

## **Evaluation of the therapeutic benefits and harms of inhaled insulins: Inhaled insulin (Exubera) – Rapid report**

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Exubera® is the first inhaled insulin approved for diabetes treatment. The product consists of a special preparation of insulin (dry powder based on human insulin) and a special device for use in inhalation. Treatment with Exubera® has only been approved for adults, not children or adolescents.

The pharmacokinetics and pharmacodynamics of Exubera® are similar to those found with short-acting subcutaneous human insulin or insulin analogues. The duration of action is about the same as that of short-acting human insulin. The time to onset of action is about the same as with short-acting insulin analogues (also referred to as rapid-acting insulin analogues). It is thus possible to use Exubera® as a substitute for short-acting human insulin or a short-acting insulin analogue.

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.” (Summary of Product Characteristics). There are no available studies in which Exubera® is compared with subcutaneous short-acting human insulin or short-acting insulin analogues in patients with type 2 diabetes, within an identical therapeutic regime (e.g. intensified insulin therapy).

Potential risks - including pulmonary risks - linked to long-term use cannot be excluded. The published data do not provide any basis for the conclusion that Exubera® is a safe alternative to subcutaneous insulin for patients with type 2 diabetes.

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.” (Summary of Product Characteristics). There are two available studies in which Exubera® was compared with subcutaneous short-acting human insulin, within an identical therapeutic regime (intensified insulin therapy). Although the efficacy (based on reductions in blood sugar) was comparable, the incidence of severe hypoglycaemia was greater with Exubera® than with human insulin. From this point of view and according to current knowledge, Exubera® is not a safe alternative to subcutaneous insulin for patients with type 1 diabetes mellitus. There are no reliable comparative studies available with short-acting insulin analogues.

In the available intervention studies to compare Exubera® with subcutaneous insulin, it appears that most of the patients did not administer the subcutaneous insulin with pens, but used syringes to take up the insulin, to mix it and then to administer it. This type of treatment is only of secondary importance in Germany. Studies of this sort therefore cannot be used as a basis for statements about the satisfaction with the therapy, the convenience of the therapy or the quality of life for patients in Germany.

Although it is possible to reduce the number of subcutaneous injections with Exubera®, they cannot be totally avoided, if the additional administration of basal insulin is necessary. Moreover, self-measurement

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of blood sugar is still necessary if inhaled insulin is used. This qualifies the potential advantage of Exubera® for patients who do not want to perform insulin therapy, because of an “aversion to injections”.

The patients were specifically trained in the use of Exubera®. In addition, at least in some studies, not only printed material, but also videos and oral instruction were employed. The exact manner and intensity of the training is unclear. It is not clear whether training programmes will be used during the market launch which have been demonstrated to be suitable for guaranteeing the safe use of Exubera® and of fulfilling the specific requirements of the European registration agency.

The incidence of severe hypoglycaemia is increased with Exubera®, presumably particularly during the early morning. This was also found in studies in which the type and quantity of basal insulin were comparable in the treatment groups (Exubera® on the one hand and normal insulin on the other). The reason for this is unclear, although the formation of insulin antibodies was increased under Exubera®. On the basis of currently available information, the possibility cannot be excluded that this is the cause of the increased incidence of nocturnal hypoglycaemia with Exubera®, which is sometimes severe.

Exubera® can have a negative effect on pulmonary function. The relevance of these findings for the long-term use of Exubera® is unclear. There has been no demonstration of safety for patients with lung diseases. Exubera® is contraindicated for patients with severe bronchial asthma and severe chronic obstructive lung disease.

Treatment with Exubera® is contraindicated for smokers. Exubera® is also contraindicated for ex-smokers who have smoked within the preceding 6 months. Smoking modifies the pharmacokinetics of Exubera®, not only chronically, but also acutely, so that there is the danger of severe hypoglycaemia if the patients starts or resumes smoking.

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