

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

EXUBERA 1 mg inhalation powder pre-dispensed.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each unit dose blister contains 1 mg insulin human.

The exposure of human insulin following administration of three 1 mg blisters is significantly greater than that following a single 3 mg blister. Therefore, the 3 mg blister is not interchangeable with three 1 mg blisters (see sections 4.2, 4.4 and 5.2).

Produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed.

White powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EXUBERA is indicated for the treatment of adult patients with type 2 diabetes mellitus not adequately controlled with oral antidiabetic agents and requiring insulin therapy.

EXUBERA is also indicated for the treatment of adult patients with type 1 diabetes mellitus, in addition to long or intermediate acting subcutaneous insulin, for whom the potential benefits of adding inhaled insulin outweigh the potential safety concerns (see section 4.4).

4.2 Posology and method of administration

EXUBERA (inhaled human insulin) is a fast-acting human insulin for use in type 1 or type 2 diabetes. Inhaled human insulin may be used alone or in combination with oral antidiabetic agents and/or long or intermediate acting subcutaneously administered insulins to optimise glycaemic control.

EXUBERA is available in 1 mg and 3 mg unit dose blisters which are for administration via the lungs by oral inhalation only with the insulin inhaler.

Consecutive inhalation of three 1 mg unit dose blisters causes a significantly higher insulin exposure than inhalation of one 3 mg unit dose blister. Therefore three 1 mg unit dose blisters should not be substituted for one 3 mg unit dose blister (see sections 2, 4.4 and 5.2).

Inhaled human insulin has a faster onset of activity than subcutaneously administered fast-acting human insulin. Due to the rapid onset of activity, inhaled human insulin should be given within 10 minutes before the start of a meal.

The starting and subsequent dosage (dose and timings) should be determined individually by the physician and adjusted according to the patient's individual response and requirements (e.g. diet, physical activity and life-style).

Daily doses and timing of administration

There are no fixed rules for insulin dosage. However, a recommended starting daily dose is based on the following formula:

Body weight (kg) X 0.15 mg/kg = Total Daily Dose (mg). The total daily dose should be divided into three pre-meal doses.

Approximate guidelines for initial, pre-meal EXUBERA doses, based on patient body weight, are indicated in Table 1:

Patient Weight	Initial Dose per Meal	Approximate IU Dose	Number of 1 mg Blisters per Dose	Number of 3 mg Blisters per Dose
30 to 39.9 kg	1 mg per meal	3 IU	1	-
40 to 59.9 kg	2 mg per meal	6 IU	2	-
60 to 79.9 kg	3 mg per meal	8 IU	-	1
80 to 99.9 kg	4 mg per meal	11 IU	1	1
100 to 119.9 kg	5 mg per meal	14 IU	2	1
120 to 139.9 kg	6 mg per meal	16 IU	-	2

Table 1: Approximate Guidelines for Initial, Pre-Meal EXUBERA Dose (based on patient body weight).

A 1 mg blister of inhaled insulin is approximately equivalent to 3 IU of subcutaneously injected fast-acting human insulin. A 3 mg blister of inhaled insulin is approximately equivalent to 8 IU of subcutaneously injected fast-acting human insulin. Table 1 above presents the approximate IU dose of fast-acting human insulin for initial, pre-meal EXUBERA doses in mg.

Therefore, EXUBERA should be used with caution in patients of low body weight. The use of EXUBERA in patients requiring dose titrations of less than 1 mg is not recommended (see section 4.4).

Dose adjustment may be required based on the meal size and nutrient composition, time of day (higher insulin requirements in the morning), pre-meal blood glucose concentration, recent or anticipated exercise.

During intercurrent respiratory illness (e.g. bronchitis, upper respiratory tract infections) close monitoring of blood glucose concentrations and dose adjustment may be required on an individual basis (see section 4.4).

For further details on how to use the insulin inhaler refer to the instructions for use (IFU).

Hepatic and renal impairment

In patients with hepatic or renal impairment insulin requirements may be diminished.

Children and adolescents

Long-term safety of inhaled human insulin has not been established in paediatric patients with diabetes and its use is therefore not recommended in patients under 18 years of age (see section 5.2).

Elderly

Experience with inhaled insulin in patients ≥ 75 years of age is limited.

Congestive heart failure

Experience with inhaled insulin in patients with congestive heart failure is very limited and its use is therefore not recommended in such patients where lung function is significantly compromised.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypoglycaemia.

Patients must not smoke during therapy with EXUBERA and must have stopped smoking at least 6 months prior to starting EXUBERA therapy. If a patient starts or resumes smoking, EXUBERA must be discontinued immediately due to the increased risk of hypoglycaemia and an alternative treatment utilised (see section 5.2).

Poorly controlled, unstable, or severe asthma.

Severe (GOLD stage III or IV) Chronic obstructive pulmonary disease (COPD).

4.4 Special warnings and precautions for use

Patients started on EXUBERA must receive comprehensive instructions in the use of the inhaler (see IFU). Patients should inhale the insulin powder from the mouthpiece in one slow and steady inhalation. Patients should then hold their breath for 5 seconds and exhale normally. A consistent and standard inhalation technique should be employed to ensure both optimal and consistent drug delivery.

Patients should avoid exposing the product to high moisture or relative humidity conditions e.g. a steamy bathroom, when taking their dose.

If the insulin inhaler is inadvertently exposed to extremely moist conditions during use this usually leads to a subsequent decreased insulin dose delivered from the inhaler. In this case, the Insulin Release Unit (IRU) must be changed prior to the next inhalation (see section 6.6).

Dosing

Transferring a patient to another type or brand of insulin should be done under strict medical supervision as this may result in a change in dosage.

Consecutive inhalation of three 1 mg unit dose blisters causes a significantly higher insulin exposure than inhalation of one 3 mg unit dose blister. Therefore three 1 mg unit dose blisters should not be substituted for one 3 mg unit dose blister (see sections 2, 4.2 and 5.2).

If the 3 mg blister is temporarily unavailable, two 1 mg blisters should be substituted and blood glucose monitored closely.

A 1 mg blister of inhaled insulin is approximately equivalent to 3 IU of subcutaneously injected fast-acting human insulin. Therefore, EXUBERA should be used with caution in patients of low body weight. The use of EXUBERA in patients requiring dose titrations of less than 1 mg is not recommended (see section 4.2).

Hypoglycaemia

Hypoglycaemia, in general the most frequent undesirable effect of insulin therapy including EXUBERA and many oral antidiabetic agents, may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life threatening.

Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Hypoglycaemia can generally be corrected by immediate carbohydrate intake. In order to be able to take action immediately, patients should carry glucose with them at all times.

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly.

Usual warning symptoms may disappear in patients with longstanding diabetes.

A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin to human insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.

Before travelling between different time zones, the patient should be advised to consult the doctor, since this may mean that the patient has to take insulin and meals at different times.

Inadequate dosage or discontinuation of treatment especially in insulin-dependant diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

When used with other antidiabetic agents, the dose of each agent should be carefully adjusted to determine the optimal dose required to achieve the desired pharmacological effect.

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or stress.

Pulmonary Safety

Underlying respiratory disorders

EXUBERA should not be used in patients with lung disease such as asthma and COPD, as there are insufficient data to support the safe use in these patients.

The concomitant use of bronchodilators such as salbutamol may increase the absorption of EXUBERA and may therefore increase the risk of hypoglycaemia when used to relieve acute respiratory symptoms (see section 4.5).

Respiratory

Bronchospasm may rarely occur. Any patients experiencing such a reaction should discontinue EXUBERA and seek medical evaluation immediately. Re-administration of EXUBERA requires a careful risk evaluation, and may only be done under close medical monitoring with appropriate clinical facilities.

Decline in pulmonary function

In clinical trials small but consistent treatment group differences in decline of pulmonary function (particularly Forced Expiratory Volume in one second (FEV₁)) favouring comparator treated subjects have been observed. In clinical studies of up to two years duration, there was no accelerated decline beyond 3-6 months. These small treatment group differences resolved within 6 weeks upon discontinuation after 2 years of treatment (see sections 4.8 and 5.1).

All patients initiated on EXUBERA should have a baseline lung function examination (e.g. spirometry to measure FEV₁). The efficacy and safety of inhaled human insulin in patients with baseline FEV₁ < 70% predicted have not been established and the use of inhaled human insulin in this population is not recommended. A follow-up lung function measurement is recommended after the first 6 months of therapy. If at 6 months a decline of < 15% FEV₁ is observed, spirometry should be repeated at one year and then annually. If at 6 months a decline of 15-20% or > 500ml from baseline lung function is observed, spirometry should be repeated after 3 months.

In patients with a confirmed (i.e. at least two consecutive tests, 3 to 4 weeks apart) FEV₁ decline of > 20% from baseline, EXUBERA therapy should be discontinued and the patient monitored as clinically indicated. There is no experience with the reinstatement of EXUBERA therapy in patients whose lung function recovers.

Patients developing dyspnoea while treated with EXUBERA should be examined for pulmonary or cardiac causes. Where pulmonary oedema is present, or there is a clinically relevant reduction in pulmonary function, EXUBERA should be discontinued and the patient switched to injectable insulin.

Intercurrent Respiratory Illness

EXUBERA has been administered to patients with intercurrent respiratory illness (e.g. bronchitis, upper respiratory tract infections) during clinical trials. Increased risk of hypoglycaemia or poor glycaemic control has not been observed in these trials. During intercurrent respiratory illness close monitoring of blood glucose concentrations and dose adjustment may be required on an individual basis (see section 4.2). There is no experience with EXUBERA in patients with pneumonia.

Former Smokers

In clinical trials of Exubera, there have been 6 newly diagnosed cases of primary lung malignancies among Exubera-treated patients, and 1 newly diagnosed case among comparator treated patients. There has also been 1 post-marketing report of a primary lung malignancy in an Exubera-treated patient. In controlled clinical trials of Exubera, the incidence of new primary lung cancer per 100 patient-years of study drug exposure was 0.130 (5 cases over 3800 patient-years) for Exubera-treated patients and 0.03 (1 case over 3900 patient-years) for comparator-treated patients. There were too few cases to determine whether the emergence of these events is related to Exubera. All patients who were diagnosed with lung cancer had a prior history of cigarette smoking.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of insulin.

Substances that may enhance the blood-glucose lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, monoamino oxidase (MAO) inhibitors, non-selective beta-blocking agents, salicylates and sulphonamide antibiotics.

Administration of salbutamol prior to EXUBERA may result in increased insulin absorption (see section 5.2).

Administration of fluticasone prior to EXUBERA does not appear to affect insulin absorption (see section 5.2).

Active smoking greatly enhances whereas passive exposure to tobacco smoke in non-smokers decreases the rate and extent of absorption of EXUBERA (see sections 4.3 and 5.2).

Substances that may reduce the blood-glucose lowering effect include corticosteroids, danazol, oral contraceptives, thyroid hormones, growth hormone, sympathomimetic agents and thiazides. Octreotide/lanreotide may both decrease or increase insulin requirements.

Beta-blocking agents may mask the symptoms of hypoglycaemia. Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

Administration of EXUBERA 10 minutes prior to administration of salbutamol did not affect the bronchodilatory response to salbutamol in non-diabetic subjects with mild-moderate asthma.

Other drugs that may alter pulmonary absorption or lung permeability have not been studied. Close monitoring of blood glucose concentrations and dose titration as appropriate are recommended when inhaled human insulin is used in these patients. Caution should be exercised with concomitant use of EXUBERA and such drugs.

4.6 Pregnancy and lactation

There is no clinical experience with EXUBERA use in pregnancy. Inhaled insulin frequently induces insulin antibodies, the risk of which to the foetus is not known. Therefore, EXUBERA should not be used during pregnancy. When an EXUBERA treated patient becomes pregnant appropriate subcutaneous insulin should be substituted for inhaled insulin.

Breast-feeding women may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

As with other insulins, the patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

4.8 Undesirable effects

The safety of EXUBERA alone, or in combination with subcutaneous insulin or oral agents has been evaluated in clinical studies of more than 2700 patients with type 1 or type 2 diabetes, including more than 1975 adults exposed for greater than 6 months and more than 745 adults for greater than 2 years.

The table below contains adverse reactions seen in controlled clinical studies including more than 1970 patients exposed to EXUBERA.

Body System	Very Common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1000, < 1/100)
Infections and Infestations			Pharyngitis
Metabolism and Nutritional Disorders	Hypoglycaemia		
Respiratory, Thoracic and Mediastinal Disorders	Cough	Dyspnoea Productive Cough Throat Irritation Dry Throat	Epistaxis Bronchospasm Wheezing Dysphonia Pharyngolaryngeal Pain Tonsillar Disorder
Gastrointestinal Disorders			Dry Mouth
General Disorders and Administration Site Conditions			Chest Pain

Note: In the overall clinical program, including uncontrolled extension studies, there were two reports of pleural effusion in which a treatment-related effect could not be excluded.

Hypoglycaemia

As with other insulins, hypoglycaemia was the most frequently observed undesirable effect in patients treated with EXUBERA.

Cough

The cough tended to occur within seconds to minutes after insulin inhalation and was predominantly mild in severity. This cough decreased over time. One percent of patients discontinued EXUBERA treatment due to cough.

Dyspnoea

The majority (> 95%) of dyspnoea was reported as mild to moderate. In EXUBERA treated subjects 0.4% discontinued treatment due to dyspnoea.

Chest pain

A range of different chest symptoms were reported as treatment-related adverse reactions and were referred to as non-specific chest pain. The majority (> 95%) of these events was reported as mild to moderate. One subject in the EXUBERA and one in the comparator group discontinued treatment due to chest pain. Importantly, the incidence of all-causality adverse events related to coronary artery disease, such as angina pectoris or myocardial infarction was not increased with the use of EXUBERA.

Other reactions

FEV₁ decline

Small treatment group differences in decline of FEV₁ were observed in the EXUBERA group relative to comparator therapy. In clinical studies of up to two years duration, there was no accelerated decline beyond 3-6 months. Discontinuation of EXUBERA therapy after 2 years resulted in resolution of treatment group differences within 6 weeks (see sections 4.4 and 5.1).

A decline from baseline in FEV₁ of $\geq 15\%$ occurred in 1.3% of EXUBERA-treated type 1 subjects and in 5.0% of EXUBERA-treated type 2 subjects.

Insulin antibodies

Insulin antibodies may develop during treatment with all insulins including EXUBERA. In clinical trials, insulin antibodies developed more frequently and mean levels of insulin antibodies were higher in patients who switched their subcutaneous human insulin to EXUBERA compared to subjects who remained on subcutaneous human insulin. Insulin antibody levels were higher in patients with type 1 diabetes compared to type 2 diabetes and plateaued within 6-12 months of exposure in both groups. No clinical significance of these antibodies has been identified.

Hypersensitivity reactions

As with other insulins, generalised allergic reactions may occur very rarely. Such reactions to insulin or the excipients may, for example, be associated with generalised skin reactions, angio-oedema, bronchospasm, hypotension and shock and may be life-threatening (see section 4.4 Respiratory).

Oedema and refraction abnormalities of the eye

Insulin therapy may cause sodium retention and oedema. Refraction abnormalities of the eye may occur upon initiation of insulin therapy. These effects are usually transitory.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin relative to food intake, energy expenditure or both.

Mild episodes of hypoglycaemia usually can be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes, with coma, seizure, or neurological impairment may be treated with intramuscular/subcutaneous glucagon (0.5 to 1 mg) or concentrated intravenous glucose. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal products used in diabetes, ATC code: A10AF01

Mode of Action

Human insulin lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects, increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis, increases lipogenesis in the liver and adipose tissue and inhibits lipolysis. It also promotes the uptake of amino acids into cells and promotes protein synthesis and enhances the uptake of potassium into cells.

Inhaled human insulin, like fast-acting insulin analogues, has a more rapid onset of glucose lowering activity compared to subcutaneously administered soluble human insulin. Inhaled human insulin has a duration of glucose lowering activity comparable to subcutaneously administered fast-acting human insulin and longer than fast-acting insulin analogues (see Figure 1).

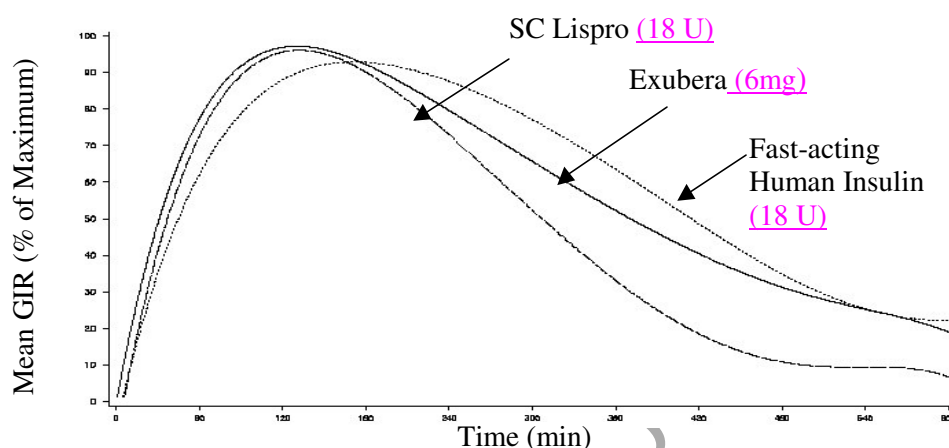


Figure 1. Mean Glucose Infusion Rate (GIR) Normalised to GIR_{max} for Each Subject Treatment Versus Time in Healthy Volunteers.

When human insulin is inhaled, the onset of glucose lowering activity is within 10-20 minutes, the maximum effect is exerted approximately 2 hours after inhalation. The duration of action lasts approximately 6 hours.

In subjects with type 1 or type 2 diabetes, inhaled human insulin has a faster onset of glucose lowering effect in the early hours after dosing when compared with subcutaneously administered fast-acting human insulin.

The intra-subject variability of glucose lowering activity of inhaled human insulin was generally comparable to that of subcutaneously administered fast-acting human insulin in subjects with type 1 and 2 diabetes mellitus.

Use of inhaled human insulin is associated with an increase in frequency, and levels of insulin antibodies. In a prospective exploratory 6 month study in subjects with type 1 diabetes, alterations in the glucose pharmacodynamics with inhaled human insulin were not observed.

Information on Clinical Trials

Controlled clinical trials in type 1 or type 2 diabetes have shown that EXUBERA achieves and maintains effective glycaemic control comparable to subcutaneously administered fast-acting human insulin.

Type 1 Diabetes

In clinical trials in type 1 diabetes, patients using a regimen of EXUBERA in combination with long- or intermediate-acting insulin had similar reductions in HbA1c compared with patients taking subcutaneous insulin alone. The percentage of patients who achieved a goal of HbA1c < 7.0% was comparable between the treatment groups.

Fasting plasma glucose levels were significantly lower in patients treated with regimens including EXUBERA compared with those treated with subcutaneously administered fast-acting human insulin only regimens.

Type 2 Diabetes

Patients in a clinical trial for type 2 diabetes, who used a regimen of EXUBERA in combination with long- or intermediate-acting insulin, had similar changes in HbA1c compared with patients treated with subcutaneous insulin alone.

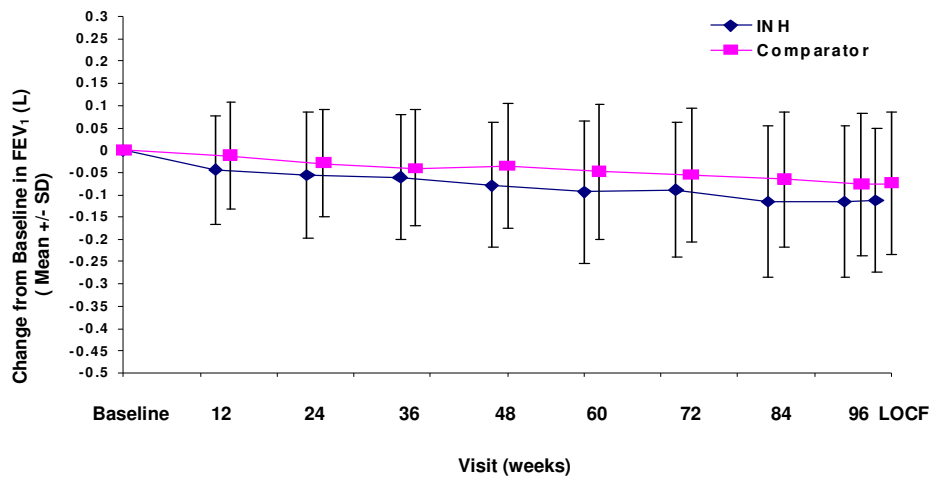
Fasting plasma glucose levels were significantly lower in patients treated with EXUBERA regimens compared with those treated with subcutaneous insulin.

In clinical trials involving patients with type 2 diabetes not sufficiently controlled with oral agents alone, patients using a regimen of EXUBERA alone or in combination with oral agents, had greater improvements in HbA1c compared with patients treated with oral agents alone. In most of these studies the percentages of patients achieving HbA1c < 7.0% were higher for patients using a regimen including EXUBERA compared to patients on oral agents alone. Fasting plasma glucose was similar to or lower in patients using a regimen including EXUBERA compared to patients treated with oral agents alone. In patients with type 2 diabetes sufficiently controlled with oral agents the glycaemic control was not further improved by inhaled insulin.

FEV₁ decline

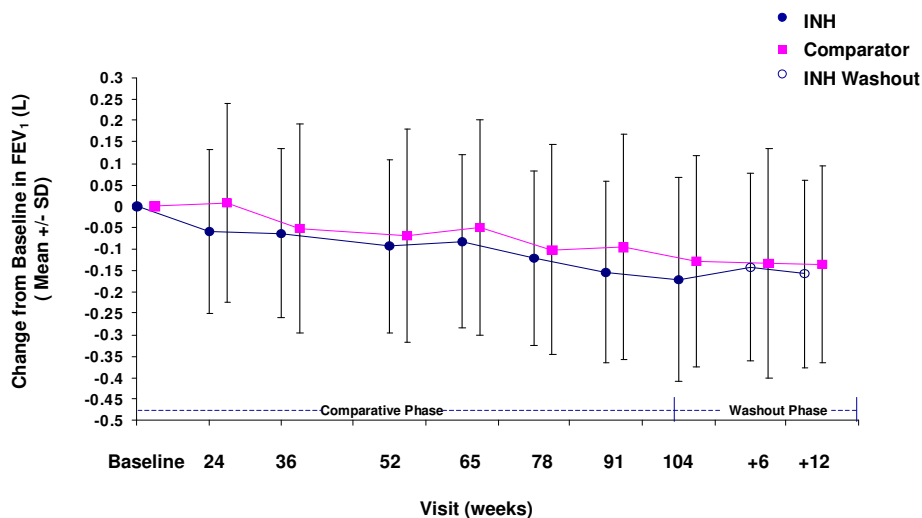
Randomised, open label parallel group studies were conducted to examine FEV₁ changes following initiation of EXUBERA therapy in type 1 and 2 subjects. Both EXUBERA and comparator treated subjects experienced declines in lung function over time during these trials (Figures 2 and 3). Small treatment group differences (favouring comparator) in change from baseline of 0.034L in type 1 and 0.039L in type 2 occurred after 2 years of therapy.

A decline from baseline in FEV₁ of $\geq 15\%$ occurred in 1.3% of EXUBERA-treated and 1.0% of comparator-treated type 1 subjects and in 5.0% of EXUBERA-treated and 3.4% of comparator-treated type 2 subjects.



N=Number of Subjects at Baseline, week 12, week 24, week 36, week 48, week 60, week 72, week 84, week 96, LOCF.
 INH N= 236, 231, 233, 233, 235, 235, 226, 217, 208, 236. Comparator N= 253, 238, 252, 248, 252, 249, 230, 224, 216, 253.

Figure 2. Observed Change from Baseline in FEV₁ (L) in patients with type 1 diabetes mellitus.



N=Number of Subjects at Baseline, week 52, week 104, week +6, week +12.
 INH and INH washout N=158, 155, 143, 139, 123. Comparator N=145, 143, 125, 129, 120.

Figure 3. Observed Change from Baseline in FEV₁ (L) in patients with type 2 diabetes mellitus.

In Phase 2/3 trials, 9 out of 2498 subjects treated with EXUBERA were discontinued from trials due to a decline in pulmonary function whose end of study FEV₁ showed a decline of $\geq 15\%$ from baseline. These subjects experienced an average decrease in FEV₁ of 21% (range 16%-33%) from baseline and were treated with EXUBERA for an average of 23 months. 6 of these discontinued subjects underwent follow-up pulmonary function testing. Of these patients, 5 exhibited a significant improvement in FEV₁ following discontinuation of therapy and one subject did not decrease further from the end of study value. No further information is available for the remaining 3 subjects who discontinued.

FEV₁ reversibility

In type 1 subjects, resolution of small treatment group differences (0.010L favouring comparator) occurred within 2 weeks of EXUBERA cessation following 12 weeks of therapy. In type 2 subjects, resolution of small treatment group differences (0.039L favouring comparator) occurred within 6 weeks of EXUBERA cessation following 2 years of therapy (Figure 3). In a smaller group (n=36) of mixed type 1 and 2 subjects treated with EXUBERA for > 36 months, cessation of therapy resulted in a mean FEV₁ increase of 0.036L over the subsequent 6 months.

5.2 Pharmacokinetic properties

Absorption

Inhaled human insulin is delivered by the pulmonary route. Inhaled human insulin is absorbed as rapidly as fast-acting insulin analogues and more rapidly than subcutaneously administered fast-acting human insulin in healthy subjects and in subjects with type 1 or type 2 diabetes (see Figure 4).

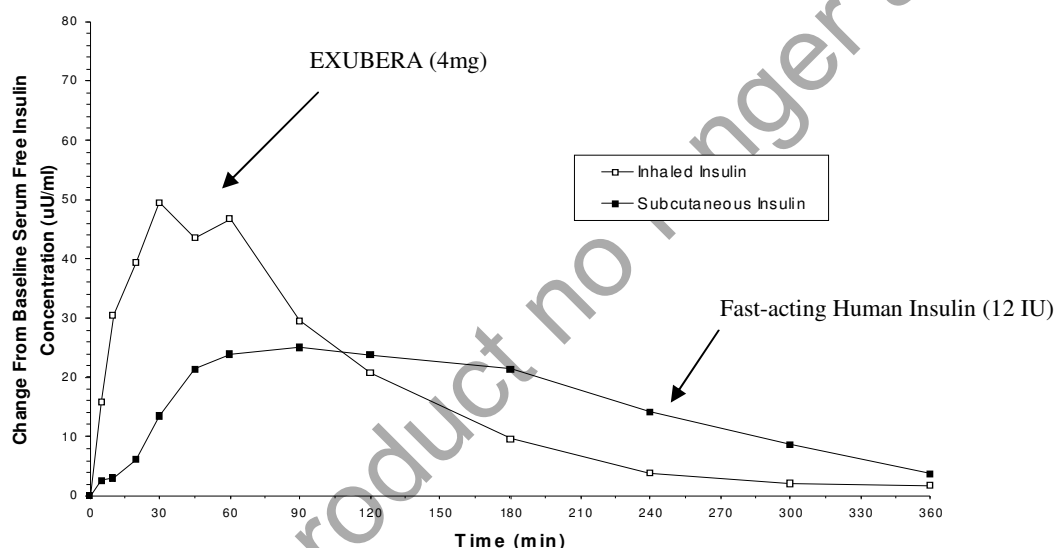


Figure 4: Mean changes in serum free insulin concentrations ($\mu\text{U}/\text{mL}$) after inhalation of 4mg of human insulin or subcutaneous injection of 12 IU fast-acting human insulin in obese subjects with type 2 diabetes.

The time to peak insulin concentration (T_{max}) is generally half of that for subcutaneously administered fast-acting human insulin. Peak insulin concentration is reached generally by 45 minutes for inhaled human insulin. Intrasubject variability of time to peak insulin concentrations was less for inhaled human insulin than for subcutaneous fast-acting human insulin in subjects with type 1 or 2 diabetes.

In subjects with type 1 diabetes mellitus, inhaled human insulin had a comparable intrasubject variability of AUC to subcutaneously administered fast-acting human insulin. For C_{max} , the intrasubject variability of inhaled insulin is greater than that of subcutaneously administered fast-acting human insulin. In obese subjects with type 2 diabetes, intrasubject variability was comparable to or less than that of subcutaneously administered fast-acting human insulin for C_{max} and AUC.

The relative bioavailability of EXUBERA compared to subcutaneous fast-acting human insulin is approximately 10%. Unlike subcutaneous insulin preparations, the bioavailability of EXUBERA is not influenced by Body Mass Index.

In a study in healthy subjects, systemic exposure (AUC and C_{max}) of inhaled human insulin

increased in an approximately dose proportional fashion from 1 mg to 6 mg when a maximum of two blisters from either strength or their combination was administered. In a study where the dosage form of three 1 mg blisters was compared with one 3 mg blister, C_{max} and AUC of inhaling three 1 mg blisters were approximately 30% and 40% greater, respectively, than that of inhaling from one 3 mg blister, indicating that three 1 mg blisters are not interchangeable with one 3 mg blister (see sections 2, 4.2 and 4.4).

An approximately 40% higher bioavailability of three 1 mg unit dose blisters compared to one 3 mg unit dose blister was observed in healthy subjects. An explanation for the differences in bioavailability appears to be the different energy to mass ratio between the 1 and 3 mg unit blisters since with less powder in the blister the inhaler is more efficient in breaking up or de-agglomerating the powder leading to a larger proportion of smaller aerodynamic particle sizes for the 1 mg blister (see sections 2 and 4.4).

Distribution

Following oral inhalation of a single dose of human insulin approximately 30% of the total blister content remains in the blister or device, 20% is deposited in the oropharynx, 10% in the conducting airways and 40% reaches the deep lung.

Animal studies did not show that inhaled human insulin accumulates in the lung.

Special Populations

Smoking

Smoking greatly increases the rate and extent of absorption of inhaled human insulin (C_{max} about 3 to 5 times and AUC about 2 to 3 times higher) and therefore could increase the risk of hypoglycaemia (see sections 4.3 and 4.5).

When EXUBERA was administered to healthy volunteers following 2-hours of passive exposure to cigarette smoke in a controlled experimental setting, insulin AUC and C_{max} were reduced by approximately 17 and 30%, respectively (see section 4.5).

Respiratory Diseases (Underlying Lung Disease)

In non-diabetic subjects with mild to moderate asthma, AUC and C_{max} for inhaled human insulin in the absence of treatment with a bronchodilator was slightly less than in subjects without asthma.

In non-diabetic subjects with COPD, the absorption of inhaled human insulin appeared greater compared with that in subjects without COPD (see section 4.4).

Administration of salbutamol 30 minutes prior to EXUBERA in non-diabetic subjects with mild-moderate asthma resulted in an increase in insulin AUC and C_{max} of between 25 and 51% compared to when EXUBERA was administered alone (see sections 4.2 and 4.5).

Administration of fluticasone 30 minutes prior to EXUBERA did not affect the pharmacokinetics of EXUBERA in non-diabetic subjects with mild-moderate asthma (see section 4.5).

Renal impairment

The effect of renal impairment on the absorption of inhaled human insulin has not been studied (see section 4.2).

Hepatic impairment

The effect of hepatic impairment on the absorption of inhaled human insulin has not been studied (see section 4.2).

Gender

In subjects with diabetes and in subjects without diabetes, no apparent differences in absorption of inhaled human insulin were observed between men and women.

Children and adolescents

In children (6-11 years) and adolescents (12-17 years) with type 1 diabetes, inhaled human insulin was absorbed more rapidly than fast-acting human insulin. Bioavailability of inhaled human insulin relative to subcutaneously administered fast-acting human insulin was comparable to that of adult subjects with type 1 diabetes (see section 4.2).

Elderly

In older subjects with type 2 diabetes, inhaled human insulin was absorbed more rapidly than subcutaneously administered fast-acting human insulin. Bioavailability of inhaled human insulin relative to subcutaneously administered fast-acting human insulin was comparable to those in younger adult subjects with type 2 diabetes.

5.3 Preclinical safety data

Inhalation toxicity studies in rats and monkeys for up to 6 months gave no evidence for a special risk to the respiratory tract due to insulin inhalation powder.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Glycine
Sodium Citrate (as dihydrate)
Sodium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening the foil overwrap: 3 months.

6.4 Special precautions for storage

Store below 30°C. Store in the original package in order to protect from moisture.

After opening the foil overwrap: Store below 25°C.

Do not refrigerate or freeze the unit dose blisters.

The inhaler and its components should be stored and used in a dry place.

Do not refrigerate or freeze the insulin inhaler.

6.5 Nature and contents of container

One blister card contains 6 perforated unit dose blisters (PVC/Aluminium). Five blister cards are in a clear plastic (PET) thermoformed tray with a desiccant and covered with a clear plastic (PET) lid. The tray is sealed in a foil laminate pouch with a desiccant.

Packaging sizes supplied:

- Cardboard box containing 30 x 1 PVC/Aluminium perforated unit dose blisters (1 pouch)
- Cardboard box containing 60 x 1 PVC/Aluminium perforated unit dose blisters (2 pouches)
- Cardboard box containing 90 x 1 PVC/Aluminium perforated unit dose blisters (3 pouches)
- Cardboard box containing 180 x 1 PVC/Aluminium perforated unit dose blisters (6 pouches)
- Cardboard box containing 270 x 1 PVC/Aluminium perforated unit dose blisters (9 pouches)
- Cardboard box containing 60 x 1 PVC/Aluminium perforated unit dose blisters (2 pouches) and 2 spare Insulin Release Units (IRU)
- Cardboard box containing 270 x 1 PVC/Aluminium perforated unit dose blisters (9 pouches) and 6 spare Insulin Release Units (IRU)
- A kit containing 90 x 1 PVC/Aluminium perforated unit dose blisters (3 pouches), 1 insulin inhaler, 1 spare chamber and 6 spare Insulin Release Units (IRU)

Additional insulin inhaler, insulin release units and chamber packages are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

EXUBERA unit dose blisters must only be used with the insulin inhaler.

The insulin inhaler should be replaced annually.

The Insulin Release Unit (IRU) should be replaced once every 2 weeks.

If the insulin inhaler is inadvertently exposed to extremely moist conditions during use this usually leads to a subsequent decreased insulin dose delivered from the inhaler. In this case, the Insulin Release Unit (IRU) must be changed prior to the next inhalation (see section 4.4).

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road, Sandwich,
Kent, CT13, 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/327/001
EU/1/05/327/002
EU/1/05/327/003
EU/1/05/327/004
EU/1/05/327/005
EU/1/05/327/006
EU/1/05/327/007
EU/1/05/327/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/01/2006

10. DATE OF REVISION OF THE TEXT

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

EXUBERA 3 mg inhalation powder pre-dispensed.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each unit dose blister contains 3 mg insulin human.

The exposure of human insulin following administration of three 1 mg blisters is significantly greater than that following a single 3 mg blister. Therefore, the 3 mg blister is not interchangeable with three 1 mg blisters (see sections 4.2, 4.4 and 5.2).

Produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed.

White powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EXUBERA is indicated for the treatment of adult patients with type 2 diabetes mellitus not adequately controlled with oral antidiabetic agents and requiring insulin therapy.

EXUBERA is also indicated for the treatment of adult patients with type 1 diabetes mellitus, in addition to long or intermediate acting subcutaneous insulin, for whom the potential benefits of adding inhaled insulin outweigh the potential safety concerns (see section 4.4).

4.2 Posology and method of administration

EXUBERA (inhaled human insulin) is a fast-acting human insulin for use in type 1 or type 2 diabetes. Inhaled human insulin may be used alone or in combination with oral antidiabetic agents and/or long or intermediate acting subcutaneously administered insulins to optimise glycaemic control.

EXUBERA is available in 1 mg and 3 mg unit dose blisters which are for administration via the lungs by oral inhalation only with the insulin inhaler.

Consecutive inhalation of three 1 mg unit dose blisters causes a significantly higher insulin exposure than inhalation of one 3 mg unit dose blister. Therefore three 1 mg unit dose blisters should not be substituted for one 3 mg unit dose blister (see sections 2, 4.4 and 5.2).

Inhaled human insulin has a faster onset of activity than subcutaneously administered fast-acting human insulin. Due to the rapid onset of activity, inhaled human insulin should be given within 10 minutes before the start of a meal.

The starting and subsequent dosage (dose and timings) should be determined individually by the physician and adjusted according to the patient's individual response and requirements (e.g. diet, physical activity and life-style).

Daily doses and timing of administration

There are no fixed rules for insulin dosage. However, a recommended starting daily dose is based on the following formula:

Body weight (kg) X 0.15 mg/kg = Total Daily Dose (mg). The total daily dose should be divided into three pre-meal doses.

Approximate guidelines for initial, pre-meal EXUBERA doses, based on patient body weight, are indicated in Table 1:

Patient Weight	Initial Dose per Meal	Approximate IU Dose	Number of 1 mg Blisters per Dose	Number of 3 mg Blisters per Dose
30 to 39.9 kg	1 mg per meal	3 IU	1	-
40 to 59.9 kg	2 mg per meal	6 IU	2	-
60 to 79.9 kg	3 mg per meal	8 IU	-	1
80 to 99.9 kg	4 mg per meal	11 IU	1	1
100 to 119.9 kg	5 mg per meal	14 IU	2	1
120 to 139.9 kg	6 mg per meal	16 IU	-	2

Table 1: Approximate Guidelines for Initial, Pre-Meal EXUBERA Dose (based on patient body weight).

A 1 mg blister of inhaled insulin is approximately equivalent to 3 IU of subcutaneously injected fast-acting human insulin. A 3 mg blister of inhaled insulin is approximately equivalent to 8 IU of subcutaneously injected fast-acting human insulin. Table 1 above presents the approximate IU dose of fast-acting human insulin for initial, pre-meal EXUBERA doses in mg.

Therefore, EXUBERA should be used with caution in patients of low body weight. The use of EXUBERA in patients requiring dose titrations of less than 1 mg is not recommended (see section 4.4).

Dose adjustment may be required based on the meal size and nutrient composition, time of day (higher insulin requirements in the morning), pre-meal blood glucose concentration, recent or anticipated exercise.

During intercurrent respiratory illness (e.g. bronchitis, upper respiratory tract infections) close monitoring of blood glucose concentrations and dose adjustment may be required on an individual basis (see section 4.4).

For further details on how to use the insulin inhaler refer to the instructions for use (IFU).

Hepatic and renal impairment

In patients with hepatic or renal impairment insulin requirements may be diminished.

Children and adolescents

Long-term safety of inhaled human insulin has not been established in paediatric patients with diabetes and its use is therefore not recommended in patients under 18 years of age (see section 5.2).

Elderly

Experience with inhaled insulin in patients \geq 75 years of age is limited.

Congestive heart failure

Experience with inhaled insulin in patients with congestive heart failure is very limited and its use is therefore not recommended in such patients where lung function is significantly compromised.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Hypoglycaemia.

Patients must not smoke during therapy with EXUBERA and must have stopped smoking at least 6 months prior to starting EXUBERA therapy. If a patient starts or resumes smoking, EXUBERA must be discontinued immediately due to the increased risk of hypoglycaemia and an alternative treatment utilised (see section 5.2).

Poorly controlled, unstable, or severe asthma.

Severe (GOLD stage III or IV) Chronic obstructive pulmonary disease (COPD).

4.4 Special warnings and precautions for use

Patients started on EXUBERA must receive comprehensive instructions in the use of the inhaler (see IFU). Patients should inhale the insulin powder from the mouthpiece in one slow and steady inhalation. Patients should then hold their breath for 5 seconds and exhale normally. A consistent and standard inhalation technique should be employed to ensure both optimal and consistent drug delivery.

Patients should avoid exposing the product to high moisture or relative humidity conditions e.g. a steamy bathroom, when taking their dose.

If the insulin inhaler is inadvertently exposed to extremely moist conditions during use this usually leads to a subsequent decreased the insulin dose delivered from the inhaler. In this case, the Insulin Release Unit (IRU) must be changed prior to the next inhalation (see section 6.6).

Dosing

Transferring a patient to another type or brand of insulin should be done under strict medical supervision as this may result in a change in dosage.

Consecutive inhalation of three 1 mg unit dose blisters causes a significantly higher insulin exposure than inhalation of one 3 mg unit dose blister. Therefore three 1 mg unit dose blisters should not be substituted for one 3 mg unit dose blister (see sections 2, 4.2 and 5.2).

If the 3 mg blister is temporarily unavailable, two 1 mg blisters should be substituted and blood glucose monitored closely.

A 1 mg blister of inhaled insulin is approximately equivalent to 3 IU of subcutaneously injected fast-acting human insulin. Therefore, EXUBERA should be used with caution in patients of low body weight. The use of EXUBERA in patients requiring dose titrations of less than 1 mg is not recommended (see section 4.2).

Hypoglycaemia

Hypoglycaemia, in general the most frequent undesirable effect of insulin therapy including EXUBERA and many oral antidiabetic agents, may occur if the insulin dose is too high in relation to

the insulin requirement. Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life threatening.

Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Hypoglycaemia can generally be corrected by immediate carbohydrate intake. In order to be able to take action immediately, patients should carry glucose with them at all times.

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly.

Usual warning symptoms may disappear in patients with longstanding diabetes.

A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin to human insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.

Before travelling between different time zones, the patient should be advised to consult the doctor, since this may mean that the patient has to take insulin and meals at different times.

Inadequate dosage or discontinuation of treatment especially in insulin-dependant diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

When used with other antidiabetic agents, the dose of each agent should be carefully adjusted to determine the optimal dose required to achieve the desired pharmacological effect.

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or stress.

Pulmonary Safety

Underlying respiratory disorders

EXUBERA should not be used in patients with lung disease such as asthma and COPD, as there are insufficient data to support the safe use in these patients.

The concomitant use of bronchodilators such as salbutamol may increase the absorption of EXUBERA and may therefore increase the risk of hypoglycaemia when used to relieve acute respiratory symptoms (see section 4.5).

Respiratory

Bronchospasm may rarely occur. Any patients experiencing such a reaction should discontinue EXUBERA and seek medical evaluation immediately. Re-administration of EXUBERA requires a careful risk evaluation, and may only be done under close medical monitoring with appropriate clinical facilities.

Decline in pulmonary function

In clinical trials small but consistent treatment group differences in decline of pulmonary function (particularly Forced Expiratory Volume in one second (FEV₁)) favouring comparator treated subjects have been observed. In clinical studies of up to two years duration, there was no accelerated decline beyond 3-6 months. These small treatment group differences resolved within 6 weeks upon discontinuation after 2 years of treatment (see sections 4.8 and 5.1).

All patients initiated on EXUBERA should have a baseline lung function examination (e.g. spirometry to measure FEV₁). The efficacy and safety of inhaled human insulin in patients with baseline FEV₁ < 70% predicted have not been established and the use of inhaled human insulin in this population is not recommended. A follow-up lung function measurement is recommended after the first 6 months of therapy. If at 6 months a decline of < 15% FEV₁ is observed, spirometry should be repeated at one year and then annually. If at 6 months a decline of 15-20% or > 500ml from baseline lung function is observed, spirometry should be repeated after 3 months.

In patients with a confirmed (i.e. at least two consecutive tests, 3 to 4 weeks apart) FEV₁ decline of > 20% from baseline, EXUBERA therapy should be discontinued and the patient monitored as clinically indicated. There is no experience with the reinstatement of EXUBERA therapy in patients whose lung function recovers.

Patients developing dyspnoea while treated with EXUBERA should be examined for pulmonary or cardiac causes. Where pulmonary oedema is present, or there is a clinically relevant reduction in pulmonary function, EXUBERA should be discontinued and the patient switched to injectable insulin.

Intercurrent Respiratory Illness

EXUBERA has been administered to patients with intercurrent respiratory illness (e.g. bronchitis, upper respiratory tract infections) during clinical trials. Increased risk of hypoglycaemia or poor glycaemic control has not been observed in these trials. During intercurrent respiratory illness close monitoring of blood glucose concentrations and dose adjustment may be required on an individual basis (see section 4.2). There is no experience with EXUBERA in patients with pneumonia.

Former Smokers

In clinical trials of Exubera, there have been 6 newly diagnosed cases of primary lung malignancies among Exubera-treated patients, and 1 newly diagnosed case among comparator treated patients. There has also been 1 post-marketing report of a primary lung malignancy in an Exubera-treated patient. In controlled clinical trials of Exubera, the incidence of new primary lung cancer per 100 patient-years of study drug exposure was 0.130 (5 cases over 3800 patient-years) for Exubera-treated patients and 0.03 (1 case over 3900 patient-years) for comparator-treated patients. There were too few cases to determine whether the emergence of these events is related to Exubera. All patients who were diagnosed with lung cancer had a prior history of cigarette smoking.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of insulin.

Substances that may enhance the blood-glucose lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, monoamino oxidase (MAO) inhibitors, non-selective beta-blocking agents, salicylates and sulphonamide antibiotics.

Administration of salbutamol prior to EXUBERA may result in increased insulin absorption (see section 5.2).

Administration of fluticasone prior to EXUBERA does not appear to affect insulin absorption (see section 5.2).

Active smoking greatly enhances whereas passive exposure to tobacco smoke in non-smokers decreases the rate and extent of absorption of EXUBERA (see sections 4.3 and 5.2).

Substances that may reduce the blood-glucose lowering effect include corticosteroids, danazol, oral contraceptives, thyroid hormones, growth hormone, sympathomimetic agents and thiazides. Octreotide/lanreotide may both decrease or increase insulin requirements.

Beta-blocking agents may mask the symptoms of hypoglycaemia. Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

Administration of EXUBERA 10 minutes prior to administration of salbutamol did not affect the bronchodilatory response to salbutamol in non-diabetic subjects with mild-moderate asthma.

Other drugs that may alter pulmonary absorption or lung permeability have not been studied. Close monitoring of blood glucose concentrations and dose titration as appropriate are recommended when inhaled human insulin is used in these patients. Caution should be exercised with concomitant use of EXUBERA and such drugs.

4.6 Pregnancy and lactation

There is no clinical experience with EXUBERA use in pregnancy. Inhaled insulin frequently induces insulin antibodies, the risk of which to the foetus is not known. Therefore, EXUBERA should not be used during pregnancy. When an EXUBERA treated patient becomes pregnant appropriate subcutaneous insulin should be substituted for inhaled insulin.

Breast-feeding women may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

As with other insulins, the patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

4.8 Undesirable effects

The safety of EXUBERA alone, or in combination with subcutaneous insulin or oral agents has been evaluated in clinical studies of more than 2700 patients with type 1 or type 2 diabetes, including more than 1975 adults exposed for greater than 6 months and more than 745 adults for greater than 2 years.

The table below contains adverse reactions seen in controlled clinical studies including more than 1970 patients exposed to EXUBERA.

Body System	Very Common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1000, < 1/100)
Infections and Infestations			Pharyngitis
Metabolism and Nutritional Disorders	Hypoglycaemia		
Respiratory, Thoracic and Mediastinal Disorders	Cough	Dyspnoea Productive Cough Throat Irritation Dry Throat	Epistaxis Bronchospasm Wheezing Dysphonia Pharyngolaryngeal Pain Tonsillar Disorder
Gastrointestinal Disorders			Dry Mouth
General Disorders and Administration Site Conditions			Chest Pain

Note: In the overall clinical program, including uncontrolled extension studies, there were two reports of pleural effusion in which a treatment-related effect could not be excluded.

Hypoglycaemia

As with other insulins, hypoglycaemia was the most frequently observed undesirable effect in patients treated with EXUBERA.

Cough

The cough tended to occur within seconds to minutes after insulin inhalation and was predominantly mild in severity. This cough decreased over time. One percent of patients discontinued EXUBERA treatment due to cough.

Dyspnoea

The majority (> 95%) of dyspnoea was reported as mild to moderate. In EXUBERA treated subjects 0.4% discontinued treatment due to dyspnoea.

Chest pain

A range of different chest symptoms were reported as treatment-related adverse reactions and were referred to as non-specific chest pain.. The majority (> 95%) of these events was reported as mild to moderate. One subject in the EXUBERA and one in the comparator group discontinued treatment due to chest pain. Importantly, the incidence of all-causality adverse events related to coronary artery disease, such as angina pectoris or myocardial infarction was not increased with the use of EXUBERA.

Other reactions

FEV₁ decline

Small treatment group differences in decline of FEV₁ were observed in the EXUBERA group relative to comparator therapy. In clinical studies of up to two years duration, there was no accelerated decline beyond 3-6 months. Discontinuation of EXUBERA therapy after 2 years resulted in resolution of treatment group differences within 6 weeks (see sections 4.4 and 5.1).

A decline from baseline in FEV₁ of $\geq 15\%$ occurred in 1.3% of EXUBERA-treated type 1 subjects and in 5.0% of EXUBERA-treated type 2 subjects.

Insulin antibodies

Insulin antibodies may develop during treatment with all insulins including EXUBERA. In clinical trials, insulin antibodies developed more frequently and mean levels of insulin antibodies were higher in patients who switched their subcutaneous human insulin to EXUBERA compared to subjects who remained on subcutaneous human insulin. Insulin antibody levels were higher in patients with type 1 diabetes compared to type 2 diabetes and plateaued within 6-12 months of exposure in both groups. No clinical significance of these antibodies has been identified.

Hypersensitivity reactions

As with other insulins, generalised allergic reactions may occur very rarely. Such reactions to insulin or the excipients may, for example, be associated with generalised skin reactions, angio-oedema, bronchospasm, hypotension and shock and may be life-threatening (see section 4.4 Respiratory).

Oedema and refraction abnormalities of the eye

Insulin therapy may cause sodium retention and oedema. Refraction abnormalities of the eye may occur upon initiation of insulin therapy. These effects are usually transitory.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin relative to food intake, energy expenditure or both.

Mild episodes of hypoglycaemia usually can be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes, with coma, seizure, or neurological impairment may be treated with intramuscular/subcutaneous glucagon (0.5 to 1 mg) or concentrated intravenous glucose. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal products used in diabetes, ATC code: A10AF01

Mode of Action

Human insulin lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects, increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis, increases lipogenesis in the liver and adipose tissue and inhibits lipolysis. It also promotes the uptake of amino acids into cells and promotes protein synthesis and enhances the uptake of potassium into cells.

Inhaled human insulin, like fast-acting insulin analogues, has a more rapid onset of glucose lowering activity compared to subcutaneously administered soluble human insulin. Inhaled human insulin has a duration of glucose lowering activity comparable to subcutaneously administered fast-acting human insulin and longer than fast-acting insulin analogues (see Figure 1).

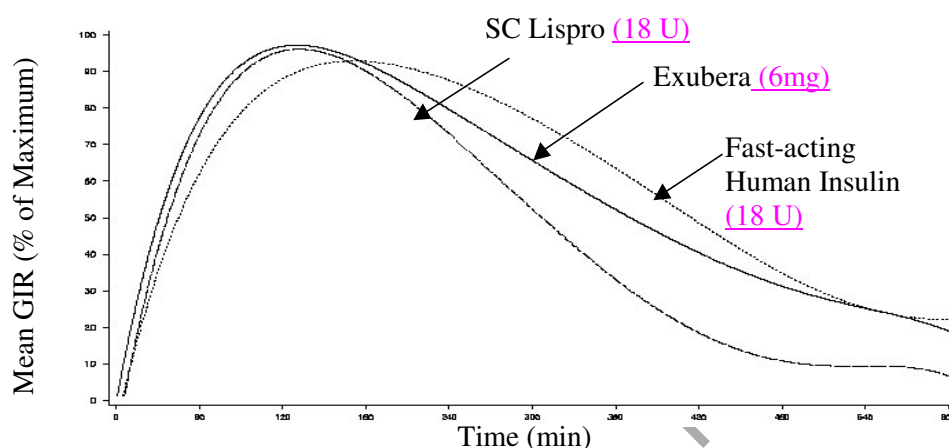


Figure 1. Mean Glucose Infusion Rate (GIR) Normalised to GIRmax for Each Subject Treatment Versus Time in Healthy Volunteers.

When human insulin is inhaled, the onset of glucose lowering activity is within 10-20 minutes, the maximum effect is exerted approximately 2 hours after inhalation. The duration of action lasts approximately 6 hours.

In subjects with type 1 or type 2 diabetes, inhaled human insulin has a faster onset of glucose lowering effect in the early hours after dosing when compared with subcutaneously administered fast-acting human insulin.

The intra-subject variability of glucose lowering activity of inhaled human insulin was generally comparable to that of subcutaneously administered fast-acting human insulin in subjects with type 1 and 2 diabetes mellitus.

Use of inhaled human insulin is associated with an increase in frequency, and levels of insulin antibodies. In a prospective exploratory 6 month study in subjects with type 1 diabetes, alterations in the glucose pharmacodynamics with inhaled human insulin were not observed

Information on Clinical Trials

Controlled clinical trials in type 1 or type 2 diabetes have shown that EXUBERA achieves and maintains effective glycaemic control comparable to subcutaneously administered fast-acting human insulin.

Type 1 Diabetes

In clinical trials in type 1 diabetes, patients using a regimen of EXUBERA in combination with long- or intermediate-acting insulin had similar reductions in HbA1c compared with patients taking subcutaneous insulin alone. The percentage of patients who achieved a goal of HbA1c < 7.0% was comparable between the treatment groups.

Fasting plasma glucose levels were significantly lower in patients treated with regimens including EXUBERA compared with those treated with subcutaneously administered fast-acting human insulin only regimens.

Type 2 Diabetes

Patients in a clinical trial for type 2 diabetes, who used a regimen of EXUBERA in combination with long- or intermediate-acting insulin, had similar changes in HbA1c compared with patients treated with subcutaneous insulin alone.

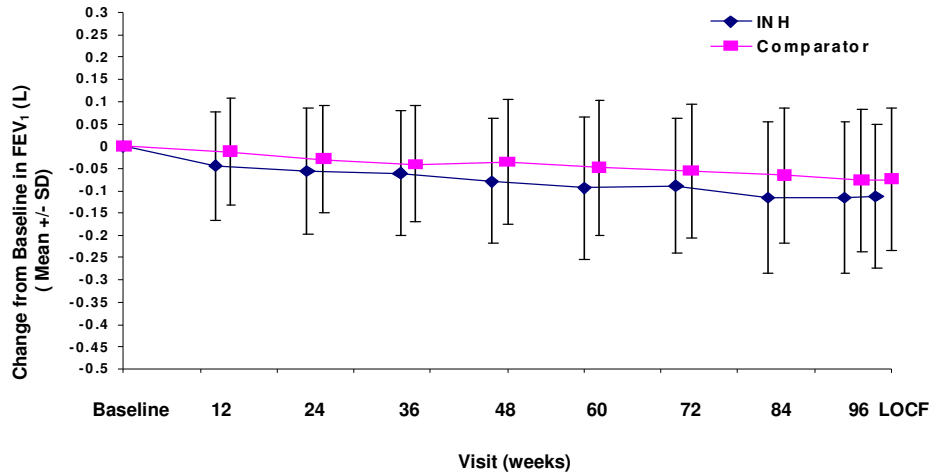
Fasting plasma glucose levels were significantly lower in patients treated with EXUBERA regimens compared with those treated with subcutaneous insulin.

In clinical trials involving patients with type 2 diabetes not sufficiently controlled with oral agents alone, patients using a regimen of EXUBERA alone or in combination with oral agents, had greater improvements in HbA1c compared with patients treated with oral agents alone. In most of these studies the percentages of patients achieving HbA1c < 7.0% were higher for patients using a regimen including EXUBERA compared to patients on oral agents alone. Fasting plasma glucose was similar to or lower in patients using a regimen including EXUBERA compared to patients treated with oral agents alone. In patients with type 2 diabetes sufficiently controlled with oral agents the glycaemic control was not further improved by inhaled insulin.

FEV₁ decline

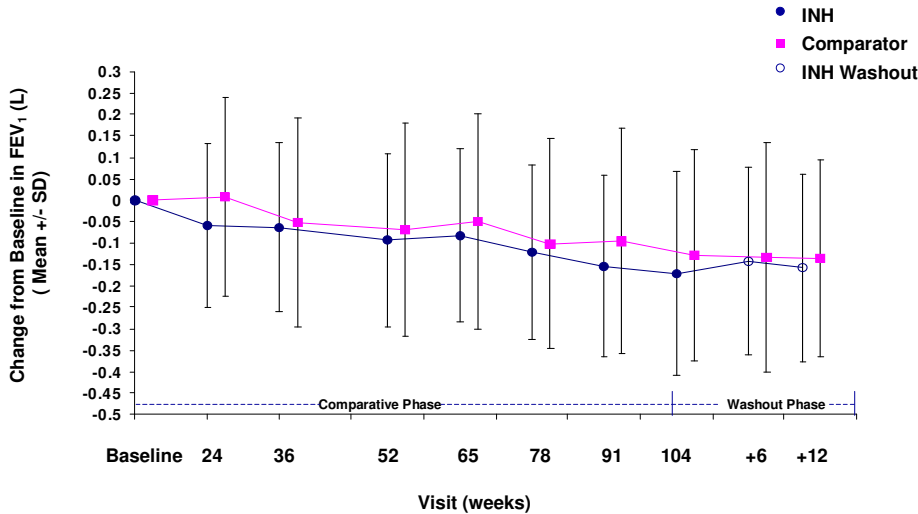
Randomised, open label parallel group studies were conducted to examine FEV₁ changes following initiation of EXUBERA therapy in type 1 and 2 subjects. Both EXUBERA and comparator treated subjects experienced declines in lung function over time during these trials (Figures 2 and 3). Small treatment group differences (favouring comparator) in change from baseline of 0.034L in type 1 and 0.039L in type 2 occurred after 2 years of therapy.

A decline from baseline in FEV₁ of $\geq 15\%$ occurred in 1.3% of EXUBERA-treated and 1.0% of comparator-treated type 1 subjects and in 5.0% of EXUBERA-treated and 3.4% of comparator-treated type 2 subjects.



N=Number of Subjects at Baseline, week 12, week 24, week 36, week 48, week 60, week 72, week 84, week 96, LOCF.
 INH N= 236, 231, 233, 233, 235, 235, 226, 217, 208, 236. Comparator N= 253, 238, 252, 248, 252, 249, 230, 224, 216, 253.

Figure 2. Observed Change from Baseline in FEV₁ (L) in patients with type 1 diabetes mellitus.



N=Number of Subjects at Baseline, week 52, week 104, week +6, week +12.
 INH and INH washout N=158, 155, 143, 139, 123. Comparator N=145, 143, 125, 129, 120.

Figure 3. Observed Change from Baseline in FEV₁ (L) in patients with type 2 diabetes mellitus.

In Phase 2/3 trials, 9 out of 2498 subjects treated with EXUBERA were discontinued from trials due to a decline in pulmonary function whose end of study FEV₁ showed a decline of $\geq 15\%$ from baseline. These subjects experienced an average decrease in FEV₁ of 21% (range 16%-33%) from baseline and were treated with EXUBERA for an average of 23 months. 6 of these discontinued subjects underwent follow-up pulmonary function testing. Of these patients, 5 exhibited a significant improvement in FEV₁ following discontinuation of therapy and one subject did not decrease further from the end of study value. No further information is available for the remaining 3 subjects who discontinued.

FEV₁ reversibility

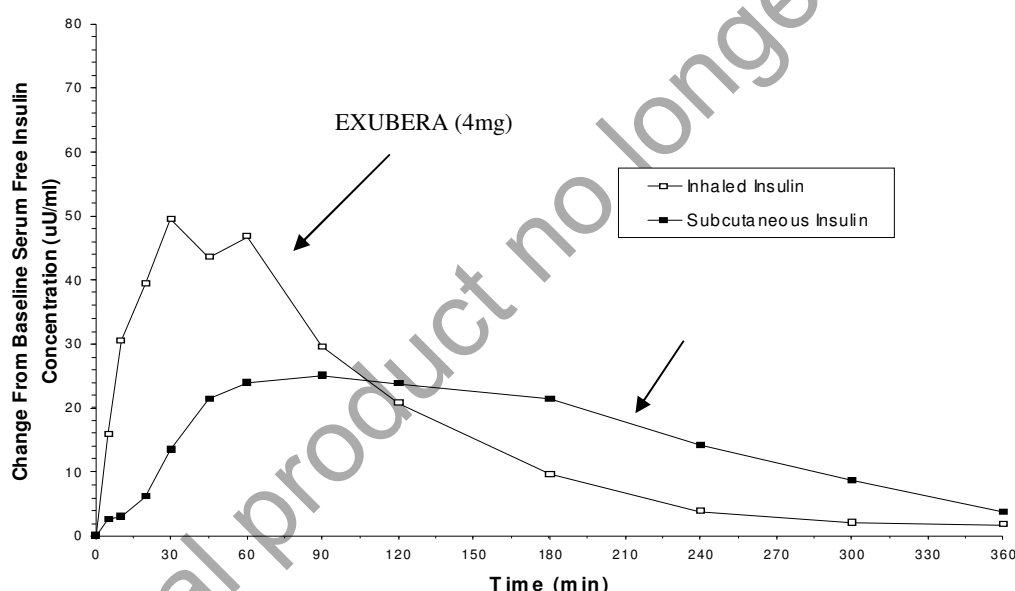
In type 1 subjects, resolution of small treatment group differences (0.010L favouring comparator) occurred within 2 weeks of EXUBERA cessation following 12 weeks of therapy. In type 2 subjects, resolution of small treatment group differences (0.039L favouring comparator) occurred within 6 weeks of EXUBERA cessation following 2 years of therapy (Figure 3). In a smaller group (n=36) of mixed type 1 and 2 subjects treated with EXUBERA for > 36 months, cessation of therapy resulted in a mean FEV₁ increase of 0.036L over the subsequent 6 months.

5.2 Pharmacokinetic properties

Absorption

Inhaled human insulin is delivered by the pulmonary route. Inhaled human insulin is absorbed as rapidly as fast-acting insulin analogues and more rapidly than subcutaneously administered fast-acting human insulin in healthy subjects and in subjects with type 1 or type 2 diabetes (see Figure 4).

Figure 4: Mean changes in serum free insulin concentrations ($\mu\text{U}/\text{mL}$) after inhalation of 4mg of human insulin or subcutaneous injection of 12 IU fast-acting human insulin in obese subjects with type 2 diabetes.



The time to peak insulin concentration (T_{max}) is generally half of that for subcutaneously administered fast-acting human insulin. Peak insulin concentration is reached generally by 45 minutes for inhaled human insulin. Intrasubject variability of time to peak insulin concentrations was less for inhaled human insulin than for subcutaneous fast-acting human insulin in subjects with type 1 or 2 diabetes.

In subjects with type 1 diabetes mellitus, inhaled human insulin had a comparable intrasubject variability of AUC to subcutaneously administered fast-acting human insulin. For C_{max} , the intrasubject variability of inhaled insulin is greater than that of subcutaneously administered fast-acting human insulin. In obese subjects with type 2 diabetes, intrasubject variability was comparable to or less than that of subcutaneously administered fast-acting human insulin for C_{max} and AUC.

The relative bioavailability of EXUBERA compared to subcutaneous fast-acting human insulin is approximately 10%. Unlike subcutaneous insulin preparations, the bioavailability of EXUBERA is not influenced by Body Mass Index.

In a study in healthy subjects, systemic exposure (AUC and C_{max}) of inhaled human insulin

increased in an approximately dose proportional fashion from 1 mg to 6 mg when a maximum of two blisters from either strength or their combination was administered. In a study where the dosage form of three 1 mg blisters was compared with one 3 mg blister, C_{max} and AUC of inhaling three 1 mg blisters were approximately 30% and 40% greater, respectively, than that of inhaling from one 3 mg blister, indicating that three 1 mg blisters are not interchangeable with one 3 mg blister (see sections 2, 4.2 and 4.4).

An approximately 40% higher bioavailability of three 1 mg unit dose blisters compared to one 3 mg unit dose blister was observed in healthy subjects. An explanation for the differences in bioavailability appears to be the different energy to mass ratio between the 1 and 3 mg unit blisters since with less powder in the blister the inhaler is more efficient in breaking up or de-agglomerating the powder leading to a larger proportion of smaller aerodynamic particle sizes for the 1 mg blister (see sections 2 and 4.4).

Distribution

Following oral inhalation of a single dose of human insulin approximately 30% of the total blister content remains in the blister or device, 20% is deposited in the oropharynx, 10% in the conducting airways and 40% reaches the deep lung.

Animal studies did not show that inhaled human insulin accumulates in the lung.

Special Populations

Smoking

Smoking greatly increases the rate and extent of absorption of inhaled human insulin (C_{max} about 3 to 5 times and AUC about 2 to 3 times higher) and therefore could increase the risk of hypoglycaemia (see sections 4.3 and 4.5).

When EXUBERA was administered to healthy volunteers following 2-hours of passive exposure to cigarette smoke in a controlled experimental setting, insulin AUC and C_{max} were reduced by approximately 17 and 30%, respectively (see section 4.5).

Respiratory Diseases (Underlying Lung Disease)

In non-diabetic subjects with mild to moderate asthma, AUC and C_{max} for inhaled human insulin in the absence of treatment with a bronchodilator was slightly less than in subjects without asthma.

In non-diabetic subjects with COPD, the absorption of inhaled human insulin appeared greater compared with that in subjects without COPD (see section 4.4).

Administration of salbutamol 30 minutes prior to EXUBERA in non-diabetic subjects with mild-moderate asthma resulted in an increase in insulin AUC and C_{max} of between 25 and 51% compared to when EXUBERA was administered alone (see sections 4.2 and 4.5).

Administration of fluticasone 30 minutes prior to EXUBERA did not affect the pharmacokinetics of EXUBERA in non-diabetic subjects with mild-moderate asthma (see section 4.5).

Renal impairment

The effect of renal impairment on the absorption of inhaled human insulin has not been studied (see section 4.2).

Hepatic impairment

The effect of hepatic impairment on the absorption of inhaled human insulin has not been studied (see section 4.2).

Gender

In subjects with diabetes and in subjects without diabetes, no apparent differences in absorption of inhaled human insulin were observed between men and women.

Children and adolescents

In children (6-11 years) and adolescents (12-17 years) with type 1 diabetes, inhaled human insulin was absorbed more rapidly than fast-acting human insulin. Bioavailability of inhaled human insulin relative to subcutaneously administered fast-acting human insulin was comparable to that of adult subjects with type 1 diabetes (see section 4.2).

Elderly

In older subjects with type 2 diabetes, inhaled human insulin was absorbed more rapidly than subcutaneously administered fast-acting human insulin. Bioavailability of inhaled human insulin relative to subcutaneously administered fast-acting human insulin was comparable to those in younger adult subjects with type 2 diabetes.

5.3 Preclinical safety data

Inhalation toxicity studies in rats and monkeys for up to 6 months gave no evidence for a special risk to the respiratory tract due to insulin inhalation powder.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Glycine
Sodium Citrate (as dihydrate)
Sodium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening the foil overwrap: 3 months.

6.4 Special precautions for storage

Store below 30°C. Store in the original package in order to protect from moisture.

After opening the foil overwrap: Store below 25°C.

Do not refrigerate or freeze the unit dose blisters.

The inhaler and its components should be stored and used in a dry place.

Do not refrigerate or freeze the insulin inhaler.

6.5 Nature and contents of container

One blister card contains 6 perforated unit dose blisters (PVC/Aluminium). Five blister cards are in a clear plastic (PET) thermoformed tray with a desiccant and covered with a clear plastic (PET) lid. The tray is sealed in a foil laminate pouch with a desiccant.

Packaging sizes supplied:

- Cardboard box containing 30 x 1 PVC/Aluminium perforated unit dose blisters (1 pouch)
- Cardboard box containing 60 x 1 PVC/Aluminium perforated unit dose blisters (2 pouches)
- Cardboard box containing 90 x 1 PVC/Aluminium perforated unit dose blisters (3 pouches)
- Cardboard box containing 180 x 1 PVC/Aluminium perforated unit dose blisters (6 pouches)
- Cardboard box containing 270 x 1 PVC/Aluminium perforated unit dose blisters (9 pouches)
- Cardboard box containing 60 x 1 PVC/Aluminium perforated unit dose blisters (2 pouches) and 2 spare Insulin Release Units (IRU)
- Cardboard box containing 90 x 1 PVC/Aluminium perforated unit dose blisters (3 pouches) and 2 spare Insulin Release Units (IRU)
- Cardboard box containing 180 x 1 PVC/Aluminium perforated unit dose blisters (6 pouches) and 2 spare Insulin Release Units (IRU)
- Cardboard box containing 270 x 1 PVC/Aluminium perforated unit dose blisters (9 pouches) and 6 spare Insulin Release Units (IRU)
- A kit containing 90 x 1 PVC/Aluminium perforated unit dose blisters (3 pouches), 1 insulin inhaler, 1 spare chamber and 6 spare Insulin Release Units (IRU)

Additional insulin inhaler, insulin release units and chamber packages are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

EXUBERA unit dose blisters must only be used with the insulin inhaler.

The insulin inhaler should be replaced annually.

The Insulin Release Unit (IRU) should be replaced once every 2 weeks.

If the insulin inhaler is inadvertently exposed to extremely moist conditions during use this usually leads to a subsequent decreased the insulin dose delivered from the inhaler. In this case, the Insulin Release Unit (IRU) must be changed prior to the next inhalation (see section 4.4).

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road, Sandwich,
Kent, CT13, 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/327/009
EU/1/05/327/010
EU/1/05/327/011
EU/1/05/327/012
EU/1/05/327/013
EU/1/05/327/014
EU/1/05/327/015
EU/1/05/327/016
EU/1/05/327/017
EU/1/05/327/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/01/2006

10. DATE OF REVISION OF THE TEXT

Medicinal product no longer authorised

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Pfizer Manufacturing Frankfurt GmbH & Co. KG
Industry Park Hoechst
65926 Frankfurt am Main
Germany

Name and address of the manufacturer responsible for batch release

Heinrich Mack Nachf. GmbH & Co. KG
Heinrich Mack Strasse 35
89257 Illertissen
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- The Marketing Authorisation Holder must implement nationally an educational plan, prior to marketing, and as agreed with the competent authorities in the Member States.

As part of this plan, the Marketing Authorisation Holder will provide health care professionals with educational materials for healthcare professionals and patients that are aimed at risk minimisation and will support safe and effective use for the product by the patient.

Educational material shall consist of information aiming to minimise adverse events and support effective use through adequate education about:

- a) The need for consistent and standard inhalation technique to ensure both optimal and consistent product delivery
- b) Special precaution with the insulin inhaler
- c) Hypoglycemia
- d) 1 mg and 3 mg dose inequivalence
- e) Magnitude of titration steps and resulting precautions
- f) The change in pulmonary function and the need for pulmonary function monitoring
- g) Smoking in relation to induced alteration in pharmacokinetics
- h) Rare pulmonary events
- i) Increased insulin antibody levels
- j) Recommendation for special populations; underlying lung diseases such as asthma and COPD, congestive heart failure, pregnancy, children and adolescent

- **OTHER CONDITIONS**

The MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

An updated Risk Management Plan, as per the CHMP Guideline on Risk Management Systems for medicinal products for human use, should be submitted at the same time as the PSURs, within 60 days of an important (Pharmacovigilance or Risk minimisation) milestone being reached or when the results of a study becoming available or at the request of the Competent authority.

Medicinal product no longer authorised

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton/Unit dose blisters (30, 60, 90, 180 and 270)

1. NAME OF THE MEDICINAL PRODUCT

EXUBERA 1 mg inhalation powder pre-dispensed
Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each unit dose blister contains 1 mg insulin human.

3. LIST OF EXCIPIENTS

Also contains: Mannitol, glycine, sodium citrate (as dihydrate), sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder pre-dispensed

30 x 1 perforated unit dose blisters
60 x 1 perforated unit dose blisters
90 x 1 perforated unit dose blisters
180 x 1 perforated unit dose blisters
270 x 1 perforated unit dose blisters

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use.
For use only with the insulin inhaler.
Read package leaflet and instructions for use of the inhaler before use.

Do not substitute three 1 mg blisters for one 3 mg blister. If 3 mg blisters are unavailable, use only two 1 mg blisters as replacement.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Store in the original package in order to protect from moisture.

After opening the foil overwrap: Store below 25°C. Use within 3 months of opening.

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/327/001
EU/1/05/327/002
EU/1/05/327/003
EU/1/05/327/004
EU/1/05/327/005

13. BATCH NUMBER

BN: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

EXUBERA 1 mg

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{NATURE/TYPE}

1. NAME OF THE MEDICINAL PRODUCT

EXUBERA 1 mg inhalation powder pre-dispensed
Insulin human

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

3. EXPIRY DATE

EXP{MMYYYY}

4. BATCH NUMBER

Lot{number}

5. OTHER

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON INTERMEDIATE PACKAGING

FOIL OVERWRAP

1. NAME OF THE MEDICINAL PRODUCT

EXUBERA 1 mg inhalation powder pre-dispensed
Insulin human

2. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder pre-dispensed
30x 1 perforated unit dose blisters

3. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use

Do not substitute three 1 mg blisters for one 3 mg blister. If 3 mg blisters are unavailable, use only two 1 mg blisters as replacement.

4. EXPIRY DATE

EXP: {MM/YYYY}

5. NAME OF MARKETING AUTHORISATION HOLDER

Pfizer Limited

6. BATCH NUMBER

Lot{number}

7. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton/Unit dose blisters (60, 90, 270)

1. NAME OF THE MEDICINAL PRODUCT

EXUBERA 1 mg inhalation powder pre-dispensed
Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each unit dose blister contains 1 mg insulin human.

3. LIST OF EXCIPIENTS

Also contains: Mannitol, glycine, sodium citrate (as dihydrate), sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder pre-dispensed

Box containing: 60 x 1 PVC/Aluminium perforated unit dose blisters (2 pouches) and 2 spare Insulin Release Units (IRU)

Box containing: 270 x 1 PVC/Aluminium perforated unit dose blisters (9 pouches) and 6 spare Insulin Release Units (IRU)

Box containing: 90 x 1 PVC/Aluminium perforated unit dose blisters (3 pouches), 1 insulin inhaler, 1 spare chamber and 6 spare Insulin Release Units (IRU)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use.

For use only with the insulin inhaler.

Read package leaflet and instructions for use of the inhaler before use.

Do not substitute three 1 mg blisters for one 3 mg blister. If 3 mg blisters are unavailable, use only two 1 mg blisters as replacement.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Store in the original package in order to protect from moisture.

After opening the foil overwrap: Store below 25°C. Use within 3 months of opening.

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/327/006
EU/1/05/327/007
EU/1/05/327/008

13. BATCH NUMBER

BN: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

EXUBERA 1 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton/Unit dose blisters (30, 60, 90, 180 and 270)

1. NAME OF THE MEDICINAL PRODUCT

EXUBERA 3 mg inhalation powder pre-dispensed
Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each unit dose blister contains 3 mg insulin human.

3. LIST OF EXCIPIENTS

Also contains: Mannitol, glycine, sodium citrate (as dihydrate), sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder pre-dispensed

30 x 1 perforated unit dose blisters
60 x 1 perforated unit dose blisters
90 x 1 perforated unit dose blisters
180 x 1 perforated unit dose blisters
270 x 1 perforated unit dose blisters

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use.
For use only with the insulin inhaler.
Read package leaflet and instructions for use of the inhaler before use.

Do not substitute three 1 mg blisters for one 3 mg blister. If 3 mg blisters are unavailable, use only two 1 mg blisters as replacement.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Store in the original package in order to protect from moisture.

After opening the foil overwrap: Store below 25°C. Use within 3 months of opening.

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/327/009
EU/1/05/327/010
EU/1/05/327/011
EU/1/05/327/012
EU/1/05/327/013

13. BATCH NUMBER

BN: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

EXUBERA 3 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{NATURE/TYPE}

1. NAME OF THE MEDICINAL PRODUCT

EXUBERA 3 mg inhalation powder pre-dispensed
Insulin human

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

3. EXPIRY DATE

EXP{MMYYYY}

4. BATCH NUMBER

Lot{number}

5. OTHER

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON INTERMEDIATE PACKAGING

FOIL OVERWRAP

1. NAME OF THE MEDICINAL PRODUCT

EXUBERA 3 mg inhalation powder pre-dispensed

Insulin human

2. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder pre-dispensed

30x 1 perforated unit dose blisters

3. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use

Do not substitute three 1 mg blisters for one 3 mg blister. If 3 mg blisters are unavailable, use only two 1 mg blisters as replacement.

4. EXPIRY DATE

EXP: {MM/YYYY}

5. NAME OF MARKETING AUTHORISATION HOLDER

Pfizer Limited

6. BATCH NUMBER

Lot{number}

7. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton/Unit dose blisters (60, 90, 180, 270)

1. NAME OF THE MEDICINAL PRODUCT

EXUBERA 3 mg inhalation powder pre-dispensed
Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each unit dose blister contains 3 mg insulin human.

3. LIST OF EXCIPIENTS

Also contains: Mannitol, glycine, sodium citrate (as dihydrate), sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder pre-dispensed

Box containing: 60 x 1 PVC/Aluminium perforated unit dose blisters (2 pouches) and 2 spare Insulin Release Units (IRU)

Box containing: 90 x 1 PVC/Aluminium perforated unit dose blisters (3 pouches) and 2 spare Insulin Release Units (IRU)

Box containing: 180 x 1 PVC/Aluminium perforated unit dose blisters (6 pouches) and 2 spare Insulin Release Units (IRU)

Box containing: 270 x 1 PVC/Aluminium perforated unit dose blisters (9 pouches) and 6 spare Insulin Release Units (IRU)

Box containing: 90 x 1 PVC/Aluminium perforated unit dose blisters (3 pouches), 1 insulin inhaler, 1 spare chamber and 6 spare Insulin Release Units (IRU)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use.

For use only with the insulin inhaler.

Read package leaflet and instructions for use of the inhaler before use.

Do not substitute three 1 mg blisters for one 3 mg blister. If 3 mg blisters are unavailable, use only two 1 mg blisters as replacement.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Store in the original package in order to protect from moisture.

After opening the foil overwrap: Store below 25°C. Use within 3 months of opening.

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/327/014
EU/1/05/327/015
EU/1/05/327/016
EU/1/05/327/017
EU/1/05/327/018

13. BATCH NUMBER

BN: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

EXUBERA 3 mg

Medicinal product no longer authorised

Medicinal product no longer authorised

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

EXUBERA 1 mg inhalation powder pre-dispensed EXUBERA 3 mg inhalation powder pre-dispensed Insulin human

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, diabetes nurse or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What EXUBERA is and what it is used for
2. Before you take EXUBERA
3. How to take EXUBERA
4. Possible side effects
5. How to store EXUBERA
6. Further information

Taking three separate 1 mg unit dose blisters delivers more insulin to your lungs than a single 3 mg unit dose blister does. Three 1 mg unit dose blisters should not be substituted for one 3mg blister (see section 2, "Take special care with EXUBERA", section 3, "How to take EXUBERA" and section 6 "Further information").

A unit dose blister is the individual container in which the insulin powder is packaged and will be called a blister in the rest of this leaflet.

1. WHAT EXUBERA IS AND WHAT IT IS USED FOR

EXUBERA is an inhalation powder contained in blisters. The contents of the blisters should be breathed in through your mouth into your lungs using the insulin inhaler.

EXUBERA is an anti-diabetic agent that lowers your blood sugar.

EXUBERA is a fast-acting insulin. This means that it will start to lower your blood sugar 10-20 minutes after you take it, with a maximum effect at 2 hours and the effect will last for around 6 hours.

EXUBERA is often given in combination with other diabetes treatments.

EXUBERA is used to reduce high blood sugar in adult patients with type 2 diabetes mellitus who need insulin.

EXUBERA can also be used to treat type 1 diabetes in adults whose level of blood sugar is not well-controlled by insulin injections.

Diabetes is a disease in which your body does not produce enough insulin to control the level of blood sugar.

2. BEFORE YOU TAKE EXUBERA

Do not take EXUBERA

- **If you feel hypoglycaemia (low blood sugar) coming on.** See the information at the end of section 4 “Possible side effects” of this leaflet for further advice.
- **If you are allergic** to insulin, the active ingredient contained in EXUBERA or any of the other ingredients of EXUBERA. If you suspect an allergy to EXUBERA, speak to your doctor immediately.
- **If you smoke, or if you have smoked in the last six months** you must not take EXUBERA as you may have extra risk of hypoglycaemia (very low blood sugar). Please speak to your doctor immediately if you take EXUBERA and resume smoking or have smoked in the last 6 months before starting to take EXUBERA.
- If you have poorly controlled, unstable, or severe asthma.
- If you have severe (GOLD stage III or IV), Chronic Obstructive Pulmonary Disease (COPD).

Take special care with EXUBERA

Please follow closely the instructions for dosage, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor or nurse.

Before you start taking EXUBERA your doctor or nurse will tell you how to use the inhaler properly. Please also read the “Instructions for Use” of the inhaler at the end of the package leaflet carefully before taking EXUBERA. Make sure that you can use the inhaler properly as this could affect the amount of insulin you breathe in.

You should avoid taking EXUBERA in moist conditions e.g. a bathroom following a steamy shower as this will usually give you a lower insulin dose than you need (see “Instructions for Use” at the end of the package leaflet for advice).

If you accidentally expose your inhaler to moist conditions during use, this will usually decrease the dose of insulin you take. In this case you must change the Insulin Release Unit (IRU) prior to your next inhalation.

Dosing

Your doctor will prescribe your starting pre-meal dose of EXUBERA based on your body weight. This may include a mix of 1 mg (green coloured) and 3 mg (blue coloured) blisters. It is important to follow your doctor’s instructions exactly.

A 1 mg unit dose blister is approximately equal to 3 IU of fast-acting subcutaneous insulin and a 3 mg unit dose blister is approximately equal to 8 IU of fast-acting subcutaneous insulin.

Dose adjustments may be required based on meal size and nutrient composition, time of day (higher insulin requirements in the morning), pre-meal blood glucose concentration, recent or planned exercise.

Do not use three separate 1 mg blisters in place of one 3 mg blister, as this will give you a much higher insulin dose (see “How to take EXUBERA” for further advice).

If you have low body weight check with your doctor if you can use EXUBERA. If you need dose titrations of less than 1 mg it is recommended you do not use EXUBERA (see section 3 “How to take EXUBERA” for further advice and section 6 “Further information”).

Special patient groups

If your liver or kidneys do not function well speak to your doctor, who may advise that you use lower insulin doses.

If you are under 18 years of age, please speak to your doctor, as use of EXUBERA is not recommended for patients under 18 years of age.

There is little experience with EXUBERA in patients older than 75 years.

There is very little experience with EXUBERA in patients with congestive heart failure. EXUBERA is not recommended if you have breathing difficulties with congestive heart failure.

Lung diseases

Talk to your doctor if you have any lung disease such as asthma, emphysema or chronic bronchitis. EXUBERA is not recommended for patients with lung disease. Also, if you experience breathing difficulties that you have not previously discussed with your doctor, you should discuss them before starting EXUBERA treatment.

Before starting treatment your doctor will carry out a simple test on your lung function to decide whether EXUBERA is the right treatment for you. Once you start treatment, your doctor will check your lung function again after 6 months and at other times to see how well you are tolerating EXUBERA.

If you notice an immediate and severe worsening of your breathing soon after taking a dose of EXUBERA, you should stop taking EXUBERA and tell your doctor immediately or go to the casualty department at your nearest hospital.

You should also tell your doctor if you develop any other increasing breathing difficulties while taking EXUBERA.

Illness and injuries

If you are ill or have a major injury, then your blood sugar may increase (hyperglycaemia) or if you are not eating enough your blood sugar may become too low (hypoglycaemia). In such situations, the management of your diabetes may require a lot of care and you may need to seek advice from your doctor or nurse.

If you have infection in your airways (such as bronchitis or upper respiratory tract infection) while taking EXUBERA you should monitor your blood glucose frequently and you may need to adjust your EXUBERA dose. Please talk to your doctor if you have problems administering EXUBERA or controlling your blood glucose. There is no experience with EXUBERA in patients with infection of the deep lung (pneumonia).

Please see the end of section 4 for important information about hypoglycaemia and hyperglycaemia and its treatment.

Travel

Before travelling, consult your doctor or nurse to talk about timings of meals and insulin administration while travelling, the possible effects of changing to different time zones on blood sugar levels and control and the availability of EXUBERA in the countries you are visiting.

Taking other medicines

Some medicines cause the blood sugar level to fall, some cause it to rise, others may have both effects, depending on the situation. In each case, it may be necessary to adjust your insulin dosage to avoid too low or too high blood sugar levels. Be careful not only when you start another medicine, but also when you stop it.

Tell your doctor about all medicines that you are taking, including those you have bought without a prescription (such as from a Pharmacy or other shop). Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar to fall include diabetes tablets, angiotensin converting enzyme (ACE) inhibitors (used for the treatment of certain heart conditions, high blood pressure or elevated protein/albumin in the urine), monoamine oxidase (MAO) inhibitors (used for the treatment of depression), certain beta-blockers (used for the treatment of certain heart conditions and high blood pressure), salicylates (e.g. aspirin, used to relieve pain and lower fever) and sulphonamide antibiotics.

Medicines that may cause your blood sugar to rise include corticosteroids (used to treat inflammatory conditions, except topical administration), danazol (used for the treatment of some female hormonal disorders), oral contraceptives (used for birth control), thyroid hormones (used for the treatment of malfunction of the thyroid gland), growth hormones (used in endocrine conditions), sympathomimetic agents (used for the treatment of asthma) and thiazides (used in special endocrine conditions).

The use of a bronchodilator (reliever inhaler) for asthma or other airway conditions may cause a more pronounced fall in blood sugar in response to inhaled insulin (see section 2 “Do not take EXUBERA” and section 2 “Take special care with EXUBERA”).

Your blood sugar level may either fall or rise if you take beta-blockers or drink alcohol. Beta-blockers may weaken the warning symptoms of a hypoglycaemic reaction or suppress them entirely. Alcohol may increase the action of insulin and cause low blood sugar levels. Octreotide/lanreotide (used in special endocrine conditions) may change the need for insulin.

If you smoke, the amount of insulin your body absorbs will be increased and you will have a greater risk of hypoglycaemia. If you are taking EXUBERA, do not smoke (see section 2, “Do not take EXUBERA”).

In contrast, exposure to other people’s cigarette smoke may decrease the amount of insulin your body absorbs.

Pregnancy and breast-feeding

There is **no** experience on the use of EXUBERA in pregnant women. EXUBERA should not be taken during pregnancy. Inform your doctor or nurse if you are planning to become pregnant or if you are already pregnant. Your doctor may replace EXUBERA with an injectable insulin for your diabetes.

Your insulin dosage may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if you have too low blood sugar (hypoglycaemia). Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor about the advisability of driving if you have:

- frequent episodes of hypoglycaemia,
- reduced or absent warning signs of hypoglycaemia.

3. HOW TO TAKE EXUBERA

EXUBERA should be taken within 10 minutes before the start of a meal.

Your doctor will decide how much EXUBERA you will initially need based on your weight and recommend any changes after that based on your diet and amount of exercise.

A 1 mg blister of EXUBERA gives you about the same insulin dose as 3 IU of subcutaneously injected fast-acting insulin human. A 3 mg blister of EXUBERA gives you about the same insulin dose as 8 IU of subcutaneously injected fast-acting insulin human. If you have low body weight check with your doctor if you can use EXUBERA. If you need dose titrations of less than 1 mg it is recommended you do not use EXUBERA.

Always make sure you have the correct strength and number of EXUBERA blisters available before taking your dose. It is important that you take the number of 1 mg and 3 mg blisters that your doctor recommends in the combination that he or she recommends.

Do not use three 1 mg blisters in place of one 3 mg blister, as this will give you a much higher dose of insulin. If you temporarily run out of 3 mg blisters, two 1 mg blisters should be used and you should monitor your blood glucose levels closely. You should contact your doctor or pharmacist as soon as possible to get more 3 mg blisters. If you are unsure contact your doctor, nurse or pharmacist.

Preparing to take EXUBERA

To use an EXUBERA blister, first separate the blister from the spine by tearing along the tear line (perforation).

Do not open the blister containing EXUBERA. The blister will be punctured inside the inhaler when you use it. Do not swallow the contents of the blister.

EXUBERA should only be breathed in through your mouth and should only be taken with your insulin inhaler.

Always follow your doctor's instructions about when and how to take EXUBERA. Please see the "Instructions for Use" at the end of the package leaflet for advice on how to use your insulin inhaler, and how to care for it. Check with your doctor, nurse or pharmacist if you have any questions regarding EXUBERA or the insulin inhaler.

Mistakes in dosage

Please discuss with your doctor what you should do if you were to take too much or too little EXUBERA, or if you miss a dose, so that you know what to do.

–If you **have taken too much insulin**, you may develop hypoglycaemia. Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood

sugar. For information on the treatment of hypoglycaemia, see the end of section 4 “Possible side effects”.

–If you **have missed a dose of insulin or if you have taken too low a dose**, your blood sugar level may become too high. Check your blood sugar frequently. For further information on hyperglycaemia, see the end of section 4 “Possible side effects”.

4. POSSIBLE SIDE EFFECTS

Like all medicines, EXUBERA can have side effects, although not everybody gets them.

Side effects reported very commonly

(Seen in more than 1 in 10 patients)

Hypoglycaemia - As with all insulin therapy, the most common side effect with EXUBERA is hypoglycaemia (too low blood sugar). Please see the end of this section for important further information about hypoglycaemia and its treatment.

Cough - A cough may occur within seconds to minutes after inhaling EXUBERA. The cough is usually mild and often gets better over time.

Side effects reported commonly

(Seen in less than 1 in 10 but more than 1 in 100 patients)

Commonly reported side effects are mild to moderate shortness of breath (dyspnoea), productive cough, throat irritation and dry throat.

Side effects reported uncommonly

(Seen in less than 1 in 100 but more than 1 in 1000 patients).

Uncommon side effects are inflammation of the throat (pharyngitis), nose bleed (epistaxis), airway constriction with difficulties breathing (bronchospasm), wheezing, voice alteration (dysphonia), throat pain (pharyngolaryngeal pain), tonsillar disorder, dry mouth and chest pain.

Other side effects

Some patients have experienced fluid in the lung lining (pleural effusion).

Insulin treatment can cause the body to produce antibodies to insulin (substances that bind to insulin). Development of such antibodies is seen more commonly in patients treated with EXUBERA compared to subcutaneous insulin. Although these antibodies may be produced, they do not have any effect on your blood glucose control.

A small decrease in your lung function may occur during EXUBERA treatment, although you should not notice any symptoms. This change occurs within the first months of treatment and usually doesn't worsen as you continue treatment. If you stop therapy with EXUBERA, your lung function will usually return to your normal level. If you notice a change in your breathing while taking EXUBERA inform your doctor.

Severe allergic reactions to insulin are very rare. Such reactions to insulin or to the other ingredients can cause skin reactions, severe swelling of skin or mucous membranes (angio-oedema), shortness of breath, a fall in blood pressure and may become life threatening.

Changes to your sight may occur upon starting insulin therapy. These changes are usually mild and go away with time.

Insulin treatment may also cause temporary build-up of water in the body with swelling in the calves and ankles.

If any of these side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

If your blood sugar is too low (hypoglycaemia)

Your blood sugar levels may fall too much, if for example:

- you take too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose or are unable to consume carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you take more physical exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from a feverish illness or from another illness,
- you are taking or have stopped taking certain other medicines (see section 2, “Taking other medicines”).

Hypoglycaemia (low blood sugar levels) are also more likely to occur if:

- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Symptoms that tell you that your blood sugar level is falling too much or too fast may be, for example: sweating, clammy skin, anxiety, fast heartbeat, high blood pressure, palpitations and irregular heartbeat, chest pain (angina pectoris). These symptoms often develop before the symptoms of a low sugar level in the brain.

The following symptoms indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia (“warning symptoms”) may change, be weaker or may be missing altogether if:

- you are elderly,
- you have had diabetes for a long time
- due to diabetes, you suffer from a certain type of nervous disease (autonomic neuropathy),
- you have recently suffered hypoglycaemia (e.g. the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, “Taking other medicines”).

In such a case, you may develop severe hypoglycaemia (and even lose consciousness) before you are aware of the problem. Try always to keep familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that might otherwise be overlooked. While you are not confident about recognising your warning symptoms, avoid situations (e.g. driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do in case of hypoglycaemia

1. Do not take more insulin. Immediately take about 10 to 20 gram sugar, e.g. as glucose, sugar cubes or a sugar-sweetened drink. (Measure once as spoonfuls or lumps of sugar or glucose tablets to see how much this means). Caution: please remember that artificial sweeteners and foods with artificial sweeteners (e.g. diet drinks) are of no help in hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (e.g. bread). Your doctor or nurse will have discussed this with you.
3. If the hypoglycaemia comes back again take another 10 to 20 gram sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Always carry some sugar (at least 20 grams) with you.

If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections may be justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

If your blood sugar is too high (hyperglycaemia)

Your blood sugar level may be too high, if for example:

- you have not taken enough insulin, or if it has become less effective, e.g. through incorrect storage,
- you are doing less physical exercise, you are under stress (emotional distress, excitement), or if you have an injury, operation, feverish illness or certain other diseases,
- you are taking or have taken certain other medicines (see section 2, “Taking other medicines”).

Symptoms that may tell you that your blood sugar levels are too high:

thirst, increased need to pass water, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heartbeat, and glucose and ketone bodies in urine may be signs of too high blood sugar. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

Test your blood sugar level and your urine for ketones as soon as any such symptoms of hyperglycaemia occur as described above. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

Carry some information with you to show you are diabetic.

5. HOW TO STORE EXUBERA

Keep out of the reach and sight of children.

Store below 30°C. Store in the original package in order to protect from moisture.

After opening the foil overwrap: store below 25°C and use within 3 months of opening.

Do not refrigerate or freeze the blisters.

Do not use EXUBERA if you notice that a blister is not properly sealed or damaged.

Do not use EXUBERA after the expiry date (EXP) stated on the pack or unit dose blisters.

For instructions on how to look after your insulin inhaler see “Instructions for Use” at the end of the package leaflet.

6. FURTHER INFORMATION

What EXUBERA contains

- The active substance is insulin human. Each unit dose blister contains 1 mg or 3 mg of the active substance insulin human.
- The other ingredients are: mannitol, glycine, sodium citrate (as dihydrate) and sodium hydroxide.

Taking three separate 1 mg blisters delivers more insulin to your lungs than a single 3 mg blister does. Three 1 mg blisters should not be substituted for one 3 mg blister (see section 2, “Take special care with EXUBERA” and section 3, “How to take EXUBERA”).

What EXUBERA looks like and contents of the pack

EXUBERA is an inhalation powder, pre-dispensed, and is supplied as tear-off unit dose blisters marked with either ‘1 mg EXUBERA’ with green ink or ‘3 mg EXUBERA’ with blue ink. For the 1 mg product, the spine of the blister card has one raised ridge with the individual blisters embossed with one raised dot each. For the 3 mg product, the spine of the blister card has three raised ridges with the individual blisters embossed with three raised dots each. There are 6 blisters on each card and 5 cards per tray. The tray is sealed in a plastic foil pouch with a desiccant, which keeps the medicine dry and should not be eaten.

EXUBERA is available in the following pack sizes:

- A pack containing 30, 60, 90, 180 and 270 x 1 of 1 mg PVC/Aluminium perforated unit dose blisters
- A pack containing 30, 60, 90, 180 and 270 x 1 of 3 mg PVC/Aluminium perforated unit dose blisters
- A pack containing 60 x 1 of 1 mg PVC/Aluminium perforated unit dose blisters (2 pouches) and 2 spare Insulin Release Units (IRU)
- A pack containing 270 x 1 of 1 mg PVC/Aluminium perforated unit dose blisters (9 pouches) and 6 spare Insulin Release Units (IRU)
- A pack containing 60 x 1 of 3 mg PVC/Aluminium perforated unit dose blisters (2 pouches) and 2 spare Insulin Release Units (IRU)
- A pack containing 90 x 1 of 3 mg PVC/Aluminium perforated unit dose blisters (3 pouches) and 2 spare Insulin Release Units (IRU)
- A pack containing 180 x 1 of 3 mg PVC/Aluminium perforated unit dose blisters (6 pouches) and 2 spare Insulin Release Units (IRU)
- A pack containing 270 x 1 of 3 mg PVC/Aluminium perforated unit dose blisters (9 pouches) and 6 spare Insulin Release Units (IRU)
- A kit containing 90 x 1 of 1 mg PVC/Aluminium perforated unit dose blisters (3 pouches), 1 insulin inhaler, 1 spare chamber and 6 spare Insulin Release Units (IRU)
- A kit containing 90 x 1 of 3 mg PVC/Aluminium perforated unit dose blisters (3 pouches), 1 insulin inhaler, 1 spare chamber and 6 spare Insulin Release Units (IRU)

Additional insulin inhaler, insulin release units and chamber packages are available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder is Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom.

The manufacturer is Heinrich Mack Nachf. GmbH & Co. KG, Heinrich Mack Strasse 35, 89257, Illertissen, Germany.

For any information about this medicine, please contact the local EXUBERA Customer Care Centre.

België /Belgique / Belgien

Klanteninformatiedienst voor EXUBERA/
EXUBERA-Service-Center/Service Client local
EXUBERA
Tél/Tel: 0800 30432
Tél/Tel: + 32 (0)2 554 62 11

Luxembourg/Luxemburg

Service Client local EXUBERA/EXUBERA-
Service-Center
Tél/Tel: 8002 5350
Tél/Tel: + 32 (0)2 554 62 11

България

EXUBERA-център за работа с клиенти
Тел: 080014441
Тел: +359 2 970 4333

Magyarország

EXUBERA ügyfélszolgálat
Tel. 06-80-203-279
Tel.: + 36 1 488 37 00

Česká republika

EXUBERA centrum péče o zákazníky
Tel: 800106108
Tel: + 420 283 004 111

Malta

EXUBERA Customer Care Centre
Tel: 800 62451
Tel: + 356 21 220717

Danmark

EXUBERA kundecenter
Tlf: 80 60 10 40
Tlf: + 45 44 20 11 00

Nederland

Klanteninformatiedienst voor EXUBERA
Tel: 0800 3982372
Tel: + 31 (0)10 406 43 01

Deutschland

EXUBERA-Service-Center
Tel: 0800 3982372
Tel: + 49 (0)721 6101 9000

Norge

EXUBERA kundetelefon
Tlf: 800 74444
Tlf: + 47 67 52 61 00

Eesti

EXUBERA Kliendi Tugikeskus
Tel: + 372 6 405 328

Österreich

EXUBERA-Service-Center
Tel: 0800 80 80 42
Tel: + 43 (0)1 521 15 0

Ελλάδα

Κέντρο Εξυπηρέτησης και Ενημέρωσης
Πελατών του EXUBERA
Τηλ: 80011 83333
Τηλ: + 30 210 6785 797

Polska

Lokalne telefoniczne centrum informacyjne dla
pacjenta
Tel.: 0800 80 88 80
Tel.: + 48 22 335 61 00

España

Centro local de Atención al Cliente de Exubera
Tel: 900 900866
Tel: + 34 91 490 99 00

France

Service Client local EXUBERA
Tél: 0800 438 438
Tél: + 33 (0)1 58 07 34 40

Ireland

EXUBERA Customer Care Centre
Tel: 1 800 882 392
Tel: + 44 (0)1737 331111

Ísland

EXUBERA neytendaþjónusta
Tel: 044 20 11 00
Tel: + 354 535 7000

Italia

Customer Care locale di EXUBERA
Tel: 0800 021354
Tel: + 39 06 33 18 21

Κύπρος

Κέντρο Εξυπηρέτησης και Ενημέρωσης
Πελατών του EXUBERA
Τηλ: 800 92656
Τηλ: +30 210 6785 798

Latvija

EXUBERA pacientu atbalsta centrs
Tel: + 371 670 35 775

Lietuva

EXUBERA pacientų priežiūros centras
Tel: 8 800 22000
Tel. + 3705 2514000

Portugal

Serviço local de Atendimento ao utilizador de
EXUBERA
Tel: 800 206746
Tel: + 351 21 423 5500

România

EXUBERA – Centrul de Relații cu Clienții
Tel.: 0800 390 000
Tel.: +40 (0)21 207 28 00

Slovenija

Center za svetovanje o zdravilu EXUBERA
Tel: 080 2682
Tel: + 386 1 52 11 400

Slovenská republika

EXUBERA Centrum starostlivosti o pacientov
Tel: 0800 101 001
Tel: +421-2-3355 5500

Suomi/Finland

EXUBERA-asiakaspalvelunumero
Puh/Tel: 0800 915 133
Puh/Tel: + 358 (0)9 43 00 40

Sverige

Kundservice för EXUBERA
Tel: 020 88 80 80
Tel: + 46 (0)8 5505 2000

United Kingdom

EXUBERA Customer Care Centre
Tel: 0845 850 0198
Tel: + 44 (0)1737 331111

This leaflet was last approved in

Insulin Inhaler Instructions for Use

Read all of this leaflet carefully before starting to use your insulin inhaler

Keep this leaflet. You may need to read it again.

Always make sure you have the correct blisters available before using your insulin inhaler. Also, read the Patient Information Leaflet for, EXUBERA 1 mg and 3 mg powder for inhalation pre-dispensed.

REPLACING YOUR INHALER AND THE INSULIN RELEASE (IRU)

You should change your insulin inhaler once a year from the date you first use the inhaler. You should change the IRU in your insulin inhaler every 2 weeks. The IRU must be changed after accidental exposure to extremely moist conditions, e.g. steamy bathroom.

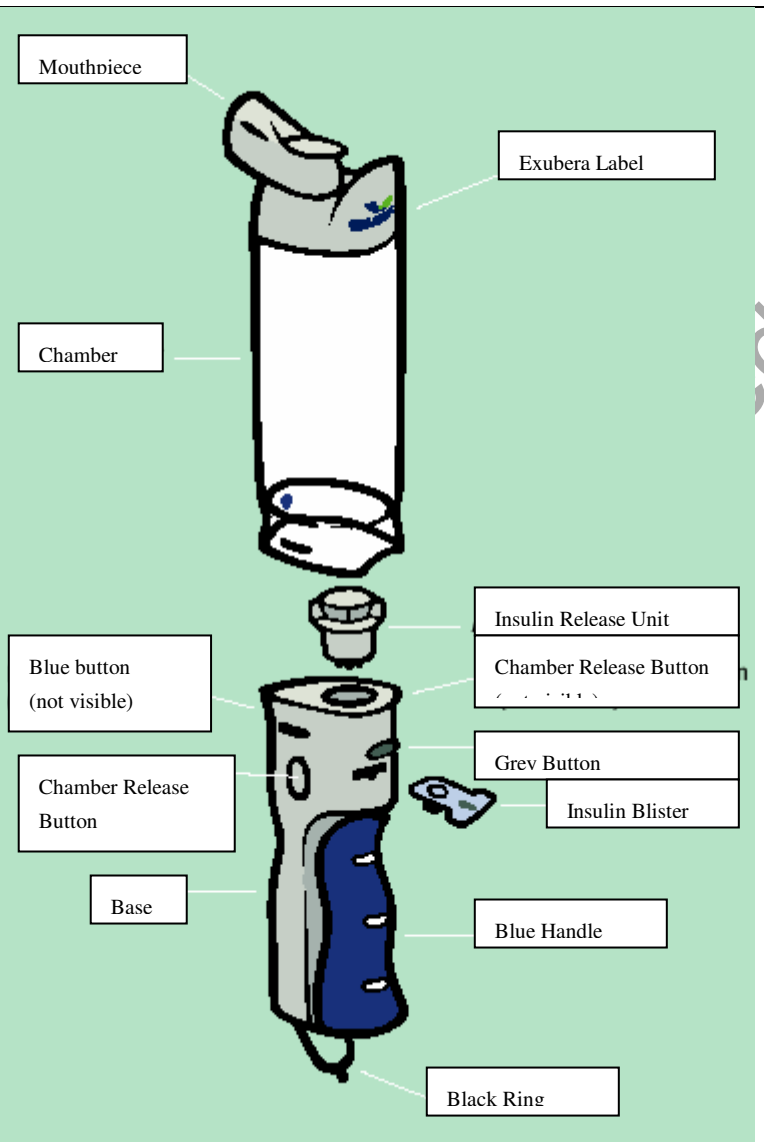
HOW TO STORE YOUR INSULIN INHALER

Keep out of the reach and sight of children.
Store the insulin inhaler in a dry place at room temperature.

Do not store the insulin inhaler in the refrigerator or freezer.

Medicinal product no longer authorised

KNOW THE PARTS OF YOUR INSULIN INHALER



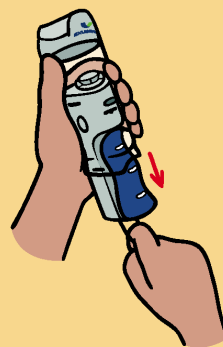
HOW TO TAKE YOUR DOSE

1. Set up your insulin inhaler

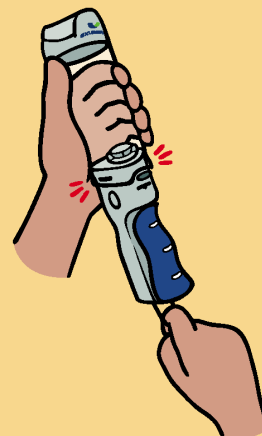
Hold your insulin inhaler in your hand. Be sure that the word "EXUBERA" at the top faces you.



Hold the black ring at the bottom of the base and use it to pull the base out of the chamber.



You will hear a click when the inhaler is fully extended and locked into place. The bottom of the chamber MUST be above the grey button.



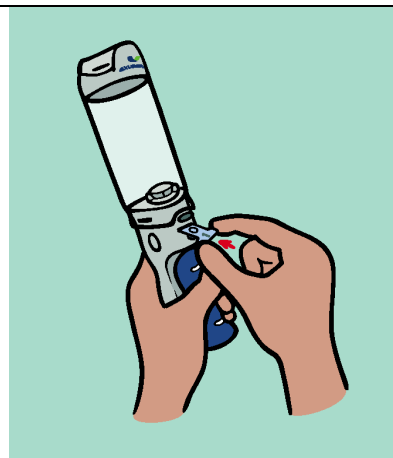
2. Load your insulin blister

Hold the insulin blister by the tab with printed side up with the notch pointed towards the insulin inhaler, insert the blister.

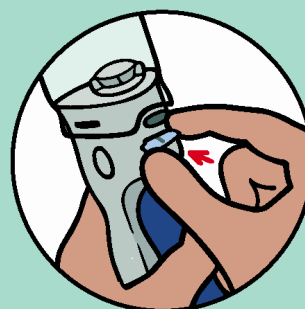
The 1 mg blister is printed with green ink and has one raised dot on the protruding end of each blister.

The 3 mg blister is printed with blue ink and has three raised dots on the protruding end of each blister.

The raised dots can be felt even when the blister is already inserted for reassurance that the correct dose is used.

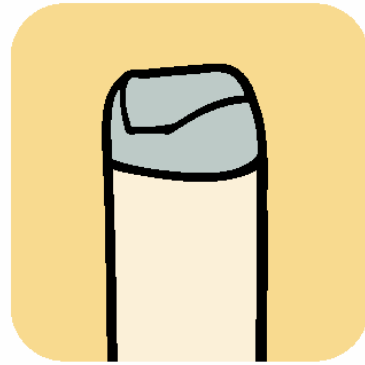


Slide the insulin blister straight into the blister slot as far as it will go.

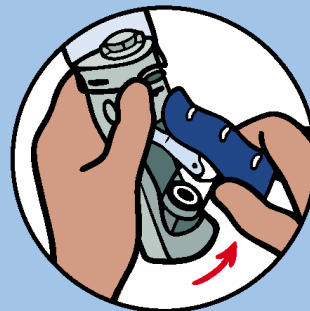


3. Getting ready to take your dose

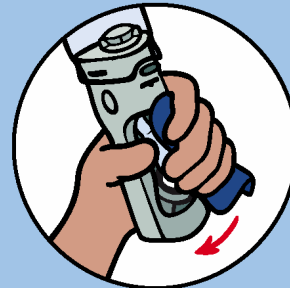
Make sure that the mouthpiece is closed.



Pull out the blue handle as far as it will go.



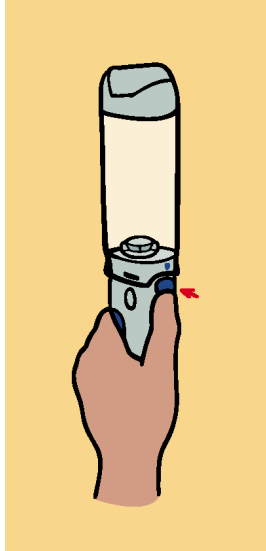
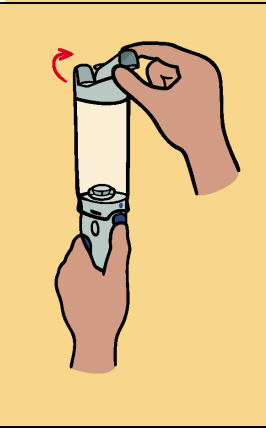
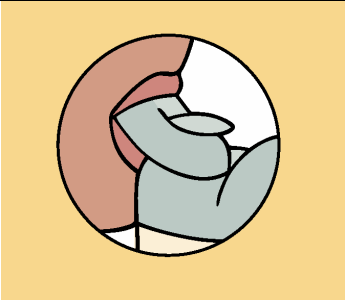
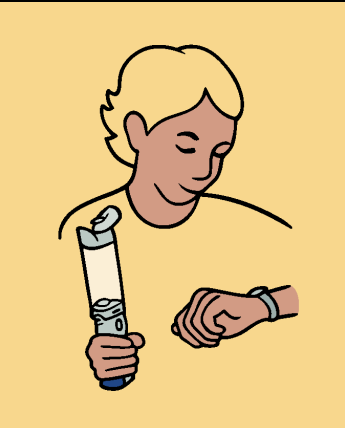
Squeeze the handle until it snaps shut.

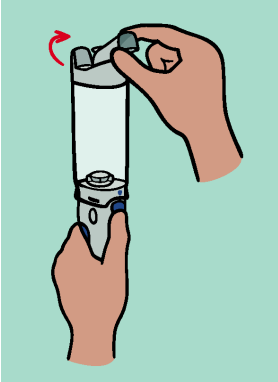

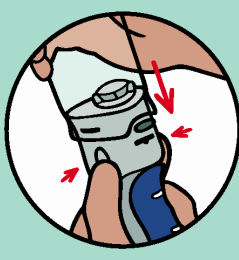



Stand or sit up straight.

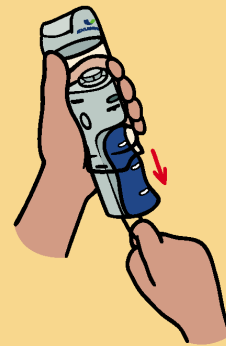
Breathe out normally.



<p>4. Inhale your insulin dose</p> <p>Perform the following steps in immediate sequence.</p> <p>Hold the insulin inhaler upright with the blue button facing towards you. Push the blue button until it clicks and watch for the insulin cloud to appear in the chamber.</p>	
<p>After the cloud appears, immediately turn the mouthpiece around. The mouthpiece should now be facing towards you.</p>	
<p>Quickly form a seal with your lips around the mouthpiece so the insulin will not leak out.</p> <p>Do not block the opening of the mouthpiece with your tongue or teeth. Do not blow into the mouthpiece.</p> <p>Slowly and deeply breathe in the insulin cloud through your mouth in one breath.</p>	
<p>Do not blow into the mouthpiece.</p> <p>Take the mouthpiece out of your mouth.</p> <p>Close your mouth and hold your breath for 5 seconds.</p> <p>Breathe out normally.</p>	

<p>5. After your dose</p> <p>Turn the mouthpiece back to its closed position.</p>	
<p>Press the grey button and pull out the insulin blister.</p> <p>If you need another blister(s) as part of your dose, repeat steps 2, 3 and 4.</p>	
<p>6. After your dosing is completed</p> <p>Squeeze the two chamber release buttons at the same time on the side of the base. Push the base back into the chamber to store.</p>	
<p>HOW TO TAKE CARE OF YOUR INSULIN INHALER</p>	
<p>It is important to follow these steps so that your insulin inhaler stays clean and works properly.</p>	
<p>Take your insulin inhaler apart</p>	
<p>Hold the insulin inhaler in your hand. Be sure that the word “EXUBERA” at the top faces you.</p>	

Hold the black ring at the bottom of the base and use it to pull the base out of the chamber.

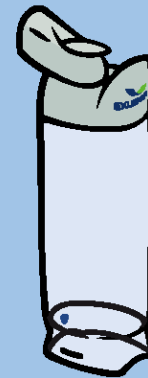


With one hand, squeeze the two chamber release Buttons at the same time on the side of the base while pulling the base all the way out of the chamber with the other hand.



Cleaning

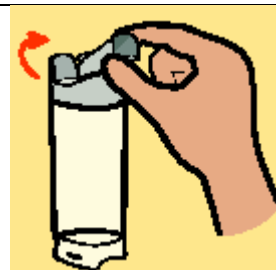
Chamber and mouthpiece – once a week

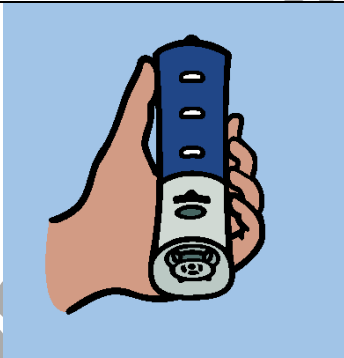


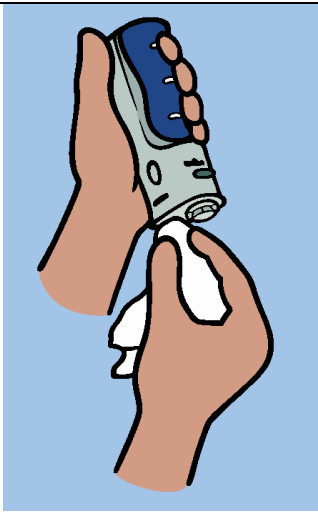
How



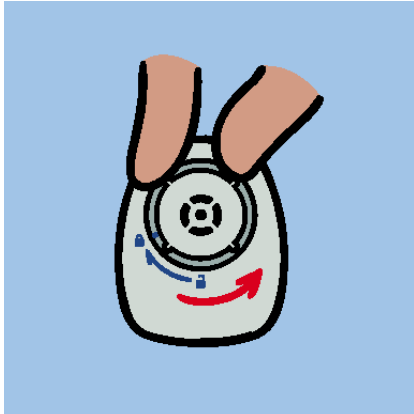
Take your insulin inhaler apart.


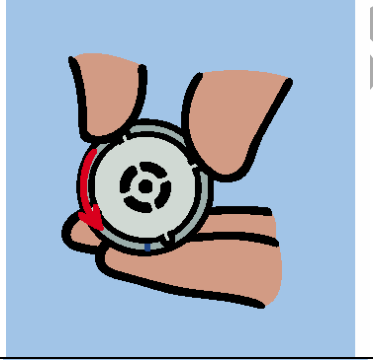
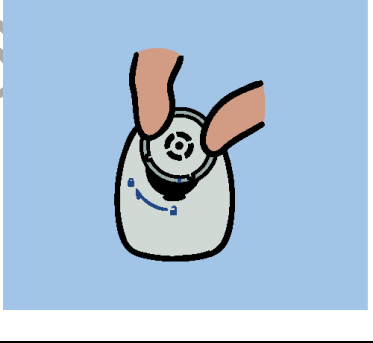
Turn the mouthpiece to the open position. See above.



Dampen a clean soft cloth and use mild liquid soap to wipe the outside and inside of the chamber and mouthpiece. Do NOT put the chamber in the dishwasher.	
Thoroughly rinse the soap out of the chamber and mouthpiece with warm water.	
Allow to air dry. Ensure that no water droplets remain, and then close the mouthpiece. Reattach the chamber to the base.	
For instructions on how to attach the chamber to the base refer to the section “Put your insulin inhaler together”.	
If the washed chamber is not dry prior to taking your next dose, use your spare chamber.	
Base - once a week	

How	
<p>Do not put the base in water.</p> <p>Do not get the inside of the IRU wet.</p> <p>Do not use soap or any other cleanser.</p> <p>Dampen a clean soft cloth with water.</p> <p>While cleaning the top of the base be careful not to get any water into the IRU. Do not take the IRU out at this time. Keep the blue handle closed</p> <p>Wipe only the TOP and OUTSIDE surfaces of the Base. Do not wipe the blister slot</p>	

<p>Put your insulin inhaler together</p> <p>Line the top of the base with the open end of the chamber. The blue dot on the bottom of the chamber must be on the same side as the blue button.</p> <p>Squeeze the two chamber release buttons at the same time on the side of the base. Push the base back into the chamber to store.</p>	
<p>Store your insulin inhaler in a dry place at room temperature.</p>	
<p>REPLACING YOUR INSULIN RELEASE UNIT (IRU)</p>	
<p>Change the IRU</p> <p>Every 2 weeks</p> <p>You should avoid taking EXUBERA in moist conditions e.g. a bathroom following a steamy shower as this will usually give you a lower insulin dose than you need (see package leaflet on the blisters for advice).</p> <p>If you accidentally expose your inhaler to moist conditions during use, this will usually decrease the dose of insulin you take. In this case you must change the IRU prior to your next inhalation.</p>	
<p>How</p>	
<p><u>Take out the used IRU</u></p> <p>While the chamber is removed from the base (see “Take your insulin inhaler apart”), hold the base in your hand with the grey button facing you. Turn the used IRU about a one-quarter turn counter clockwise towards the unlock symbol.</p>	

<p>Pull the used IRU up and out of the base and discard.</p> <p>Dispose of the used IRU safely according to local requirements or check with your healthcare professional.</p>	
<p><u>Put in a new IRU</u></p> <p>Remove the IRU from its packaging.</p> <p>Hold the new IRU so the top is facing you. You will see a blue line on it. While holding the IRU with one hand, turn the top counter-clockwise as far as it will go.</p>	
<p>Line up the blue line on the top of the IRU with the unlock symbol on the top of the base.</p> <p>Push the IRU gently into the base. Do not force, it should easily drop into place. (If the new IRU does not drop into place or fits tightly, remove and try again).</p>	
<p>Turn the top of the IRU clockwise until the blue line points to the lock symbol on the top of the base. The new IRU is now locked in place.</p>	