



Therapeutic Class ReviewSM

Diabetes - insulin human inhalation powder (Exubera[®])

September 2006

New Product for Review:

Insulin human inhalation (Exubera[®])

Dossier Provided by Manufacturer: Yes

Dossier Evaluation: 3

- 1- dossier w/missing components
- 2- all components present, except pharmacoeconomic model
- 3- all components present (comprehensive)

Executive Summary

- Insulin human inhalation (Exubera) is the first inhaled insulin delivery system to be approved by the FDA.
 - The insulin is delivered by oral route as an aerosolized powder delivered by a proprietary inhaler. The insulin powder is packaged in 1mg and 3mg foil blisters.
 - Pharmacodynamic properties are similar to the rapid-acting insulins.
- Insulin human inhalation (Exubera) will be initially marketed for type 2 diabetes patients who have failed one or two oral agents. This marketing focus is likely to compete with the market niche currently occupied by thiazolidinediones (Actos, Avandia).
- The FDA allowed all of the Exubera clinical trials to be of an open-label design. While the reasons for allowing this trial design were likely valid, they do not diminish the uncertainty that an open-label design introduces in the results of these trials.
- The FDA clinical review:
 - Concluded that insulin human inhalation (Exubera) appears to be effective in control of hyperglycemia in type 2 diabetes (alone and in combination with oral agents or in combination with a longer acting SC insulin).
 - Expressed concerns regarding the efficacy of insulin human inhalation (Exubera) for
 - Adult type 1 diabetics.
 - Type 1 diabetic children and adolescents (an off-label use).
- The most significant safety concern with insulin human inhalation (Exubera) (relative to other insulin products) are pulmonary side effects.
 - A greater decline in lung function was observed with insulin human inhalation (Exubera) than other insulin products over a 2 year period.

- This effect appeared to be reversible in type 2 patients, but the data was indeterminate for type 1 patients.
- As such, longer-term safety trials (planned 8 year duration) are underway at the request of the FDA.
- Other issues/considerations regarding insulin human inhalation (Exubera):
 - Contraindicated in patients who smoke or who have unstable or poorly controlled lung disease.
 - Ongoing pulmonary function assessments are recommended at time of therapy initiation and six months, then annually thereafter.
 - Three 1mg blisters are not equal to one 3mg blister. This is another potential safety concern.
 - Acceptance of the inhaler device by the general diabetic population is unknown.
 - Activation of the device requires some degree of manual dexterity and strength.
 - Routine cleaning and maintenance is required for proper function.
 - The inhaler device is larger and heavier than a standard MDI (6 inches long retracted, 11 inches long extended).

Decision

- Insulin human inhalation (Exubera) is non-preferred/non-formulary status of because there is (are):
 - No useful evidence for improved efficacy over existing formulary agents at this time. Long term practice experience is needed to help define the role and value of insulin human inhalation (Exubera) in the management of diabetes.
 - Unresolved issues concerning pulmonary safety.
 - Unknown patient acceptance or improved compliance in an uncontrolled setting.
 - Unknown clinical benefits and risks (safety, proper use of device) in a uncontrolled setting
 - Higher cost relative to other formulary agents.

Products

Drug Product ^{1,2}	Date of FDA Approval ²	FDA Approved Indication(s)	Dose/Route	Potential Off-Label Use(s)
INSULIN				
regular human insulin: (Humulin® R)	10/1982	Diabetes mellitus – Type 1, Type 2, gestational, pregnancy, diabetic ketoacidosis, hyperglycemic-hyperosmolar nonketotic coma	Individualized per patient's needs.	- Diabetic ketoacidosis - Hyperglycemic-hyperosmolar nonketotic coma
regular human insulin: (Novolin® R)	06/1991	Diabetes mellitus – Type I, Type 2, gestational, pregnancy, diabetic ketoacidosis, hyperglycemic-hyperosmolar nonketotic coma	Individualized per patient's needs.	- Diabetic ketoacidosis - Hyperglycemic-hyperosmolar nonketotic coma
insulin aspart: (Novolog®)	06/2000	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	
insulin lispro: (Humalog®)	06/1996	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	
insulin glulisine (Apidra®)	04/2004	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	

insulin human inhalation (Exubera®)	01/2006	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs, but typically 12mg – 18mg / day.	Pediatric DM
isophane (NPH): (Humulin® N)	10/1982	Diabetes mellitus – Type 1, Type 2, gestational, pregnancy, diabetic ketoacidosis, hyperglycemic-hyperosmolar nonketotic coma	Individualized per patient's needs.	- Hyperkalemia - Diabetic neuropathy - Diabetic macrovascular disease - Latent autoimmune diabetes in adults - Myocardial infarction
isophane (NPH): (Novolin® N)	07/1991	Diabetes mellitus – Type 1, Type 2, gestational, pregnancy, diabetic ketoacidosis, hyperglycemic-hyperosmolar nonketotic coma	Individualized per patient's needs.	- Hyperkalemia - Diabetic neuropathy - Diabetic macrovascular disease - Latent autoimmune diabetes in adults - Myocardial infarction
detemir : (Levemir®) ³	6/2005	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	
glargine: (Lantus®)	04/2000	Diabetes mellitus Type 1 in adults and pediatric 6 yrs and older, Type 2 in adults	Individualized per patient's needs.	
lispro 75/25: (Humalog® Mix)	12/1999	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	
aspart 70/30: (NovoLog® Mix)	11/2001	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	
OTHER ANTI-DIABETIC AGENTS				
Glipizide (generic)	05/1984	Diabetes mellitus, Type II (Used alone or in combination)	5 - 40mg orally daily	Diabetic microangiopathy; Gestational diabetes
Glipizide and Metformin HCl (Metaglip®)	10/2002	Diabetes mellitus, Type II	<u>Monotherapy:</u> 2.5 mg/250 mg daily up to 10 mg/2000 mg per day in divided doses <u>Combination therapy:</u> 2.5 mg/500 mg or 5mg/500mg BID; max. 20 mg/2000 mg daily	
Glyburide (generic)	05/1984	Diabetes mellitus, Type II (Used alone or in combination)	2.5 - 5 mg daily	Gestational diabetes
Glyburide and Metformin HCl (Glucovance®)	07/2000	Diabetes mellitus, Type II	1.25 mg/250 mg orally once or twice daily <u>Previously treated:</u> 2.5 mg/500 mg to 5 mg/500 mg orally twice daily; max. 20 mg/2000 mg once daily	
Metformin (generic)	03/1995	Diabetes mellitus, Type II (Used alone or in combination)	500 mg orally twice daily or 850 mg once daily	
Pioglitazone (Actos®)	07/1999	Diabetes mellitus, Type II (Used alone or in combination)	<u>Monotherapy:</u> 15-30 mg orally once daily; max. 45 mg daily <u>Combination therapy:</u> max. 30 mg orally daily	

Drug Product ^{1,2}	Date of FDA Approval ²	FDA Approved Indication(s)	Dose/Route	Potential Off-Label Use(s)
INSULIN				
OTHER ANTI-DIABETIC AGENTS				
Rosiglitazone maleate (Avandia [®])	05/1999	Diabetes mellitus, Type II Diabetes mellitus, Type II in combination with insulin, metformin, or sulfonylurea. (Used alone or in combination)	<u>Monotherapy</u> : 4 mg once daily or 2mg twice daily; max. 8 mg daily <u>Concomitant with insulin</u> : 4 mg orally daily; max. 4 mg/day <u>Concomitant with metformin or sulfonylureas</u> : 4 mg orally once daily or 2 mg twice daily	
Rosiglitazone maleate and Metformin HCl (Avandamet [®])	10/2002	Diabetes mellitus, type 2 (NIDDM) (not to be given as initial therapy).	2mg/500mg – 4mg/1000mg orally twice daily	
pramlintide acetate (Symlin [®])	03/2005	Diabetes mellitus, Type I and Type II In adjunct to insulin therapy.	Type I Diabetes: 15 - 60 mcg. Type II Diabetes: 60 - 120mcg	Weight loss
Exenatide (Byetta [®])	04/2005	Diabetes mellitus, Type II patients with inadequate glycemic control on metformin, sulfonylurea, combination of metformin + sulfonylurea. (Used as adjunctive therapy only)	5 - 10mcg SQ twice daily	Weight loss

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