

Insulin Inhalation – Pfizer/ Nektar Therapeutics

HMR 4006, Inhaled PEG-Insulin – Nektar, PEGylated Insulin – Nektar

Abstract

Nektar Therapeutics (formerly Inhale Therapeutic Systems) has developed a pulmonary drug delivery system for insulin [*HMR 4006, Exubera®*].

The rationale behind developing a pulmonary drug delivery system is to ensure that insulin powder is delivered deep into the lungs, where it is easily absorbed into the bloodstream, in a hand-held inhalation device. The device converts the insulin powder particles into an aerosol cloud for the patient to inhale. No propellants are used. The inhaler requires no power source and the clear chamber ensures that the patient knows immediately when all the insulin has been inhaled.

Nektar Therapeutics, developers of the inhalation device and formulation process, has licensed the system to Pfizer. Under the terms of the agreement, Pfizer will lead the clinical development of inhaled insulin, while working with Nektar Therapeutics to develop the technology required for packaging the product.

Pfizer has an agreement with Hoechst Marion Roussel (now Aventis Pharma) for developing, manufacturing and promoting inhaled insulin. Under the terms of the collaboration, Aventis Pharma will supply recombinant insulin to Nektar Therapeutics to process it into dry powder for incorporation into the inhaler device. Nektar Therapeutics will receive royalties on sales of inhaled insulin marketed by Pfizer and Aventis Pharma, and milestone payments and research support from Pfizer. Aventis Pharma's codename for the product is HMR 4006.

Profil, a CRO in Germany, is cooperating with Pfizer/Aventis Pharma in the development of inhaled insulin.

In March 2004, Pfizer and Aventis announced that the European Medicines Evaluation Agency (EMA) accepted the filing of the MAA for inhaled insulin (*Exubera®*) for the treatment of type 1 and type 2 diabetes mellitus. The two companies are working with the US FDA to determine the timing for the submission of the NDA in the US.^[1]

Pfizer completed five pivotal phase III clinical trials with inhaled insulin in patients with type 1 and type 2 diabetes mellitus in 120 centres worldwide, and will use a fourth prototype inhaler device that is half the size of the first prototype, and has reduced manufacturing costs.

Pfizer and its partner, Aventis Pharma, are conducting additional long-term pulmonary safety data studies in patients with type 1 and type 2 diabetes.^[2] Pfizer is also conducting phase III clinical trials with inhaled insulin in paediatric patients aged 6–17 years.

Nektar Therapeutics is using its Advanced PEGylation technology to develop a dry powder-inhaled polyethylene glycol (PEG) formulation for delivering pep-

tides efficiently across the lungs and to promote prolonged serum concentration of the peptide. PEG is a neutral, water-soluble, nontoxic polymer comprising any number of repeating units of ethylene oxide. PEGylation is designed to increase the size of the active molecule and ultimately improve drug performance by optimising pharmacokinetics, increasing bioavailability, and decreasing immunogenicity and dosing frequency.

The investigation has begun with inhaled, long-acting (PEGylated) insulin [*inhaled PEG-insulin*, *PEGylated insulin – Nektar*], and is funded by Pfizer.

Preclinical results of a dry powder formulation of inhaled PEG-insulin presented at the 63rd Scientific Sessions of the American Diabetes Association (ADA-2003) [June 2003, New Orleans, LA, USA] demonstrated prolonged systemic activity of insulin in dogs.^[3]

Nektar Therapeutics was granted US patent 5 997 848 on a method for delivering inhalable insulin. The patent covers a method for delivering of 0.5–15mg of aerosol dry powder insulin per dosing session in 1–4 individual dosages into the deep lung for systemic absorption. The patent does not specify the formulation of insulin or aerosol delivery device.

Nektar Therapeutics estimated in June 2002 that Exubera® could earn the company potential revenues of >\$US200 million.

Table 1. Features and properties

WHO ATC code	A10A (Insulins and Analogues)
EphMRA ATC code	A10C (Human Insulins and Analogues)
Originator	Nektar Therapeutics: USA
Licensee companies	Pfizer: Europe; USA Aventis: USA
Highest development phase	Phase III (USA)
Properties	
Mechanism of action	Ornithine decarboxylase stimulants
Pharmacodynamics	Antiglycaemic effect; prolonged systemic activity in dogs following administration of inhaled PEG-insulin
Route	Inhalation
Adverse events	Rare: Cough, Hypoglycaemia, Weight gain

1. Profile

1.1 Pharmacokinetics

The metabolic effects of inhaled insulin and insulin administered by SC or IV injections were assessed in a randomised, open study in 11 volunteers. The onset of the effect occurred faster in volunteers receiving inhaled insulin (87.2U) compared with subcutaneous (SC) injection (10.2 or 5.5U). The $t_{\max}$ values were 86 and 182 min, respectively. The relative bioavailability of inhaled insulin was

12% of that of SC administered insulin. The intraindividual variability of the effect of inhaled insulin was 14% for the maximal glucose infusion rate, 15% for the maximal effect, and 16% for the total amount of glucose infused.^[4]

In an intraindividual variability study, maximal insulin concentration was achieved more rapidly and had a 70% greater peak value compared with SC administration. Systemic insulin exposure over 2h (AUC_{0-2h}) with inhaled insulin was 87% greater than after SC administration, whereas a 6-h exposure was comparable with that after SC administration.^[5]

Table II. Drug development history

Jan 1997	Phase-II for Type-2 diabetes mellitus in US (Inhalation)
Jan 1997	Phase-II for Type-1 diabetes mellitus in US (Inhalation)
Nov 1998	Phase-III for Type-2 diabetes mellitus in US (Inhalation)
Nov 1998	Phase-III for Type-1 diabetes mellitus in US (Inhalation)
Jan 2000	Inhale Therapeutic Systems has been issued US patent on a method for delivering inhalable insulin
May 2000	Phase-III for Type-1 diabetes mellitus in Europe (Inhalation)
May 2000	Phase-III for Type-2 diabetes mellitus in Europe (Inhalation)
Jun 2000	Pfizer has merged with Warner-Lambert
Sep 2000	Pfizer has licensed delivery technology from Battelle Pulmonary Therapeutics
Jul 2001	The NDA and MAA filing schedule for Exubera appears likely to be revised
Jan 2002	Pfizer and Aventis are planning to initiate a long-term pulmonary safety data study with inhaled insulin in diabetic patients for inclusion in the NDA
Oct 2002	Pfizer and Aventis decided to complete long-term studies in patients with type 1 and type 2 diabetes
Jan 2003	Inhale Therapeutic Systems is now called Nektar Therapeutics
Jun 2003	Prein Diabetes mellitus in USA (Inhalation, PEGylated formulation)
Jul 2003	Profile reviewed with information presented at the 10th Annual Meeting of the Biotechnology Industry Organisation (BIO-2003)
Mar 2004	Preregistration for Type-1 diabetes mellitus in Europe (Inhalation)
Mar 2004	Preregistration for Type-2 diabetes mellitus in Europe (Inhalation)

1.2 Adverse Events

Type 1 diabetes mellitus: In a 6-month, phase III study in 335 patients with type 1 diabetes, patients receiving inhalable insulin prior to meals combined with a single long-time insulin injection at bedtime experienced mild-to-moderate cough more frequently than patients receiving two to three daily injections of insulin. The incidence and prevalence of cough decreased during the course of the study. However, small relative decreases in one of the lung function tests were detected in patients receiving inhalable insulin.^[6,7]

In 69 patients with type 2 diabetes mellitus failing to adequately respond to sulphonylureas and/or metformin (≥ 1.5 g/day), adjunctive therapy with inhaled insulin three times daily for 3 months prior to meals was well tolerated. No change in pulmonary function was observed during the therapy. One patient reported severe hypoglycaemia (blood glucose 54 mg/dL).^[8]

In a 3-month, multicentre, phase III study in 145 patients with type 2 diabetes receiving inhaled insulin or rosiglitazone in conjunction with a diet and exercise, the majority of adverse events were mild to

moderate in both treatment groups. Hypoglycaemia rates and weight gain, however, were higher in insulin recipients. There were no significant differences between the groups in assessments of pulmonary function tests.^[9]

1.3 Pharmacodynamics

1.3.1 Diabetes

In an open study in 18 volunteers undergoing a hyperinsulinaemic euglycaemic insulin clamp, single doses of inhaled insulin 6mg had a faster onset of action than regular insulin 18U SC inj. Inhaled insulin also reached its peak effect within a time that was shorter than that of insulin lispro (18U SC inj) and comparable with regular insulin. The duration of the effect of inhaled insulin was shorter than insulin lispro and longer than regular insulin.^[10]

Data presented showed that 309 patients with type 2 diabetes who had failed to meet recommended blood glucose levels with combination oral therapy, achieved better glycaemic control with inhaled insulin compared with patients who received only oral agents. Patients receiving inhaled insulin demonstrated greater decreases in both fasting and post-

prandial glucose levels compared with patients receiving only oral antidiabetics.^[11]

1.4 Therapeutic Trials

1.4.1 Diabetes

Type 1 diabetes mellitus: Seventy-two patients with type 1 diabetes mellitus were randomised to receive either inhaled insulin or subcutaneous (SC) insulin twice or three times daily prior to a meal for 3 months. All patients also received bedtime SC injection of insulin zinc suspension. Mean overall improvement in patient satisfaction was significantly greater in patients receiving inhaled insulin (35% vs 12%). Convenience and ease of use of inhaled insulin accounted for 66% of the common variance in patients' satisfaction, with a mean percentage improvement of 28% for inhaled insulin versus SC insulin.^[12,13]

A multicentre, randomised, drug-regimen comparison, route-of-administration comparison, phase III study compared the efficacy and tolerability of inhaled and subcutaneously injected insulin in combination with insulin suspension isophane in 328 patients with type 1 diabetes mellitus. Inhaled insulin + insulin suspension isophane and subcutaneously injected insulin + insulin suspension isophane were associated with similar overall glycaemic control. However, inhaled insulin + insulin suspension isophane was associated with improvements in fasting plasma glucose levels, whereas subcutaneously injected insulin + insulin suspension isophane was not.^[14]

Preprandial inhaled insulin in conjunction with long-acting insulin zinc suspension for 12 weeks improved glycaemic control in 26 patients with type 2 diabetes. No significant change in bodyweight from baseline was observed after the treatment.^[15]

In a randomised, 3-month trial in 69 (56 evaluable) patients with type 2 diabetes mellitus, pulmonary add-on therapy with inhaled insulin to the usual oral agent (sulfonylurea and/or metformin) significantly reduced the glycosylated haemoglobin (HbA_{1c}) level by 2.3% from baseline. Pulmonary insulin was well tolerated, and 97% of patients opted

to continue on pulmonary insulin after completion of the trial.^[8,16]

Similar results were obtained in a multicentre, randomised study in 22 patients with type 2 diabetes mellitus who failed treatment with oral antihyperglycaemics. Pulmonary, add-on therapy with insulin inhalation for 12 weeks significantly reduced the HbA_{1c} level at 12 weeks compared with oral antihyperglycaemics alone.^[17]

In a phase III study, 82.7% of patients receiving inhaled insulin (one to two inhalations of 1 or 3mg) achieved an 8% reduction in HbA_{1c} compared with patients receiving rosiglitazone (4mg twice daily) over 3 months. Forty-four percent of patients receiving insulin inhalation reached levels of HbA_{1c} ≤7% compared with 17.9% of rosiglitazone patients. Absolute HbA_{1c} decrease was significantly greater in the inhaled insulin treated-group than rosiglitazone-treated group (−2.4% vs −1.4%). These metabolic improvements were accompanied by changes in bodyweight (1.9kg for the inhaled insulin-treated group compared with 0.8kg for the rosiglitazone-treated group).^[18]

A phase II extension study in patients with type 1 diabetes previously receiving insulin injections and type 2 diabetes unresponsive to oral agents (total n = 83) determined whether a completed 30-month treatment with inhalable insulin provide a long-term glycaemic control. These data showed that administration of inhalable insulin secured stable reduced HbA_{1c} levels for up to 30 months of therapy (HbA_{1c} levels of 8.7%, 8.1%, 8.0% and 8.0% at baseline, 12, 18 and 24 months, respectively).^[19]

In an open-label NIH study in 140 patients with type 1 and type 2 diabetes, who completed any of the three, 3-month, randomised, controlled clinical trials, preliminary results indicated the efficacy and safety of a 24-month therapy with inhaled insulin formulation.^[20]

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