HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

31 May 2006

Insuplant 400 IU/mL
1 vial of 10 mL – CIP code: 564 510-9

Applicant: OTL Pharma

Human insulin

List II
For hospital use only.

Date of Marketing Authorisation: 24/08/1998 amended on 29/09/05 (change of Marketing Authorisation holder).

Reason for request: inclusion on the list of medicines approved for hospital use.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Human insulin 400 IU/mL

1.2. Background

Fast-acting, short-term human insulin, obtained by enzymatic modification from porcine insulin, at a concentration of 400 IU/mL, for use only with the MiniMed implantable insulin pump with intraperitoneal catheter.

Other fast-acting insulins on the market can be administered by the subcutaneous or intravenous route. These are human insulins produced by the recombinant DNA technique or human insulin analogues, at a concentration of 100 IU/mL.

1.3. Indication

Diabetes requiring insulin therapy, when use of an implantable pump is indicated.

1.4. Dosage

Principles

Insuplant has been designed for use in the MiniMed implantable insulin pump with intraperitoneal catheter. It is specially stabilised to minimise any loss of efficacy under the mechanical and thermal stress conditions of such pumps.

Target blood glucose and insulin dosage should be adjusted to suit each patient and their diet, physical activity and lifestyle.

Daily doses and schedule

When an implantable insulin pump is used, part of the insulin dose is infused continuously ("basal rate") and the rest is administered in the form of insulin boluses infused prior to meals. See the directions for use for detailed instructions about the pump, its functions, and safety precautions required.

There is no fixed rule for insulin dosage. Average insulin requirements are often around 0.5–1.0 IU per kilo of body weight per day. Basic metabolic needs represent 40–60% of the total daily requirement. Around 40–60% of the daily dose is therefore administered at the basal rate, the rest as premeal insulin boluses.

Changing to Insuplant

Dose adjustment may be necessary when changing from one insulin preparation to another, for instance, when changing:

- from an animal insulin preparation (notably bovine) to human insulin,
- from one human insulin preparation to another,
- from treatment with insulin in solution to treatment with a longer-acting insulin.

The need to adjust (e.g. to reduce) the dose may become clear when changing to the new preparation, or it may appear gradually over a period of several weeks.

After changing from an animal insulin to a human insulin, dose reduction may be necessary, especially in patients who:

- are already stabilised with relatively low glycaemia when the change takes place,
- have a tendency to hypoglycaemia,
- have previously needed high doses of insulin because of the presence of anti-insulin antibodies.

Close metabolic monitoring is recommended during the transition period and the first few weeks afterwards. In patients who need high doses of insulin because of the presence of anti-insulin antibodies, the change should be made under medical surveillance in hospital or in similar facilities.

Subsequent dose adjustment

Improved metabolic control may lead to increased sensitivity to insulin, and therefore to a reduced insulin requirement. The dose may also need to be adjusted, for instance:

- if there are changes in the patient's body weight,
- if there are changes in the patient's lifestyle,
- if any other circumstance that could increase the susceptibility to hypo- or hyperglycaemia arises (see SPC, paragraph 4.4).

Use in certain types of patient

In patients with hepatic or renal failure, and in elderly people, insulin requirements may be reduced (see SPC paragraph 4.4 , "Special warnings and precautions for use").

Administration

Insuplant is infused by the intraperitoneal route. It is designed to be administered only with the implantable MiniMed pump. **Any other modes of administration may be dangerous.**

Insulin must always be infused in strictly aseptic conditions. The equipment designed for insulin pumps (such as catheters and cannulas) makes this easier.

Patients should be warned that the concentration of 400 IU/mL (FOUR HUNDRED UNITS PER MILLILITER) of Insuplant is higher than for other insulins presented in vials or cartridges (100 IU/mL). Insuplant must not be drawn directly from the vial.

Mixing insulins

Insuplant MUST NOT be mixed with other insulins or insulin analogues.

See SPC.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

A: Alimentary tract and metabolism
10: Drugs used in diabetes
A: Insulins and analogues
B: Insulins and analogues, fast acting
01: Human insulin

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

There are no other insulins for use with an implantable insulin pump with intraperitoneal catheter.

2.2.2. Comparative assessment

Not applicable

2.3. Medicines with a similar therapeutic aim

Other fast-acting insulins for intravenous administration.

3 ANALYSIS OF AVAILABLE DATA

The applicant submitted the results of an ongoing clinical monitoring study (303). Its aim is to assess the long term safety of the pump + insulin combination. This noncomparative study was set up when the pump was approved in 1995. As of February 2006, 346 patients were actively participating in the study. Total exposure time since 1995 has been 1955 patient-years.

Overall, 33 serious undesirable events have been recorded. These are events regarded as connected to the pump or the insulin + pump system:

- 7 cases of batteries running down prematurely,
- 20 cases of bolus nondelivery due to mechanical malfunction,
- 3 cases in which the reservoir could not be filled or emptied,
- 1 increase in blood glucose 2 days after implantation (no further information),
- 2 telemetry errors.

Other studies in the Marketing Authorisation dossier were not conducted with the same insulin formulation and were not considered.

The applicant submitted 2 publications of studies. Their methodology was debatable:

1. The first study was a multicentre prospective follow-up trial[1] in 40 patients with type 1 diabetes, treated with insulin administered via peritoneal catheter, whose baseline HbA1c was 7.8 ± 0.5%. Exposure was 106 patient-years.

   No incidents were reported in 13 patients. After 36 months of treatment, mean HbA1c in these 13 patients was 7.0 ± 0.2%. One incident was reported in 27 patients:
   - the pump had to be removed in 3 patients (1 electronic failure, 2 infections at the implantation site).
   - underdelivery of insulin occurred in 24 patients.

   In these 27 patients, after 36 months of treatment, HbA1c was 7.8 ± 0.5%.

2. The second study was a retrospective open-label nonrandomised study[2] in 14 patients with type 1 diabetes, comparing Insuplant administered by peritoneal catheter with insulin lispro (Humalog) administered by the subcutaneous route using a pump. Patients were treated for 2 periods of 45 days: period A (Humalog) and period B (Insuplant). HbA1c was lower at the end of the Insuplant period (7.3% ± 0.8) than after the Humalog period (7.8% ± 0.9). However, HbA1c at baseline was not specified and a period effect may have occurred.

The Committee therefore had very little data for assessing the effect of Insuplant.

The serious undesirable events occurring during the clinical monitoring period (still ongoing) were considered to be related to the pump or to the insulin + pump system.

[1] Gin *et al*. Diabetes Metab. 2003;29:602-7
[2] Catargi *et al*. Diabetes Metab. 2002;28,133-7

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

- Diabetes is a chronic disease that can be life-threatening, either immediately or as a result of complications.
- Insuplant is used to treat hyperglycaemia.
- The efficacy/safety ratio of Insuplant administered by intraperitoneal catheter is difficult to determine given the data available.
- There are no alternatives.
- Public health benefit.
  - Type 1 diabetes is a moderate public health burden. However, the burden represented by the subpopulation suitable for insulin therapy via implantable pump with intraperitoneal catheter is low, as the number of patients concerned is small.
  - Improving the management of type 1 diabetes in order to reduce the frequency and seriousness of complications in this disease is a public health need. There is no evidence to suggest that Insuplant, administered by implantable pump with intraperitoneal catheter, will fulfil this need.
  - The data available are insufficient to estimate the impact of Insuplant, administered by implantable pump with intraperitoneal catheter, in reducing morbidity and mortality in diabetic patients who are candidates for such treatment. No reduction of morbidity and mortality related to type 1 diabetes is expected at population level.
  - Therefore, Insuplant is not expected to bring any benefit in terms of public health.

The actual benefit is substantial.

4.2. Improvement in actual benefit

Insuplant offers no improvement in Actual Benefit (added value) (IAB level V). It is an additional therapy, in combination with the implantable MiniMed pump with intraperitoneal catheter, for the management of some patients with type 1 diabetes.

4.3. Therapeutic use

Insulin therapy by the subcutaneous route is the first line therapy in type 1 diabetes.

Insulin therapy by implantable pump with intraperitoneal catheter can be used in some patients with type 1 diabetes for whom well-conducted intensified subcutaneous insulin therapy has not achieved the desired results, i.e. patients with:

- recurrent severe hypoglycaemia,
- high variability in blood glucose levels,
- inability to achieve HbA1c below 7% (notably, resistance to subcutaneous insulin).

Alternative therapies are allograft of islets of Langerhans and pancreas transplant.

4.4. Target population

According to 2 CNAMTS studies (Ricordeau 2000, 2002)[3] carried out using requests for reimbursement by National Health Insurance and extrapolated to the general population in France:

- the estimated prevalence of drug-treated diabetes was 3.06% in 1998, i.e. approx. 1.8 million diabetics (CNAMTS 2000);
- the prevalence of diabetes increased by 3.2% per year between 1998 and 2000 (CNAMTS 2002). It has been hypothesised that this rate of increase will remain constant.
- approx. 80% of patients are not given insulin therapy: 15% are treated with insulin alone and 5% with a combination of insulin + oral antidiabetics.

Extrapolation of these data to 2004 gives an estimated 1.73 million patients on oral antidiabetics alone, 324 000 patients on insulin alone, and 108 000 patients on combined insulin + oral antidiabetics.

In the ENTRED study, patients with type 1 diabetes represented around 6–8% of the diabetics treated. Extrapolating these data to all diabetics treated (2.2 million) gives an estimated 130 000–173 000 patients with type 1 diabetes in France.

There are no epidemiological data for assessing the number of patients meeting the criteria listed in paragraph 4.3 but, according to expert opinions, the target population for Insuplant is probably very small, approx. 400 patients.

4.5. Transparency Committee recommendations

The Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services for the indication and at the dosages specified in the Marketing Authorisation.

The Transparency Committee regretted that there has been no rigorous assessment of insulin therapy administered by the peritoneal route.

[3] CNAMTS (National Health Insurance fund for salaried workers). CNAMTS publications concern requests for reimbursement and do not distinguish between requests for reimbursement for the management of type 1 diabetes and type 2 diabetes.