International Conference "ADVANCES IN PNEUMOLOGY"
Poznań, 6 – 7 June, 2008

INHALED INSULIN – DOES IT BECOME REALITY?

G. Scheuch[1] and R. Siekmeier[2]

[1]Activaero GmbH, Gemünden, Germany; [2]Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany

After more than 80 years of history the American and European Drug Agencies (FDA and the EMEA) approved the first inhalable version of insulin (Exubera®) from Pfizer/Nektar early 2006. Marketing activities started in September 2006. In October 2007, Pfizer announced it would be dropping Exubera®, citing that the drug had failed to gain market acceptance. Since 1924 various attempts have been made to get away from injected insulin. Three alternative delivery methods where always discussed: Delivery to the upper nasal airways or the deep lungs and through the stomach. The delivery of an insulin pill through the stomach has many hurdles to overcome and will not discussed here. Delivery of insulin to the small area of the upper nasal airways suffers from poor transport across the nasal membranes and dosing issues. And even a mild cold could easily change the intended insulin dose. Furthermore, over 100 I.U. of insulin must be deposited into the nose to deliver 10 I.U. into the blood. The delivery of insulin through the deep lungs has access to a large surface area and the absorption into the blood happens through the extremely thin alveolar membrane. This approach seems to be the most promising. However, there is concern about the long-term effects of inhaling a growth protein into the lungs. It was assumed that the large surface area over which the insulin is spread out would minimize negative effects. But recent news indicates that, at least in smokers, the bronchial tumor rate under inhaled insulin is increased.

Several companies worked on providing inhalable insulin. The most advanced technology was Exubera® consisting of an insulin powder aerosol and a special inhalation device. Treatment has only been approved for adults aged over 18 years. It was a short-acting powder form of insulin that was inhaled before each meal. A long-acting insulin was still needed to be given each day by injection for type 1 and some type 2 diabetics. The Exubera® inhaler was about the size of a 200 ml water glass when closed. It opened to about twice the size for delivery. The lack of discreet delivery was another issue repeatedly brought up by detractors of the device.

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. It is thus possible to use Exubera® as a substitute for short-acting human insulin or insulin analogues.

Similar to other inhaled insulins, a number of side effects (coughing, shortness of breath, sore throat and dry mouth) were reported. Exubera® was not approved for smokers or anyone who has smoked in the last six months because almost twice as much of the inhaled insulin can enter the bloodstream and increase the possibility of an overdose. It was also not approved for anyone with a lung disorder (e. g. asthma, emphysema, COPD). Exercise also increases transport and likelihood of hypoglykemia.

Another major problem with Exubera® was the inability to deliver precise insulin doses. The smallest blister pack available contains the equivalent of 3 I.U. of regular insulin. This dose would make it difficult for many people using insulin to achieve accurate control which is the real goal of any insulin therapy. Someone on 60 I.U. of insulin per day would lower the blood glucose about 90 mg/dl (5 mmol) per 3 I.U. pack, while someone on 30 I.U. a day would drop 180 mg/dl (10 mmol) per pack. Precise control was not possible, especially compared to an insulin pump that can deliver one twentieth of a unit with precision.

Because of the low acceptance Exubera® was dropped from the market. To our information also the other companies (Eli Lilly in cooperation with ALKERMES, Mannkind (Technosphere, Powder),

Novo Nordisk (AERx, Liquid), Andaris (Powder)) stopped further development and it is unclear whether an inhaled form of insulin will ever be marketed.