# Insulin glulisine: a new rapid-acting insulin analogue

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## PRODUCT PROFILE


**Proprietary name:** Apidra
**Constituents:** insulin glulisine
**Indications:** treatment of adult patients with diabetes mellitus
**Dosage and method of administration:** should be given by subcutaneous injection or by continuous subcutaneous pump infusion shortly – 0-15 minutes – before or soon after meals; should be used in regimens that include an intermediate- or long-acting insulin or basal insulin analogue; not to be mixed with any preparation other than NPH human insulin
**Contraindications:** hypersensitivity to the active substance or to any of the excipients; hypoglycaemia
**Precautions:** use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic patients, may lead to hyperglycaemia and diabetic ketoacidosis; if hypoglycaemia occurs after an injection with rapid-acting analogues, it may occur earlier than with soluble human insulin; store in refrigerator
**Pregnancy and lactation:** there are no adequate data on the use of insulin glulisine in pregnant women; it is unknown whether insulin glulisine is excreted in human milk
**Interactions:** based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur; a number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring (see SPC)
**Side-effects:** *very common*: hypoglycaemia; *common:* injection-site reactions and local hypersensitivity reactions
**Presentation/cost:** vial – 1 x 10ml, £17.27; cartridge – 5 x 3ml, £29.45; pre-filled pen (OptiSet) – 5 x 3ml, £29.45

**Insulin glulisine is the latest rapid-acting insulin analogue to become available. Here Dr Narendran describes the results of clinical trials of its efficacy and tolerability, and considers its potential role in the management of diabetes.**

In health insulin secretion is low and stable with profound surges at mealtimes. The amplitude and duration of mealtime surges is affected by factors such as the carbohydrate and protein content of the meal, the insulin sensitivity of the subject and the period over which it is eaten. The challenge of insulin therapy is to reproduce this secretion profile without incurring disabling hypoglycaemia.

Following the successful isolation and increasing availability of insulin in the 1920s, attempts were made to reduce the number of daily injections. This led to the development of a long-acting protamine zinc insulin preparation in the 1930s that had a duration of action of between 18 and 24 hours and allowed patients to take the day's insulin dose in just one injection.

Since then there has been a gradual evolution towards trying to reproduce a more physiological insulin profile. In the 1950s, intermediate-acting neutral protamine Hagedorn (NPH) insulin and insulin zinc (Lente) were developed which had a duration of

| Insulin | Onset of action (minutes) | Peak action (hours) | Duration of action (hours) |
|---|---|---|---|
| soluble insulin | 30-60 | 2-4 | 6-8 |
| lispro | 15 | 1-2 | 3-5 |
| aspart | 10-20 | 1-3 | 3-5 |
| glulisine | 10-20 | 1-2 | 3-4 |

**Table 1.** Pharmacokinetic profiles of the rapid-acting insulins and soluble insulin (source: NHS UK Medicines Information website – www.ukmi.nhs.uk)

action of 12-18 hours, and these were used with soluble insulin in different split regimens. An example was the 'basal bolus' regimen that consisted of an intermediate-acting insulin, to mimic the basal insulin secretion, along with soluble insulin to mimic mealtime insulin surges.

### Absorption of soluble insulin

Insulin circulates as single molecules in the blood. At higher concentrations, such as in commercial preparations, insulin molecules tend to associate into dimers. These preparations also contain zinc that encourages dimers to further associate into groups of hexamers, which aid storage and shelf life.

Following injection, fluid is drawn into the injected insulin depot through osmosis. This leads to dilution of the insulin and dissociation of the insulin molecules, a spontaneous but gradual process that must occur before insulin can cross the capillary walls, as monomers, into the blood circulation. Patients are therefore advised to inject their soluble insulin 15 to 20 minutes before eating so that circulating insulin levels are optimal at the time their meal is being absorbed.

A significant proportion of patients find it hard to follow this advice because of the planning required, and even when they do the calculated doses may be inaccurate, particularly when the preparation of the meal is not in their control.

### Rapid-acting insulin analogues

The association between insulin molecules can be reduced by specific changes to insulin's amino-acid sequence. These changes result in faster absorption of insulin into the blood stream and allow it to be injected just before, or even immediately after, eating a meal.

To date, two such rapid-acting insulins (RAIs) have been available in the UK. Insulin lispro (Humalog) was licensed in 1996 and insulin aspart (NovoRapid) in 2000. Both of these insulins act more quickly (within 10-20 minutes) and have a shorter duration of action (three to five hours) than soluble insulin (30-60 minutes and six to eight hours, respectively; see Table 1).

A number of studies with both these RAIs have demonstrated their safety in both type 1 and type 2 diabetes, either as part of a 'basal bolus' insulin injection regimen combined with intermediate-acting insulins or in continuous subcutaneous insulin infusion (CSII). The time action profile of RAIs is well suited to mimicking the body's insulin requirement at mealtimes, and they may therefore control postprandial hyperglycaemia more effectively than soluble insulin. As a result some

patients achieve better glycaemic control with RAIs than with soluble insulin, with fewer episodes of hypoglycaemia occurring.

The benefits of RAI over soluble insulin appear to be clearer in studies involving patients with type 1 rather than type 2 diabetes, and who are using CSII rather than multiple-dose injections.[1] Therefore it would be sensible to try RAIs in these patients who are unable to achieve good glycaemic control without hypoglycaemia.

### Insulin glulisine

Insulin glulisine (Apidra) is a new analogue of human insulin and was licensed in the UK in 2005 for the treatment of adult patients with diabetes mellitus. This RAI differs from soluble insulin at position B3, where the amino acid asparagine is replaced by lycine, and at position B29, where lycine is replaced by glutamic acid. As with insulin aspart and insulin lispro these substitutions reduce dimerisation; however, unlike them insulin glulisine does not contain zinc.

Insulin glulisine can be used in conjunction with oral hypoglycaemic medication, with intermediate- and long-acting insulin, and with basal insulin analogues. Insulin glulisine can be mixed with

NPH insulin in vial, but not with any of the other insulin preparations with a prolonged duration of action. It is priced very similarly to the other RAIs.

Insulin glulisine is available as 100 units per ml in 10ml vials, as a prefilled pen (OptiSet), and 3ml cartridges for use with the OptiPen and AutoPen delivery devices. These reusable injection pens can be difficult to use, particularly by those patients with compromised manual dexterity.

### Insulin glulisine compared with soluble insulin

Insulin glulisine has been demonstrated to be absorbed more rapidly, and to reach a higher circulating insulin concentration, than soluble insulin, allowing it to be classified as an RAI (see Table 1).[2]

In a 26-week study involving 876 subjects with type 2 diabetes, premeal insulin glulisine appeared to improve glycaemic control more than did soluble insulin: $HbA_{1c}$ -0.46 *vs* -0.30 per cent.[3] However the clinical significance of this difference remains to be established.

A similar benefit over soluble insulin was also seen in a 12-week study involving 860 subjects with type 1 diabetes: $HbA_{1c}$ -0.26 *vs* -0.13

**Key points**

- the challenge of insulin therapy in diabetes is to maintain good glycaemic control and reproduce the physiological insulin secretion profile without incurring hypoglycaemia
- RAIs are absorbed much more quickly following injection and are well suited to mimicking the body's insulin requirement at mealtimes
- it would be appropriate to try RAIs in those patients who are unable to achieve good glycaemic control without hypoglycaemia
- glulisine is the latest RAI, and appears as safe and as efficacious as the other RAIs available
- glulisine appears to maintain its rapid-acting properties in obese individuals but it remains to be seen whether this translates into clinical benefit in obese patients with diabetes

per cent.[4] Interestingly, this benefit was only seen when insulin glulisine was given before the meal, and no difference was seen when given after. Insulin glulisine appears to control postprandial glucose levels more effectively than does soluble insulin in type 1 diabetes.[5]

## Insulin glulisine compared with other RAIs

In a 26-week trial of patients with type 1 diabetes, insulin glulisine achieved similar reductions in $HbA_{1c}$ as insulin lispro, and with no higher frequency of hypoglycaemia.[6]

Currently, there are no other peer-reviewed publications directly comparing the clinical efficacy of insulin glulisine with the other RAIs, although several abstracts presented at scientific meetings suggest that insulin glulisine is as efficacious and safe as insulin lispro and insulin aspart in type 1 and type 2 diabetic patients, and when administered as a CSII.

Insulin glulisine is licensed for use in CSII pumps, and in a study of 59 patients showed equivalent bioavailability, effect on $HbA_{1c}$ and catheter occlusion rates to its RAI comparator, insulin aspart.[7]

## Insulin glulisine in obese patients

The prevalence of obesity, and particularly of diabetes with obesity, is increasing in the UK. Few studies have assessed the effect of obesity on the absorption of RAIs, although the absorption of insulin glulisine following injection into the abdominal areas has been studied in obese nondiabetic individuals using euglycaemic clamps.[8] This RAI has a more rapid-acting profile than soluble insulin, and is also marginally faster-acting and reaches higher insulin concentrations than its RAI comparator, insulin lispro.

There are as yet no study results to see if this holds true in diabetic patients and it is unclear whether these marginal improvements in time action profile would translate into clinically relevant end-points, such as $HbA_{1c}$ levels and hypoglycaemia, in obese subjects.

## Conclusion

Insulin glulisine is more rapidly absorbed than soluble human insulin and fulfils the criteria for an RAI. It appears to maintain its rapid-acting characteristics in obese subjects, but whether maintaining these characteristics translates to a clinical benefit in obese diabetic patients remains to be seen in peer-reviewed randomised controlled trials.

To date the few trials published suggest that insulin glulisine is as safe and efficacious as the other RAIs presently available in the UK, and it would therefore be appropriate to use insulin glulisine in diabetic patients who are unable to achieve good glycaemic control with soluble human insulin.

## References

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