



## Therapeutic Class Review<sup>SM</sup>

### Diabetes – Sitagliptin (Januvia<sup>TM</sup>)

February 2007

**New Product for Review:**  
Sitagliptin (Januvia) [Merck]

**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

- Sitagliptin (Januvia) is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.
  - Incretins, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic peptide (GIP), are release by the intestine in response to a meal and act to regulate glucose homeostasis.
  - DPP-4 rapidly degrades GLP-1 and GIP to inactive metabolites.
  - Inhibiting DPP-4 enhances plasma concentrations of GLP-1 and GIP.
  - These increased concentrations of GLP-1 and GIP act to enhance insulin secretion and suppress glucagon secretion.
- Sitagliptin (Januvia) is dosed 100mg orally once daily. Dosage adjustments are made for renal insufficiency.
- Sitagliptin (Januvia) is the first of the DPP-4 class of oral antidiabetic agents to be approved. There are at least 4 other compounds in the pipeline.
- Sitagliptin (Januvia) is indicated in patient with type 2 diabetes:
  - As an adjunct to diet and exercise to improve glycemic control (monotherapy).
  - In combination with metformin or a PPAR $\gamma$  agonist (e.g., thiazolidinediones) when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

#### Decision

- Sitagliptin (Januvia) is non-preferred/non-formulary because of:
  - Limited long-term safety data.
  - Lack of useful evidence of better efficacy and safety compared to existing formulary/preferred options.

## Products<sup>1,3</sup>

Drug Product <sup>1,3</sup>	Date of FDA Approval <sup>2</sup>	FDA Approved Indication(s)	Dose/Route	Potential Off-Label Use(s)
<b>INSULIN</b>				
regular human insulin: (Humulin <sup>®</sup> 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 <sup>®</sup> 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 <sup>®</sup> )	06/2000	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	
insulin lispro: (Humalog <sup>®</sup> )	06/1996	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	
insulin glulisine (Apidra <sup>®</sup> )	04/2004	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	
insulin human inhalation (Exubera <sup>®</sup> )	01/2006	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs, but typically 12mg – 18mg / day.	Pediatric DM
isophane (NPH): (Humulin <sup>®</sup> 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 <sup>®</sup> 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 <sup>®</sup> ) <sup>3</sup>	6/2005	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	
glargine: (Lantus <sup>®</sup> )	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 <sup>®</sup> Mix)	12/1999	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	
aspart 70/30: (NovoLog <sup>®</sup> Mix)	11/2001	Diabetes mellitus, Type 1 and Type 2	Individualized per patient's needs.	
<b>OTHER ANTI-DIABETIC AGENTS</b>				
Glipizide (generic)	05/1984	Diabetes mellitus, Type II  (Used alone or in combination)	5 - 40mg orally daily	Diabetic microangiopathy; Gestational diabetes

Drug Product <sup>1,3</sup>	Date of FDA Approval <sup>2</sup>	FDA Approved Indication(s)	Dose/Route	Potential Off-Label Use(s)
Glipizide and Metformin HCl (Metaglip <sup>®</sup> )	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 <sup>®</sup> )	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 <sup>®</sup> )	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	
Rosiglitazone maleate (Avandia <sup>®</sup> )	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 <sup>®</sup> )	10/2002	Diabetes mellitus, type 2 (NIDDM) (not to be given as initial therapy).	2mg/500mg – 4mg/1000mg orally twice daily	
Sitagliptin (Januvia <sup>™</sup> )	10/2006	Diabetes Type II alone or in combination	100 mg orally once daily	
Repaglinide (Prandin <sup>®</sup> )	12/1997	Diabetes Type II alone or in combination	0.5 mg to 4 mg with meals	
Nateglinide (Starlix <sup>®</sup> )	12/2000	Diabetes Type II alone or in combination	120 mg TID with meals	
Acarbose (Precose <sup>®</sup> )	9/1995	Diabetes Type II alone or in combination	50 mg TID with meals	- Diabetes mellitus type 2; Prophylaxis - Dumping syndrome - Insulin resistance
Miglitol (Glyset <sup>®</sup> )	12/1996	Diabetes Type II alone or in combination	50 mg TID with	

Drug Product <sup>1,3</sup>	Date of FDA Approval <sup>2</sup>	FDA Approved Indication(s)	Dose/Route	Potential Off-Label Use(s)
			meals	
pramlintide acetate (Symlin <sup>®</sup> )	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

### Comparison Of Product Information Reported Reductions In A<sub>1C</sub>\* (Monotherapy Only)<sup>2,4-10</sup>

Drug	Baseline A <sub>1C</sub> (%)	Duration of Trial	Mean change from baseline (%)	Placebo Corrected change in A <sub>1C</sub> (%)
metformin (Glucophage <sup>®</sup> ) up to 2550 mg per day	8.4	29 weeks	-1.4	-1.8
pioglitazone (Actos <sup>®</sup> ) 30 mg to 45 mg daily	10.2 to 10.3	26 weeks	-0.3 to -0.9	-1.0 to -1.6
rosiglitazone (Avandia <sup>®</sup> ) 2 mg bid to 4 mg bid	8.9 to 9.0	26 weeks	-0.1 to -0.7	-0.9 to -1.5
repaglinide (Prandin <sup>®</sup> ) up to 4 mg daily (titration trial)	8.5	12 weeks	-0.6	-1.7
exenatide (Byetta <sup>®</sup> ) 5 to 10 mcg BID (with metformin)	8.2 to 8.3	30 weeks	-0.4 to -0.8	-0.5 to -0.9
glimepiride 8 mg once daily (Amaryl <sup>®</sup> , generic)	unknown	14 weeks	unknown	-2.0
insulin human [rDNA origin]) Inhalation Powder titrated to response (Exubera)	9.5%	12 weeks	2.2%	No placebo-controlled trials
sitagliptin (Januvia <sup>™</sup> ) 100 mg once daily	8.0	18 to 24 weeks	-0.5 to -0.6	-0.6 to -0.8

\*Note: Data are pooled from separate studies or product literature and not necessarily comparable

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