glargine decreased glycosylated haemoglobin and/or fasting blood glucose levels to a similar extent to that seen with NPH insulin in patients with insulin-dependent or non-insulin-dependent type 2 diabetes mellitus, either as monotherapy or in combination with oral hypoglycaemic agents.

▲ Insulin glargine appears to be well tolerated. A lower incidence of hypoglycaemia, especially at night, was reported in most trials with insulin glargine when compared with NPH insulin.

Features and properties of insulin glargine (glargine, HOE 71GT15, HOE 71GT80, HOE 901)	
Indications	
Type 1 and 2 diabetes mellitus	
Mechanism of action	
Long-acting human insulin analogue	
Dosage and administration	
Dosage	Titrated on an individual basis
Route of administration	Subcutaneous
Frequency of administration	Once daily
Pharmacokinetic profile (0.15 U/kg with zinc 80 mg/L)	
Peak plasma concentration	5.75 U/L
Time to disappearance of 25% dose from injection site	11h
Adverse events	
Most frequent	Hypoglycaemia



Insulin glargine

Improved glycaemic control in diabetes mellitus has been shown to lead to a reduction in the development and progression of microvascular disease (reviewed by Mandrup-Poulsen[1]). The ultimate goal of therapy is the accurate imitation of the normal physiological secretion of insulin.

Short-acting insulin preparations have been used successfully to supply mealtime insulin requirements.[2] However, the development of longer-acting insulins, in an attempt to mimic the normal basal secretion of endogenous insulin between meals, has been less successful.[2,3] Difficulties with variable absorption, peaked action profiles and inadequate durations of action have resulted in problems such as nocturnal hypoglycaemia, morning fasting hyperglycaemia and the need for multiple daily doses.[2]

An ideal long-acting insulin should be able to be administered once daily, have a flattened action profile and show minimal variability in absorption. Insulin glargine is a synthetic human insulin that has been modified, using recombinant DNA technology, in an attempt to deliver these requirements.[2,3] It will be the first commercially available long-acting human insulin analogue.

1. Pharmacodynamic Profile

Solubility of Insulin Glargine

The carboxy-terminal amino acids of the A and B chains of insulin are not involved in receptor binding. Changes in these amino acid residues can alter the solubility of insulin without affecting its biological activity.[3]

- Insulin glargine differs from native insulin in that the 21 amino acid residue on the A chain has been substituted with a glycine residue, and 2 arginine residues have been added to the B chain.[2,3] These alterations shift the isoelectric point closer to neutral, making insulin glargine more soluble in an acidic environment (compared with human insulin, which has an isoelectric point of pH 5.4).[2] Insulin glargine therefore precipitates in the neutral pH of human subcutaneous tissue, which prolongs its absorption into the bloodstream.[2] Alterations to the molecule also favour the formation of insulin hexamers which further delay absorption from the tissues.[2]

- Small amounts of zinc (15, 30 or 80 mg/L) have been added to insulin glargine formulations to further extend its absorption time.[2]

Receptor Interactions

- In rat fibroblasts, insulin glargine was similar to regular human insulin in its binding to, and activation of, human insulin receptors and in the resultant phosphorylation of insulin receptor substrate-1 (IRS-1). Dissociation from the receptors was also similar between the 2 molecules (no numerical data provided).[4]

- The human insulin analogue B10-Asp has been shown to be carcinogenic in rats. This was presumed to be secondary to mitogenic effects resulting from activation of insulin-like growth factor 1 (IGF-1) receptors (reviewed by Home[3]). *In vitro* studies using H9 cardiac myocytes have shown that, despite binding to IGF-1 receptors with a higher affinity than native insulin, insulin glargine

activates IGF-1 receptor signalling to the same extent.[5] No histological evidence of mammary gland tumour development was seen in rats treated with insulin glargine 40 international units (IU)/kg/day for 12 months.[6]

Effects in Humans

The pharmacodynamic effects of insulin glargine have been assessed in 4 small (n = 12 to 36) clinical trials in healthy volunteers[7-10] and in a single trial involving 20 patients with type 1 diabetes mellitus.[11] Neutral Protamine Hagedorn (NPH) insulin was included as a comparator in all 5 trials; placebo[7] and other long-acting insulins Ultratard®[8] and ultralente[10] were also included as comparators in 3 of the studies. A euglycaemic or isoglycaemic clamp technique maintained for 24 to 30 hours was used in all studies. All insulins were administered subcutaneously as single doses.

Patients with Type 1 Diabetes Mellitus

- In patients with type 1 diabetes mellitus, the effects of insulin glargine 0.3 U/kg or NPH insulin 0.3 U/kg on glucose infusion rates are shown in figure 1(a). The median values for onset of action (time to 50% decrease in insulin infusion rate) were 1.11 hours with insulin glargine versus 0.71 hours with NPH insulin ($p < 0.08$).[11]

- The duration of action (time to blood glucose >8.3 mmol/L minus onset of action) of insulin glargine was longer and the action profile flatter than that of NPH insulin [fig. 1(b)]; median values for duration of action were 22.8 and 13.8 hours, respectively ($p < 0.002$). However, the clamp procedure was discontinued after 24 hours due to fatigue, regardless of whether or not patients had reached the end of the insulin effect (only 14 of 20 insulin glargine-treated patients reached the end of the insulin effect within 24 hours). The plasma free insulin profile of NPH insulin was markedly peaked, whereas the profile of insulin glargine was flattened [fig. 1(c)].[11]

Healthy Volunteers

- The time-action profile of insulin glargine 0.4 U/kg with zinc 30 mg/L was less peaked than that

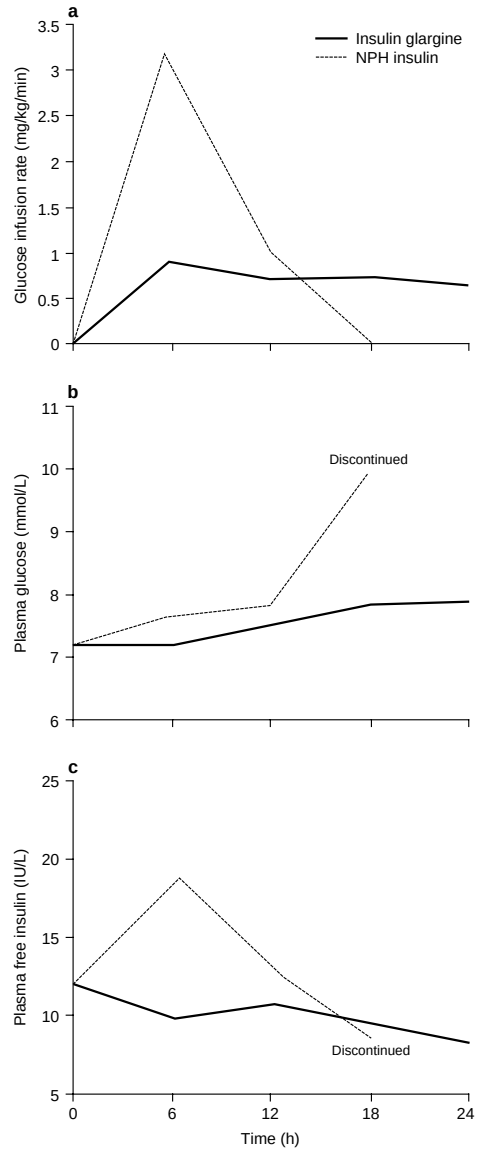


Fig. 1. Effects of a single dose of subcutaneous insulin glargine 0.3 U/kg or Neutral Protamine Hagedorn (NPH) insulin 0.3 U/kg on glucose infusion rates (a), plasma glucose (b) and plasma free insulin levels (c) in 20 patients with type 1 diabetes mellitus in a crossover, isoglycaemic clamp trial. Glucose was infused to maintain a plasma concentration of 7.2 mmol/L for up to 24 hours but the trial was stopped if glucose concentrations exceeded 11.1 mmol/L. Patients initially received a constant intravenous insulin infusion to maintain euglycaemia but this was tapered off as the subcutaneous insulin took effect.[11]

of NPH insulin 0.4 U/kg; maximum glucose infusion rates were 5.3 mg/kg/min for insulin glargine versus 7.7 mg/kg/min for NPH insulin ($p < 0.05$) in a double-blind, crossover, placebo-controlled trial in 15 healthy volunteers.[7]

• When compared with NPH insulin during the first 4 hours after administration, insulin glargine produced a significantly lower area under the curve (AUC) for glucose (1.02 *vs* 1.48 g/kg, $p < 0.01$). However, AUC values for the total duration of the study (30 hours) were not significantly different between insulins (7.93 *vs* 9.24 g/kg for NPH insulin).[7]

• Intraindividual variability in glucose lowering effect (measured as AUC of the glucose infusion rate) over the entire 24-hour clamp period was lowest with NPH insulin (19%), followed by insulin glargine (32%) and then ultralente insulin (38%) in 36 healthy volunteers in a double-blind, randomised, parallel-group trial. Study participants received insulin glargine, NPH insulin or ultralente 0.4 IU/kg then euglycaemic clamps were performed for up to 24 hours at the volunteer's own individual fasting blood glucose concentrations. However, during the time period from 12 hours after injection onwards, intraindividual variability in glucose lowering effect was lower with insulin glargine (23%) than with NPH (29%) or ultralente (55%) insulins.[10]

• Six hours after administration, glucose infusion rates peaked at 1.4, 3.5 and 0.8 mg/kg/min, respectively, with insulin glargine, NPH insulin and long-acting insulin (Ultratard®) [doses not supplied] in 15 healthy volunteers who had their blood glucose clamped at 4.5 mmol/L. Blood glucose was monitored for 24 hours in this crossover trial.[8] Exogenous serum insulin concentrations rose to 10 mU/L at 5 hours (thereafter remaining constant) with insulin glargine, peaked at 25 mU/L at 4 hours with NPH insulin and increased gradually to 9 mU/L at 14 to 22 hours with long-acting insulin.[8]

• The maximum effect of insulin glargine 0.2 U/kg, with 15 or 80 mg/L of zinc, was significantly delayed compared with NPH insulin in 12 healthy volunteers; maximum glucose infusion rates occurred at 12.08 and 12.59 hours with insulin glargine with zinc 15 or 80 mg/L versus 6.27 hours with NPH insulin ($p < 0.01$ *vs* both insulin glargine formulations).[9] The maximum glucose infusion rate was also significantly lower with insulin glargine with zinc 15 or 80 mg/L (2.1 and 1.9 mg/kg/min, respectively), compared with NPH insulin (4.0 mg/kg/min) [$p < 0.01$ *vs* NPH insulin]. Endogenous insulin secretion in each volunteer was suppressed by administration of intravenous somatostatin throughout the clamp period.[9]

2. Pharmacokinetic Profile

The absorption rate of insulin glargine versus NPH insulin has been assessed in 2 trials by measuring the disappearance of I^{125}-labelled insulin from subcutaneous injection sites in healthy volunteers[12] and patients with type 2 diabetes mellitus.[13]

• The median time to disappearance of 25% of radioactivity was 15 and 6.5 hours after the administration of 0.3 IU/kg doses of insulin glargine and NPH insulin, respectively, in 14 patients with type 2 diabetes mellitus in a crossover trial.[13] Mean residual radioactivity at 24 hours was 54.4 and 27.9% for insulin glargine and NPH insulin, respectively.[13]

• After administration of 0.15 IU/kg doses of insulin glargine or NPH insulin, the mean time to disappearance of 25% of radioactivity was 8.75 and 11 hours for insulin glargine with zinc 15 or 80 mg/L, respectively, versus 3.21 hours for NPH insulin in 12 fasted, healthy volunteers in a single-blind, crossover trial ($p < 0.0001$, comparator not stated).[12]

• AUC values for serum insulin from 0 to 6 hours were 18.3, 16.7 and 41.4 (unit not given) for insulin glargine 0.15 U/kg with zinc 15 and 80 mg/L, respectively, and NPH insulin 0.15 U/kg. Corresponding AUC values from 6 to 24 hours were 61.88, 68.12 and 88.86 (unit not given).[12]

• Maximum plasma concentrations of exogenous insulin in the first 4 hours after administration were 5.19, 5.75 and 10.82 IU/L for insulin glargine

0.15 U/kg with zinc 15 or 80 mg/L, respectively, and NPH 0.15 U/kg.[12]

3. Clinical Trials

Insulin glargine has been compared with NPH insulin in the treatment of type 1 and 2 diabetes mellitus in 7 large, multicentre, randomised trials[14-20] and in 2 small, single-centre trials.[21,22] These trials (all reported as abstracts) were not blinded, as insulin glargine is a clear solution and can be readily distinguished from NPH insulin. In all trials, insulin glargine was administered once daily at bedtime and NPH insulin was administered once daily at bedtime or twice daily (bedtime and morning). Doses were individually titrated in each patient. In clinical trials, insulin glargine was usually administered with zinc 30 or 80 mg/L, except in one small trial[22] where insulin glargine with zinc 15 or 80 mg/L was used. In all trials involving patients with insulin-dependent diabetes mellitus, patients remained on their regular preprandial, short-acting insulin regimens.

Patients with Type 1 Diabetes Mellitus

- Insulin glargine significantly decreased fasting plasma glucose (FPG) levels when compared with NPH insulin in 256 patients with type 1 diabetes mellitus in a 4-week trial (adjusted mean value at end-point was 9.2 *vs* 11.3 mmol/L for insulin glargine *vs* NPH insulin; $p < 0.0001$).[15]

- Insulin glargine decreased glycosylated haemoglobin (HbA_{1c}) levels from baseline by 0.16% compared with a 0.21% decrease with NPH insulin in 534 patients with well-controlled type 1 diabetes mellitus (mean baseline HbA_{1c} 7.7% and FPG 11.8 mmol/L) who were followed for up to 28 weeks [fig. 2(a)]. FPG decreased by 1.67 mmol/L with insulin glargine compared with a 0.33 mmol/L decrease with NPH insulin ($p < 0.01$).[14]

- Mean FPG was significantly lower after 4 weeks' treatment with insulin glargine compared with NPH insulin in 333 patients with type 1 diabetes mellitus (final adjusted mean value 10.11 mmol/L for insulin glargine *vs* 12 mmol/L for NPH insulin;

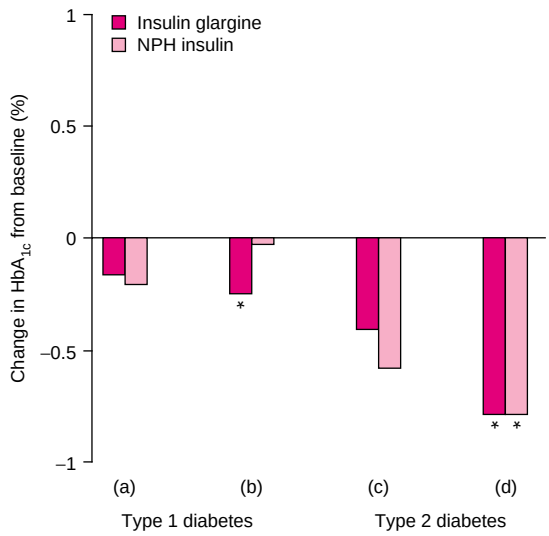


Fig. 2. Effect of insulin glargine and Neutral Protamine Hagedorn (NPH) insulin on glycosylated haemoglobin (HbA_{1c}) levels in 534 patients with type 1 diabetes mellitus over 28 weeks (a),[14] 333 patients with type 1 diabetes mellitus over 4 weeks (b),[23] 518 patients with type 2 diabetes mellitus over 28 weeks (c)[18] and 204 patients with type 2 diabetes mellitus over 4 weeks (d).[19] Where details were supplied, insulin glargine was administered once daily and NPH insulin once or twice daily and doses were individually titrated. The concentration of zinc used in the insulin glargine formulation(s) was 30 or 80 mg/L[23] or was not detailed.[14,18,19] Data reported for study (b)[23] represent a zinc concentration of 30 mg/L. Insulins were administered with preprandial regular insulin in patients with type 1[14,23] or 2[18] diabetes mellitus or with oral antidiabetic agents in patients with type 2 diabetes mellitus.[19] Mean baseline HbA_{1c} levels were 7.7, 7.96, 8.5 and >7.7% for trials (a), (b), (c) and (d), respectively. * $p \leq 0.0001$ *vs* baseline.

$p = 0.0001$). Mean baseline HbA_{1c} was 7.96% and this was significantly reduced with insulin glargine (with zinc 30 mg/L) [0.25% change; $p = 0.0001$ *vs* baseline]; the corresponding reduction with NPH insulin was 0.03% [fig. 2(b)].[23]

- Insulin glargine (n = 9) significantly decreased fasting blood glucose (FBG) when compared with NPH insulin (n = 5) in young patients (mean age approximately 24 years) with type 1 diabetes mellitus after 4 weeks' treatment. FBG decreased from

9 to 6.2 mmol/L with insulin glargine and from 10 to 9.3 mmol/L with NPH insulin ($p < 0.01$).[21] There was also a significant decrease in total insulin intake in patients receiving insulin glargine ($p < 0.04$, comparator not stated). End-point HbA_{1c} decreased by 0.4 and 0.2% versus baseline in patients receiving insulin glargine and NPH insulin, respectively.[21]

- Insulin glargine (n = 174) significantly decreased FBG compared with NPH insulin (n = 175) in children (aged 5 to 16 years) with type 1 diabetes mellitus after 6 months' treatment. Mean decreases in FBG were 1.27 and 0.7 mmol/L for insulin glargine and NPH insulin, respectively ($p = 0.0315$).[20]

- Treatment satisfaction and psychological well-being (assessed by Diabetes Treatment Satisfaction and Well-being questionnaires at baseline and weeks 8, 20 and 28) improved to a greater extent with insulin glargine than with NPH insulin in a multicentre, randomised trial involving 474 patients with type 1 diabetes mellitus. Treatment satisfaction scores improved in both treatment groups but the improvement was greater in insulin glargine recipients at week 20 ($p < 0.046$ *vs* baseline). The perceived frequency of hypo- and hyperglycaemia was lower in insulin glargine recipients ($p < 0.0162$ for hyperglycaemia at week 8; comparator not stated).[24]

Patients with Type 2 Diabetes Mellitus

Of 3 large comparative trials in patients with type 2 diabetes mellitus,[17-19] 2 involved patients with noninsulin-dependent, moderately well-controlled diabetes mellitus (HbA_{1c} >7%)[17,19] and the third involved patients with insulin-dependent type 2 diabetes mellitus.[18] In all trials, insulin glargine was compared with NPH insulin.

- Insulin glargine (n = 246) and NPH insulin once (n = 48) or twice daily (n = 207) achieved similar glycaemic control in patients with insulin-dependent type 2 diabetes mellitus who were monitored for up to 28 weeks. The mean baseline HbA_{1c} was 8.5% and this decreased by 0.41 and 0.59% with insulin glargine and NPH insulin, respectively [fig. 2(c)].[18] FPG decreased significantly in both treatment groups when compared with baseline (1.7 and 1.2 mmol/L with insulin glargine and NPH insulin, respectively; $p < 0.01$) but the difference between groups was not significant.[18]

- No statistically significant differences in glycaemic control were noted in patients receiving insulin glargine with 30 (n = 64) or 80 mg/L of zinc (n = 72) or NPH insulin (n = 68) over 4 weeks [HbA_{1c} decreased by 0.8% in all groups; fig. 2(d)]. Insulin was administered as adjunctive therapy and patients remained on their regular antidiabetic medications (sulphonylureas with or without concomitant metformin or acarbose).[19]

- No significant differences in the levels of FPG, HbA_{1c} or fructosamine were seen in 157 patients treated with NPH insulin or insulin glargine (with zinc 30 or 80 mg/L). Before the trial, all patients were receiving maximal doses of sulphonylureas with or without concomitant metformin but these antidiabetic drugs were stopped at the beginning of the trial.[17]

4. Tolerability

Insulin glargine has been well tolerated in 7 large clinical trials[14-20] and several smaller trials[12,13,21,22] with an adverse event profile reportedly similar to that of NPH insulin. In this profile, specific blood glucose levels are reported where these data were supplied.

Hypoglycaemia

- The incidence of diurnal and nocturnal hypoglycaemia (blood glucose <2 mmol/L) was significantly lower in patients with type 1 diabetes mellitus treated with insulin glargine than in those treated with NPH insulin (n = 534, $p < 0.05$; fig. 3). The incidence of severe hypoglycaemia was also lower with insulin glargine but the difference was not statistically significant between groups (fig. 3).[14]

- At least 1 hypoglycaemic episode was reported in 98% and 100% of patients who received insulin glargine with zinc 30 (n = 82) and 80 mg/L (n = 86), respectively, in addition to their regular prepran-

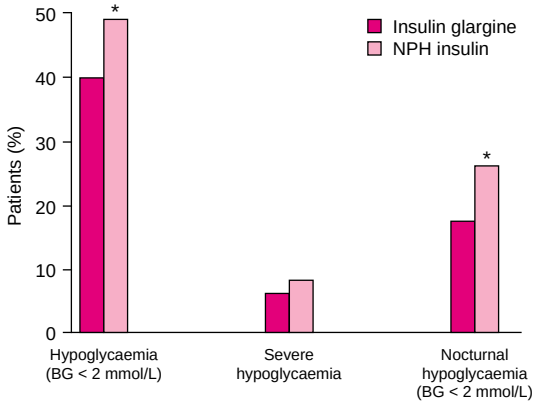


Fig. 3. Incidence of hypoglycaemia with insulin glargine and Neutral Protamine Hagedorn (NPH) insulin in 534 patients with type 1 diabetes mellitus in a randomised multicentre trial. In addition to preprandial short-acting insulin, patients received individually titrated doses of insulin glargine at bedtime or NPH insulin at bedtime or NPH insulin twice daily. **BG** = blood glucose; * $p < 0.05$.[14]

dial insulin, in a 4-week randomised trial. This compared with 93% of 88 patients who experienced hypoglycaemia with NPH insulin.[15]

- The frequency of nocturnal hypoglycaemia was significantly lower in insulin glargine recipients than in NPH insulin recipients in 333 patients with type 1 diabetes mellitus in a 4-week randomised, multicentre trial (36% with insulin glargine *vs* 55% with NPH insulin, $p = 0.0037$). However, the overall frequency of hypoglycaemia did not differ between treatment groups.[16]

- The overall frequency of hypoglycaemia was similar in 349 children with type 1 diabetes mellitus who received insulin glargine or NPH insulin for 6 months in a multicentre, randomised trial (79.3 *vs* 78.9%). However, less frequent severe (22.4 *vs* 28.6%), nocturnal (48.3 *vs* 50.9%) and severe nocturnal (12.6 *vs* 17.7%) hypoglycaemia occurred with insulin glargine than with NPH insulin.[20]

- Nocturnal hypoglycaemia occurred in 31.3% of insulin glargine recipients and 40.2% of NPH insulin recipients in a 28-week randomised, multicentre trial in 518 patients with insulin-dependent type 2 diabetes mellitus. Severe hypoglycaemia occurred in 0.4% of patients receiving insulin glargine and 2.3% receiving NPH insulin.[18]

- There were significantly fewer episodes of hypoglycaemia with insulin glargine than with NPH insulin in 204 patients with type 2 diabetes mellitus (7.3% with insulin glargine *vs* 19.1% with NPH insulin, $p < 0.037$). Patients were allowed to continue their regular oral hypoglycaemic drugs (sulphonylureas with or without metformin or acarbose) during this 4-week, multicentre trial.[19]

Other Effects

- In 1 trial,[18] patients with type 2 diabetes mellitus receiving NPH insulin (n = 255) gained more bodyweight than those receiving insulin glargine (n = 246; 1.4 *vs* 0.4kg; $p < 0.01$) over a 28-week period.

- A slightly higher incidence of mild injection site reactions (further details not supplied) was seen in 246 patients with type 2 diabetes mellitus receiving insulin glargine when compared with 255 patients receiving NPH insulin in a randomised, multicentre trial over 28 weeks.[18]

5. Insulin Glargine: Current Status

Insulin glargine is a long-acting biosynthetic insulin analogue designed to satisfy the basal insulin requirements of patients with both type 1 and 2 diabetes mellitus. It is administered as a once daily subcutaneous injection and appears to be a well tolerated, effective insulin preparation with a prolonged duration of action. Insulin glargine marketing authorisation applications for the treatment of type 1 and 2 diabetes mellitus have been filed in the US, Europe and other countries worldwide.

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