

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Insulin human [rDNA origin] Inhalation Powder (Exubera®)
9/2006

Overview

Exubera is a rapid-acting inhaled insulin with an onset of action similar to rapid acting injectable insulin and a duration similar to regular injectable insulin. It should be given within 10 minutes before a meal. Exubera is stable at room temperature (59-86 degrees F). It is FDA approved for use in adult patients with diabetes mellitus for the control of hyperglycemia. Exubera is used in combination with longer-acting insulins in patients with Type 1 diabetes. In patients with Type 2 diabetes Exubera may be used as monotherapy or in combination with oral agents or longer-acting insulins. The initial dose is based on patient weight and may require one or more inhalations per dose. It is currently supplied in 1 mg and 3 mg blister packs which are equivalent to approximately 3 units and 8 units of injectable insulin respectively. Approximately 40% of the inhaled dose reaches deep lung of which 10% is absorbed. Exubera is contraindicated in smokers or those who have discontinued smoking less than 6 months prior to starting Exubera due to 2-5 fold increase in systemic exposure and hypoglycemia. It is contraindicated in unstable or poorly controlled lung disease because of wide variations in lung function that could affect the absorption of Exubera and increase the risk of hypoglycemia or hyperglycemia. Albuterol inhalation 30 minutes prior to Exubera increases Exubera's AUC by 25%. The use of EXUBERA in patients with underlying lung disease, such as asthma or COPD, is not recommended because the safety and efficacy of EXUBERA in this population have not been established. Patients using Exubera demonstrated a greater decline in pulmonary function [FEV1 and carbon monoxide diffusion capacity (DLco)] than comparator-treatment. The mean treatment group differences were noted within the first several weeks of treatment and did not progress over the two year treatment period. These effects appear reversible within 6 weeks of drug discontinuation. All patients should have pulmonary function assessed (FEV1) prior to initiating therapy, at six months, and annually thereafter. If a decline of greater than 20% is noted on two occasions the drug should be stopped. The most common adverse drug reaction is hypoglycemia. The incidence of hypoglycemia with Exubera monotherapy or combined with oral agents (secretagogue and sensitizer) in type 2 diabetes is multiple times higher than oral agents alone (risk ratio 24-32). The overall incidence of hypoglycemia of Exubera added to ultralente or NPH is comparable to NPH plus regular insulin in type I and II diabetes, but there are more severe hypoglycemic events in the inhaled groups. Exubera ADRs that were more common than the comparators include: chest pain (4.7% vrs 3.2%), dry mouth (2.4 vrs 0.8%) cough (20%-30% vrs 9-10%, with a 1.2% discontinuation rate), sputum increase (3%-4% vrs 1%) , and epistaxis (1.3% vrs 0.4%). Exubera causes higher rates of insulin antibody production than injectable insulin. The antibodies have not been shown to be of clinical significance. Exubera is 10 times more expensive than an equivalent dose of Novolin (regular human insulin) and 2.5 times as expensive as an equivalent dose of Novolog (rapid acting insulin).

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Recommendations

- Exubera is not recommended for addition to formulary
 - It is FDA approved for use in adult patients with diabetes mellitus for the control of hyperglycemia.
 - Exubera is used in combination with longer-acting insulins in patients with Type 1 diabetes.
 - In patients with Type 2 diabetes Exubera may be used as monotherapy or in combination with oral agents or longer-acting insulins.
- Patients using Exubera at home may continue to use their own supply in the hospital if they are capable of self administration.
- Patients using Exubera at home who can not self administer will be converted to an equivalent dose of regular insulin at the same dosage frequency. (see chart below)
 - Exubera is supplied in a kit and combination packs that contain approximately a month's supply of insulin blisters for inhalation, inhaler device, and release units. (see chart below).
 - The United Kingdom did not add Exubera to the national formulary.
 - Approximately 40% of the inhaled dose reaches deep lung of which 10% is absorbed.
 - All patients should have pulmonary function assessed (FEV1) prior to initiating therapy, at six months, and annually thereafter. If a decline of greater than 20% is noted on two occasions the drug should be stopped.
 - Exubera is contraindicated in current smokers or those who have quit smoking in the last 6 months, unstable or poorly controlled asthma, COPD, and emphysema.
 - Blood glucose monitoring is recommended three or more times per day.
 - The force necessary to compress the inhaler's pump is substantial. Patients with low grip strength will be unable compress the pump.
 - Clinical trials in type I diabetes have shown no significant difference in decrease in HbA1c, % of patients achieving HbA1c < 7%, weight gain, or hypoglycemia rates.
 - Exubera TID plus ultralente at HS versus NPH AM/(Dinner or HS) plus regular insulin before each meal
 - Exubera TID plus NPH BID versus regular insulin (TID) plus NPH BID
 - Clinical trial in type II diabetes
 - Pre-meal Exubera versus rosiglitazone 4 mg twice daily in patients suboptimally controlled with diet and exercise (HbA1c 8-11%)
 - Absolute reduction in HbA1c in inhaled insulin 2.3% versus 1.4% for rosiglitazone (SS)
 - Hypoglycemia (episodes/patient/month) were higher with Exubera , 0.7 versus 0.05 (SS)
 - Oral therapy (secretagogue plus a sensitizer) plus Exubera versus oral therapy (secretagogue plus a sensitizer) versus Exubera only in patients who had failed oral therapy

	Oral Therapy (secretagogue plus sensitizer) Plus Exubera N=100	Exubera Alone N=102	Oral Therapy Alone (secretagogue plus sensitizer) N=96
Average Daily Dose Exubera	12 mg	23 mg	
HbA1c Reduction	1.9%*	1.4%*	0.2%
Hypoglycemia Rate Episodes/patient/month	1.7	1.3	0.1
Weight Gain (kg)	2.75	2.8	0

* Statistically significant versus oral agents

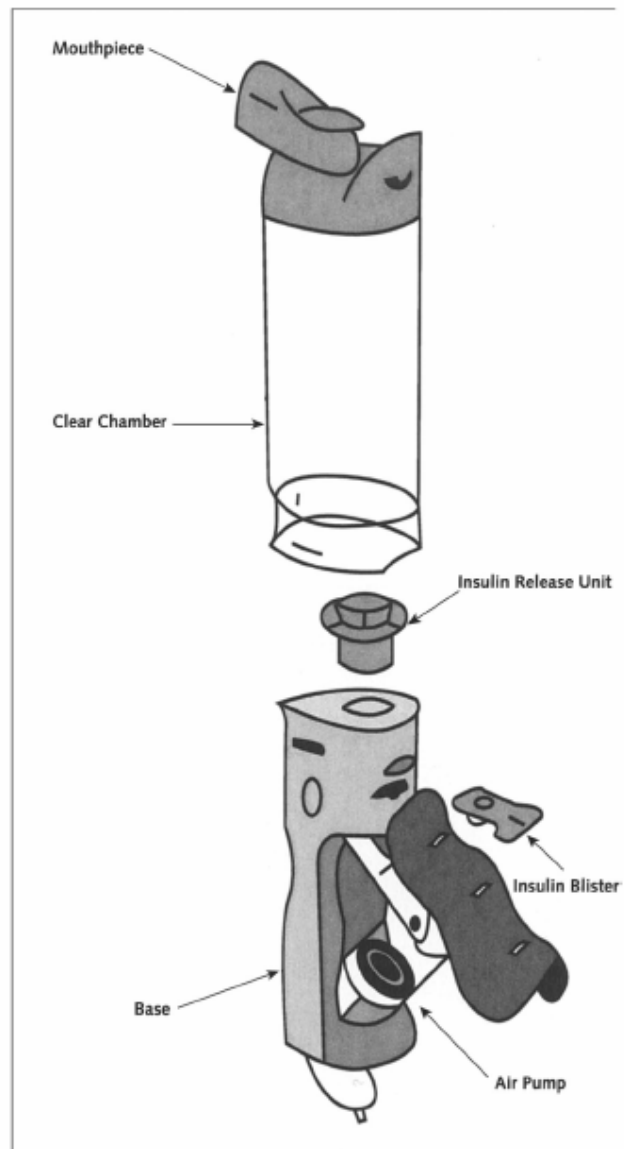
- Exubera (TID) plus ultralente HS versus NPH (twice daily) plus regular (twice daily)
 - No significant difference in HbA1c, HbA1c < 7%, or post-prandial plasma glucose
 - Lower rise of hypoglycemia for Exubera 1.4 very 1.57 episodes/patient/month (SS)
- Clinical trials have not compared Exubera to rapid acting insulins
- Exubera is 10 times more expensive than an equivalent dose of Novolin (regular human insulin) and 2.5 times as expensive as an equivalent dose of Novolog (rapid acting insulin).

	Cost for Equivalent Insulin Units per Day		
	Equivalent Insulin Units	Novolin \$10.98 per Vial	Novolog \$43.99 per Vial
Exubera kit \$141.24 Exubera inhaler x 1 Exubera chamber x 1 Exubera release unit x 2 1 mg x 180 blisters 3 mg x 90 blisters	1260 Units	\$13.84	\$55.43
Exubera combination pack 12 \$105.46 12 mg per day (4 mg before each meal) Equivalent to 11 units of insulin per dose 1 month supply for 177-220 lb patient 1 mg x 90 blisters 3 mg x 90 blisters Release Units x 2	990 Units	\$10.87	\$43.55
Exubera combination pack 15 \$131.82 15 mg per day (5 mg before each meal) Equivalent to 14 units of insulin per dose 1 month supply for 221-264 lb patient 1 mg x 180 blisters 3 mg x 90 blisters Release Units x 2	1260 Units	\$13.84	\$55.43
	Accessories Cost		
Exubera release unit 2-pack	\$4.86		
Exubera Chamber	\$14.57		

Dosage Conversion Chart	
Exubera	Regular Insulin Equivalent Dose
Inhaled Dose (mg)	Units
1	3
2	6
3	8
4	11
5	14
6	16
7	19

Note: One 3 mg insulin blister is not equivalent to three 1 mg blisters.
The insulin AUC is 40% higher when three 1 mg blisters are administered.

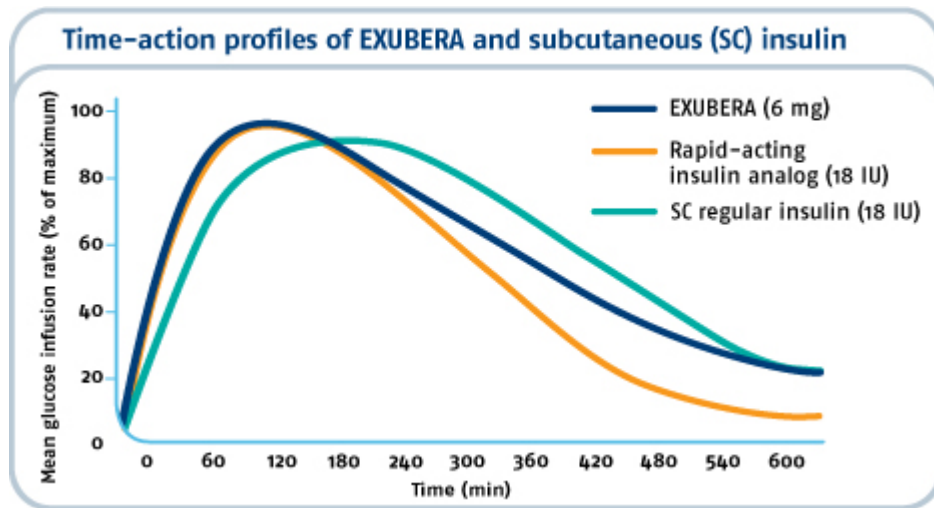
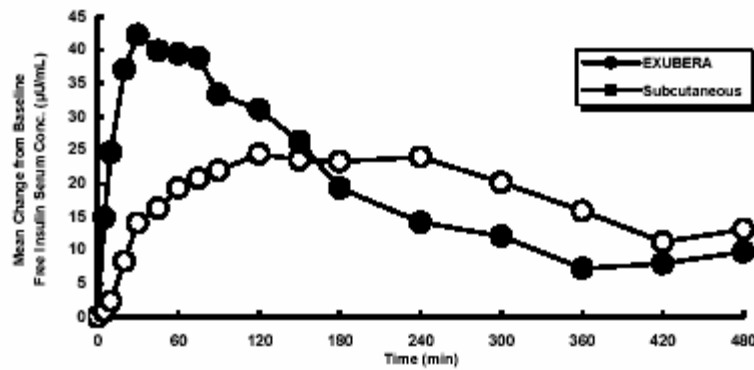
Figure 1. The inhaled insulin delivery system.



The pulmonary inhaler consists of a reusable dry powder inhaler and unit-dose blisters containing insulin powder for inhalation. The system is designed to deliver the aerosolized powder to the small airways and alveoli to enable systemic insulin absorption. The pulmonary inhaler is solely mechanical, using no batteries or electronics, and requires only modest effort by the patient to operate. The chamber is transparent to allow the patient to see the insulin cloud after powder aerosolization. The inhaler measures approximately 16.5 cm in length when in the closed position and approximately 27.5 cm when in use (fully extended). The weight is approximately 6 oz (170 g). On the basis of experience from the clinical trial program, replacement of the insulin release unit is required every 2 weeks.

Device weighs approximately 4 ounces and is 4 x 1.5 inches when closed.

Cleaning: Clean base, chamber and mouthpiece with soap and water. Do not use dishwasher, do not put the base in water.



Pharmacokinetics

- Exubera is absorbed as quickly as subcutaneously administered rapid-acting insulin analogs and more quickly than subcutaneously administered regular human insulin. The duration of action is similar to regular insulin.
- Approximately 40% of the inhaled dose reaches deep lung of which 10% is absorbed.
- Onset of glucose-lowering activity occurs within 10-20 minutes.
- Maximum effect approximately 2 hours after inhalation.
- Duration of action is ~ 6 hours.
- EXUBERA has a greater glucose-lowering effect within the first two hours after dosing compared to subcutaneously administered regular human insulin. The intra-subject variability of glucose-lowering activity of EXUBERA is generally comparable to that of subcutaneous regular human insulin
- Three one mg blisters are not equivalent to one three mg blister (AUC is 40% higher for 3 one mg blisters)
- Absorption is independent of patient BMI

Dosage

- Initial pre-meal doses may be calculated using the following formula:
- [Body weight (kg) X 0.05 mg/kg = pre-meal dose (mg)] rounded down to the nearest whole milligram number (e.g., 3.7 mg rounded down to 3 mg).
- Exubera should be given within 10 minutes before a meal.
- 1 mg blister (45% retained in blister after inhalation) = 3 IU of SC insulin
- 3 mg blister (25% retained in blister after inhalation) = 8 IU of SC insulin
- Patients should not substitute three 1 mg doses for one 3 mg dose as significant more insulin exposure would occur. If 3 mg blisters are unavailable patient should temporarily substitute two 1 mg blisters for one 3 mg blister.
- 25% (3 mg) -45% (1 mg) of the powder is retained in the blister pack after inhalation

Table 7: Approximate Guidelines for Initial, Pre-Meal EXUBERA Dose (based on patient body weight)

Patient Weight (in kg)	Patient Weight (in lb)	Initial Dose per Meal	Number of 1 mg Blisters per Dose	Number of 3 mg Blisters per Dose
30 to 39.9 kg	66 - 87 lb	1 mg per meal	1	-
40 to 59.9 kg	88 - 132 lb	2 mg per meal	2	-
60 to 79.9 kg	133 - 176 lb	3 mg per meal	-	1
80 to 99.9 kg	177 - 220 lb	4 mg per meal	1	1
100 to 119.9 kg	221- 264 lb	5 mg per meal	2	1
120 to 139.9 kg	265 - 308 lb	6 mg per meal	-	2

Findings:

- Exubera is a rapid-acting inhaled insulin with a onset of action similar to rapid acting injectable insulin and a duration similar to regular injectable insulin.
- It is FDA approved for use in adult patients with diabetes mellitus for the control of hyperglycemia.
 - Exubera is used in combination with longer-acting insulins in patients with Type 1 diabetes.
 - In patients with Type 2 diabetes Exubera may be used as monotherapy or in combination with oral agents or longer-acting insulins.
- It should be given within 10 minutes before a meal. Exubera is stable at room temperature (59-86 degrees F).
- The initial dose is based on patient weight and may require one or more inhalations per dose.
- It is currently supplied in 1 mg and 3 mg blister packs which are equivalent to approximately 3 units and 8 units of injectable insulin respectively.
- Cleaning: Clean base, chamber and mouthpiece with soap and water. Do not use dishwasher, do not put the base in water.
- Replace the release unit every two weeks
- Replace inhaler every year
- Exubera is contraindicated in smokers or those who have discontinued smoking less than 6 months prior to starting Exubera due to 2-5 fold increase in systemic exposure and hypoglycemia.
- It is contraindicated in unstable or poorly controlled lung disease because of wide variations in lung function that could affect the absorption of Exubera and increase the risk of hypoglycemia or hyperglycemia. Albuterol inhalation 30 minutes prior to Exubera increases Exubera's AUC by 25%.
- The use of EXUBERA in patients with underlying lung disease, such as asthma or COPD, is not recommended because the safety and efficacy of EXUBERA in this population have not been established.
- Patients using Exubera demonstrated a greater decline in pulmonary function [FEV1 and carbon monoxide diffusion capacity (DLco)] than comparator-treatment. The mean treatment group differences were noted within the first several weeks of treatment and did not progress over the two year treatment period. These effects appear reversible within 6 weeks of drug discontinuation.
- All patients should have pulmonary function assessed (FEV1) prior to initiating therapy, at six months, and annually thereafter. If a decline of greater than 20% is noted on two occasions the drug should be stopped.
- The most common adverse drug reaction is hypoglycemia.
 - The incidence of hypoglycemia with Exubera monotherapy or combined with oral agents in type 2 diabetes is multiple times higher than oral agents alone (risk ratio 24-32).
 - The overall incidence of hypoglycemia of Exubera added to ultralente or NPH is comparable to NPH plus regular insulin in type I and II diabetes, but there are more severe hypoglycemic events in the inhaled groups.
- Exubera ADRs that were more common than the comparators include: chest pain (4.7% vrs 3.2%), dry mouth (2.4 vrs 0.8%) cough (20%-30% vrs 9-10%, with a 1.2% discontinuation rate), sputum increase (3%-4% vrs 1%) , and epistaxis (1.3% vrs 0.4%).
- Exubera causes insulin antibody levels that are 25 times higher than injectable insulin. The antibodies have not been shown to be of clinical significance.

- Exubera is 10 times more expensive than an equivalent dose of Novolin (regular human insulin) and 2.5 times as expensive as an equivalent dose of Novolog (rapid acting insulin).

Table 2: Results of Two 24-Week, Active-Control, Open-Label Trials in Patients With Type 1 Diabetes (Studies A and B)

	Study A		Study B	
	EXUBERA (TID) + UL (QD)	SC R (BID) + NPH (BID)	EXUBERA (TID) + NPH (BID)	SC R (TID) + NPH (BID)
Sample Size	136	132	103	103
HbA _{1c} (%)				
Baseline mean	7.9	8.0	7.8	7.8
Adj. mean change from baseline	-0.2	-0.4	-0.3	-0.2
EXUBERA minus SC R ¹	0.14		-0.11	
95% CI for treatment difference	(-0.03, 0.32)		(-0.30, 0.08)	
Fasting Plasma Glucose (mg/dL)				
Baseline mean	191	198	178	191
Adj. mean change from baseline	-32	-6	-23	13
EXUBERA minus SC R	-27		-35	
95% CI for treatment difference	(-47, -6)		(-58, -13)	
2-hr Post-Prandial Glucose Concentration (mg/dL)				
Baseline mean	283	305	273	293
Adj. mean change from baseline	-21	14	-1	-3
EXUBERA minus SC R	-35		2	
95% CI for treatment difference	(-61, -8)		(-29, 32)	
Patients with end-of-study HbA _{1c} < 8% ²	64.0%	68.2%	74.8%	66.0%
Patients with end-of-study HbA _{1c} < 7%	16.9%	19.7%	28.2%	30.1%
Body Weight				
Baseline mean (kg)	77.4	76.4	76.0	76.9
Adj. mean change from baseline (kg)	0.4	1.1	0.4	0.6
EXUBERA minus SC R	-0.72		-0.24	
95% CI for treatment difference	(-1.48, 0.04)		(-1.07, 0.59)	
End of study daily insulin dose				
Short-acting insulin	13.4 mg ³	18.3 IU	10.9 mg ³	25.7 IU
Long-acting insulin	26.4 IU	37.1 IU	31.5 IU	31.9 IU

UL = Humulin[®] U Ultralente[®]; SC R = subcutaneous regular human insulin

1. A negative treatment difference favors EXUBERA

In each study the reduction in HbA_{1c}, and the rates of hypoglycemia were comparable per package insert.

Table 3: Results of a 12-Week, Active-Control, Open-Label Trial in Patients With Type 2 Diabetes Not Optimally Controlled With Dual Oral Agent Therapy (Study D)

Study D	EXUBERA monotherapy	OAs ¹	EXUBERA + OAs
Sample Size	102	96	100
HbA _{1c} (%)			
Baseline mean	9.3	9.3	9.2
Adj. mean change from baseline EXUBERA group minus OAs ²	-1.4	-0.2	-1.9
95% CI for treatment difference		-1.18 ^{2,3,5}	-1.67 ^{2,4,5}
		(-1.41, -0.95)	(-1.90, -1.44)
Fasting Plasma Glucose (mg/dL)			
Baseline mean	203	203	195
Adj. mean change from baseline EXUBERA group minus OAs	-23	1	-53
95% CI for treatment difference		-24 ³	-53 ⁴
		(-36, -11)	(-66, -41)
Patients with end-of-study HbA _{1c} < 8% ⁶	55.9%	18.8%	86.0%
Patients with end-of-study HbA _{1c} < 7%	16.7%	1.0%	32.0%
Body Weight			
Baseline mean (kg)	89.5	88.0	88.6
Adj. mean change from baseline (kg) EXUBERA group minus OAs	2.8	0.0	2.7
95% CI for treatment difference		2.80 ³	2.75 ⁴
		(1.94, 3.65)	(1.89, 3.61)

- OAs = treatment with two oral agents (an insulin secretagogue in addition to metformin or a thiazolidinedione)
- A negative treatment difference favors EXUBERA
- Comparison of EXUBERA monotherapy to combination oral agent therapy alone
- Comparison of EXUBERA plus oral agents to combination oral agent therapy alone
- $p < 0.0001$
- American Diabetes Association treatment Action Level at the time of study conduct

Hypoglycemia rates (episodes per participant-month) were: 1.7, 1.3, 0.1 for inhaled insulin plus 2 oral agents, inhaled insulin monotherapy, and 2 oral agents respectively. The risk ratios were 32 for inhaled insulin plus 2 oral agents and 24 for inhaled insulin monotherapy relative to the 2 oral agents group. One severe hypoglycemic episode was reported in the inhaled insulin group.

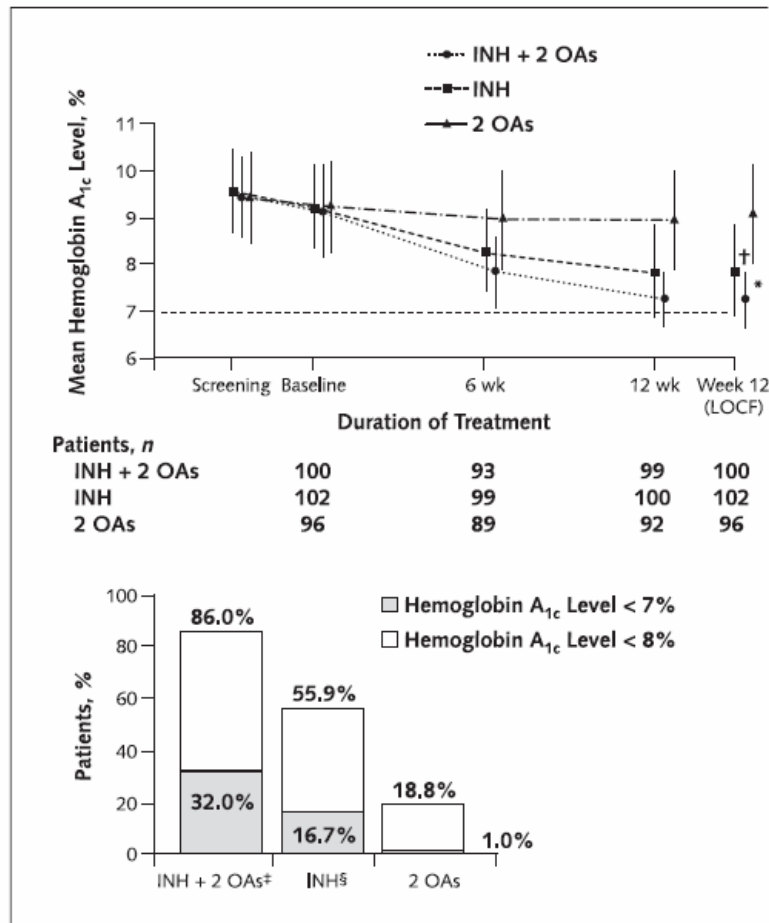
Note: The Exubera monotherapy patients received approximately twice the average daily inhaled insulin as compared to the Exubera plus oral agents (23.7 mg versus 12.2 mg per day).

HgA_{1c} reduction, reduction in fasting glucose, increased hypoglycemia rates and weight gain are statistically significant for Exubera.

Table 3. Treatment-Related Adverse Events Experienced by More than 5% of Patients

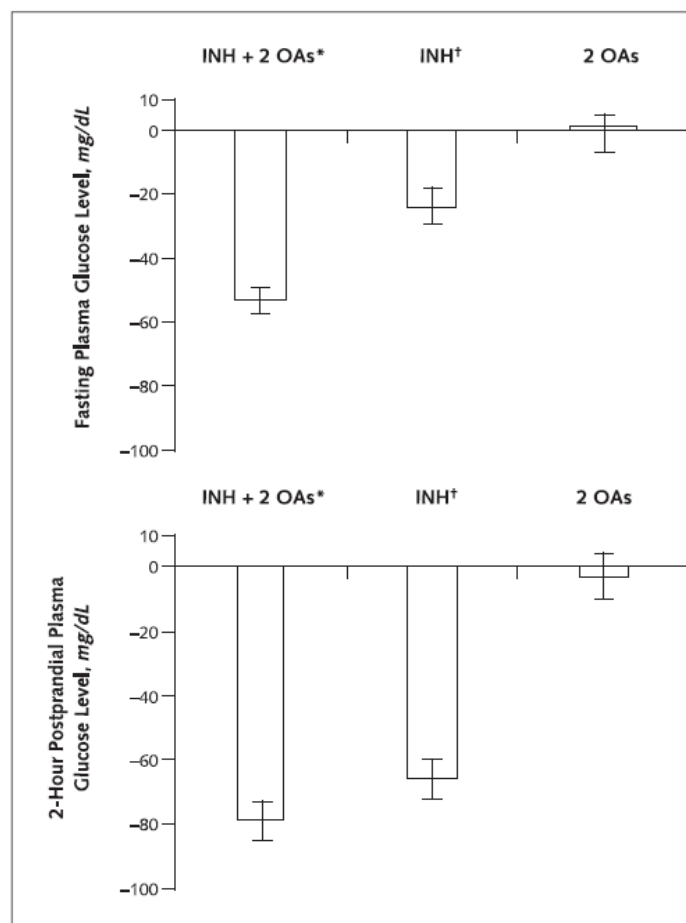
Patients with Adverse Event	Inhaled Insulin plus 2 Oral Agents (n = 103), n (%)	Inhaled Insulin Monotherapy (n = 104), n (%)	2 Oral Agents (n = 99), n (%)
Asthenia	21 (20)	24 (23)	4 (4)
Headache	6 (6)	7 (7)	0 (0)
Hypoglycemia	78 (76)	69 (66)	8 (8)
Total events	477	365	13
Severe events	0	1	0
Dizziness	11 (11)	24 (23)	3 (3)
Nervousness	3 (3)	6 (6)	0 (0)
Tremor	36 (35)	33 (32)	5 (5)
Increased cough	7 (7)	5 (5)	0 (0)
Sweating	18 (18)	21 (20)	3 (3)

Figure 3. Hemoglobin A_{1c} values during 3 months of treatment (top) and patients reaching target hemoglobin A_{1c} level at study end (bottom).



Top. Mean (SD) hemoglobin A_{1c} values during 3 months of treatment with inhaled insulin (INH) plus 2 oral agents (OAs), INH monotherapy, or 2 OAs. *INH plus 2 OAs vs. 2 OAs adjusted difference at week 12 (last observation carried forward [LOCF]), -1.67 percentage points (95% CI, -1.90 to -1.44 percentage points). †INH vs. 2 OAs adjusted difference at week 12 (LOCF), -1.18 percentage points (CI, -1.41 to -0.95 percentage point). Numbers of patients analyzed at each time point by treatment group are shown below the graph. **Bottom.** Percentages of patients reaching target hemoglobin A_{1c} values at study end with INH plus 2 OAs, INH monotherapy, or 2 OAs. ‡INH plus 2 OAs vs. 2 OAs adjusted odds ratio was 40.5 (CI, 17.0 to 96.9) for hemoglobin A_{1c} level < 8% and 44.7 (CI, 6.0 to 335.2) for hemoglobin A_{1c} level < 7%. §INH vs. 2 OAs adjusted odds ratio was 7.5 (CI, 3.6 to 15.5) for hemoglobin A_{1c} level < 8% and 19.0 (CI, 2.5 to 145.8) for hemoglobin A_{1c} level < 7%.

Figure 4. Adjusted mean change in fasting plasma glucose concentration (*top*) and 2-hour postprandial glucose concentration (*bottom*) from baseline to study end after 12 weeks of treatment.



Top. Adjusted mean change in fasting plasma glucose concentration with inhaled insulin (*INH*) plus 2 oral agents (*OAs*), *INH* monotherapy, or 2 *OAs*. *Adjusted difference at week 12, -2.9 mmol/L (-53 mg/dL) (95% CI, -3.7 mmol/L [-66 mg/dL] to -2.3 mmol/L [-41 mg/dL]). †Adjusted difference at week 12, -1.3 mmol/L (-24 mg/dL) (CI, -2.0 mmol/L [-36 mg/dL] to -0.6 mmol/L [-11 mg/dL]). Bottom. Adjusted mean change in 2-hour postprandial glucose concentration from baseline to study end after 12 weeks of treatment with *INH* plus 2 *OAs*, *INH* monotherapy, or 2 *OAs*. *Adjusted difference at week 12, -4.2 mmol/L (-76 mg/dL) (CI, -5.2 mmol/L [-93 mg/dL] to -3.2 mmol/L [-58 mg/dL]). †Adjusted difference at week 12, -3.4 mmol/L (-62 mg/dL) (CI, -4.4 mmol/L [-79 mg/dL] to -2.5 mmol/L [-45 mg/dL]).

Table 4: Results of Two 24-Week, Active-Control, Open-Label Trials in Patients With Type 2 Diabetes Previously On Oral Agent Therapy (Studies E and F)

	Study E				Study F			
	Exubera + SU ¹	Met ¹ + SU ¹	Exubera + SU ¹	Met ¹ + SU ¹	Exubera + Met ¹	Gli ¹ + Met ¹	Exubera + Met ¹	Gli ¹ + Met ¹
	High stratum ²		Low stratum ²		High stratum ²		Low stratum ²	
Sample Size	113	103	101	93	109	103	125	119
HbA _{1c} (%)								
Baseline mean	10.5	10.6	8.8	8.8	10.4	10.6	8.6	8.7
Adj. mean change from baseline	-2.2	-1.8	-1.9	-1.9	-2.2	-1.9	-1.8	-1.9
EXUBERA minus OA ³	-0.38 ^{3,4}		-0.07		-0.37 ^{3,5}		0.04	
95% CI for treatment difference	(-0.63, -0.14)		(-0.33, 0.19)		(-0.62, -0.12)		(-0.19, 0.27)	
Fasting Plasma Glucose (mg/dL)								
Baseline mean	241	237	197	198	223	243	187	196
Mean change from baseline	-46	-47	-48	-52	-42	-40	-46	-49
EXUBERA minus OA	1		4		-2		4	
95% CI for treatment difference	(-11, 12)		(-8, 16)		(-14, 10)		(-7, 15)	
Subjects with end-of-study HbA _{1c} < 8% ⁶	48.7%	44.7%	81.2%	73.1%	72.5%	56.3%	80.8%	86.6%
Subjects with end-of-study HbA _{1c} < 7%	20.4%	14.6%	30.7%	32.3%	33.9%	17.5%	40.0%	42.9%
Body Weight								
Baseline mean (kg)	80.8	79.5	79.9	81.9	88.3	87.8	90.3	88.2
Adj. mean change from baseline (kg)	3.6	-0.0	2.4	-0.3	2.8	2.5	2.0	1.6
EXUBERA minus OA	3.60		2.67		0.26		0.38	
95% CI for treatment difference	(2.81, 4.39)		(1.84, 3.51)		(-0.70, 1.21)		(-0.52, 1.27)	

1. SU = sulfonylurea, Met = metformin, Gli = glibenclamide
2. Low stratum = entry HbA_{1c} ≥8.0% to ≤9.5%; high stratum = entry HbA_{1c} >9.5% to ≤12%
3. A negative treatment difference favors EXUBERA
4. *p* = 0.002
5. *p* = 0.004
6. American Diabetes Association treatment Action Level at the time of study conduct

High stratum groups have a statistically significant decrease in HbA_{1c}.

Table 5: Results of a 24-Week, Active-Control, Open-Label Trial in Patients With Type 2 Diabetes Previously Treated With Subcutaneous Insulin (Study G)

Study G	EXUBERA (TID) + UL (QD)	SC R (BID) + NPH (BID)
Sample Size	146	149
HbA _{1c} (%)		
Baseline mean	8.1	8.2
Adj. mean change from baseline	-0.7	-0.6
EXUBERA minus SC R ¹		-0.07
95% CI for treatment difference		(-0.31, 0.17)
Fasting Plasma Glucose (mg/dL)		
Baseline mean	152	159
Adj. mean change from baseline	-22	-6
EXUBERA minus SC R		-16.36
95% CI for treatment difference		(-27.09, -5.36)
Patients with end-of-study HbA _{1c} < 8% ²	76.0%	69.1%
Patients with end-of-study HbA _{1c} < 7%	45.2%	32.2%
Body Weight		
Baseline mean (kg)	90.6	89.0
Adj. mean change from baseline (kg)	0.1	1.3
EXUBERA minus SC R		-1.28
95% CI for treatment difference		(-1.96, -0.60)
End of study daily insulin dose		
Short-acting insulin	16.6 mg ³	25.5 IU
Long-acting insulin	37.9 IU	52.3 IU

UL = Humulin® U Ultralente®; SC R = subcutaneous regular human insulin

1. A negative treatment difference favors EXUBERA
2. American Diabetes Association treatment Action Level at the time of study conduct
3. 1 mg inhaled insulin from Exubera is approximately equivalent to 3 IU of subcutaneously injected regular human insulin. See DOSAGE AND ADMINISTRATION

The hypoglycemic event rate (events per subject per month) were: 1.4 for inhaled insulin, 1.57 for insulin injection. There were 4 severe hypoglycemic events in the inhaled insulin group and 1 in the insulin injection group.

Adverse reactions

Hypoglycemia

- In type 2 patients who were not adequately controlled with single oral agent therapy, the addition of EXUBERA was associated with a higher rate of hypoglycemia than was the addition of a second oral agent.

Ear Events in Pediatric Diabetics:

- Pediatric type 1 diabetics in EXUBERA groups experienced adverse events related to the ear more frequently than did pediatric type 1 diabetics in treatment groups receiving only subcutaneous insulin. These events included otitis media (EXUBERA 6.5%; SC 3.4%), ear pain (EXUBERA 3.9%; SC 1.4%), and ear disorder (EXUBERA 1.3%; SC 0%).

Table 6: Respiratory Adverse Events Reported in $\geq 1\%$ of Any Treatment Group in Controlled Phase 2 and 3 Clinical Studies, Regardless of Causality

Adverse Event	Percent of Patients Reporting Event				
	Type 1 Diabetes		Type 2 Diabetes		
	EXUBERA N = 698	SC N = 705	EXUBERA N = 1279	SC N = 488	OAs N = 644
Respiratory Tract Infection	43.3	42.0	29.2	38.1	19.7
Cough Increased	29.5	8.8	21.9	10.2	3.7
Pharyngitis	18.2	16.6	9.5	9.6	5.9
Rhinitis	14.5	10.9	8.8	10.5	3.0
Sinusitis	10.3	7.4	5.4	10.0	2.3
Respiratory Disorder	7.4	4.1	6.1	10.2	1.7
Dyspnea	4.4	0.9	3.6	2.5	1.4
Sputum Increased	3.9	1.3	2.8	1.0	0.5
Bronchitis	3.2	4.1	5.4	3.9	4.0
Asthma	1.3	1.3	2.0	2.3	0.5
Epistaxis	1.3	0.4	1.2	0.4	0.8
Laryngitis	1.1	0.4	0.5	0.4	0.3
Pneumonia	0.9	1.1	0.9	1.6	0.6
Voice Alteration	0.1	0.1	1.3	0.0	0.3

SC = subcutaneous insulin comparator; OA = oral agent comparators

Dyspnea:

- Nearly all (>97%) dyspnea was reported as mild or moderate. A small number of EXUBERA treated patients (0.4%) discontinued treatment due to dyspnea compared to 0.1% of comparator treated patients.

Other Respiratory Adverse Events – Pharyngitis, Sputum Increased and Epistaxis

- The majority of these events were reported as mild or moderate. A small number of EXUBERA treated patients discontinued treatment due to pharyngitis (0.2%) and sputum increased (0.1%); no patients discontinued treatment due to epistaxis.

Pulmonary Function:

- All patients should have pulmonary function assessed prior to initiating therapy. The use of EXUBERA in patients with underlying lung disease, such as asthma or COPD, is not recommended because the safety and efficacy of EXUBERA in this population have not been established.
- In randomized, open-label clinical trials up to two years duration, patients treated with EXUBERA demonstrated a greater decline in FEV1 and DLCO, than comparator treated patients. The mean treatment group differences in FEV1 and DLCO, were noted within the first several weeks of treatment with EXUBERA, and did not progress over the two year treatment period. In one completed controlled clinical trial in patients with type 2 diabetes following two years of treatment with EXUBERA, patients showed resolution of the treatment group difference in FEV1 six weeks after discontinuation of therapy.

Changes in pulmonary function (Exubera vs. SC insulin)

Figure 3: Change from Baseline FEV₁ (L) in Patients with Type 1 Diabetes (Mean +/- Standard Deviation)

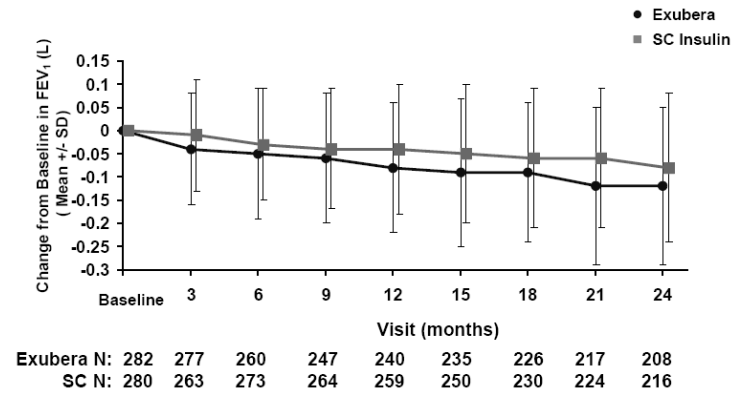


Figure 4: Change from Baseline FEV₁ (L) in Patients with Type 2 Diabetes (Mean +/- Standard Deviation)

