The Regence Group

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Medication Policy Manual	**Policy No:** dru140
Topic: Januvia®, sitagliptin-containing medications (Januvia, Janumet®)	**Date of Origin:** January 31, 2007
Revised/Effective Date: May 8, 2009	**Next Review Date:** May 2010

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Sitagliptin (Januvia®) is an oral medication used for the treatment of type 2 diabetes. Sitagliptin blocks the dipeptidyl peptidase-4 (DPP-4) enzyme. By blocking this enzyme, insulin production increases, glucose production in the liver goes down, and blood sugar levels decrease. Sitagliptin/metformin (Janumet®) is an oral combination product used for the treatment of type 2 diabetes.

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Policy/Criteria

I. Most contracts require prior authorization approval of sitagliptin prior to coverage. Sitagliptin may be considered medically necessary for the treatment of type 2 diabetes when criteria A and B below are met.

A. There is documentation that the patient's A1C value is over 7%.

AND

B. Treatment with metformin is contraindicated, not tolerated, or has been inadequate in reducing A1C to goal of 7% or less after 90 days of therapy.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence considers sitagliptin to be a self-administered medication.

B. When prior authorization is approved, sitagliptin may be authorized in quantities not to exceed the equivalent of 100 mg daily.

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Sitagliptin is considered investigational when used for any condition other than diabetes, including, but not limited to:

A. Pre-diabetes/prevention of diabetes

B. Weight loss

C. Metabolic syndrome

D. Type 1 diabetes

Position Statement

Background

- The American Diabetes Association has established a treatment algorithm for type 2 diabetes. [2, 3]
  - The recommended therapy for newly diagnosed type 2 diabetes includes using metformin in addition to lifestyle interventions.
  - Metformin can lower A1c by about 1.8% compared to placebo and is associated with reducing complications of diabetes.

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- * If a goal A1C of ≤7% is not achieved, then the addition of either basal insulin, a sulfonylurea, or a thiazolidinedione is recommended, depending on individual patient considerations.
- * If the goal A1C is then not reached, the addition of a medication from one of the other classes is recommended.
- * Ultimately, the use of intensive insulin + metformin ± a thiazolidinedione is recommended, if needed, to achieve the goal A1C level.

Goal of Treatment

- The American Diabetes Association has set an A1C treatment goal for patients with diabetes to not exceed 7%. [2]
  - Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes.
  - * Recent large-scale, randomized controlled trials have failed to find a significant long-term benefit of intensive glycemic control (A1C goals less than 6.5%) for lowering cardiovascular (macrovascular) risk. [2, 19-21]
  - * Intensive glycemic control (A1C goals less than 6.5%) may increase mortality in some patients. [19]
- The American Association of Clinical Endocrinologists (AACE) treatment guidelines suggest an A1C treatment target for patients with diabetes of 6.5%. However, this recommendation was last updated in 2007 prior to the availability of the most recent diabetes treatment outcomes trials that raise concerns about aggressive A1C lowering.[3]

Sitagliptin Overview

- Sitagliptin can lower A1c by about 0.6% compared to placebo over 24 weeks of treatment, but has not been proven to reduce complications of diabetes.

- Metformin can lower A1c by about 1.8% compared to placebo and associated with reducing complications of diabetes.

Clinical Efficacy

- In two reliable, randomized, controlled trials sitagliptin reduced A1C compared to placebo by 0.6% to 0.8%. [5,6]

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- There is reliable evidence that sitagliptin therapy reduces A1C when added to metformin, pioglitazone or sulfonylureas. [7-8, 16, 17]

    * Combination with metformin (1000 mg to 2000 mg daily), lowered A1C by up to 1.0% (depending on metformin dosage) over metformin alone.

    * Combination with pioglitazone (30 mg or 45 mg daily), lowered A1C by up to 0.7% over pioglitazone alone.

    * Combination with metformin alone or glimepiride and metformin lowered A1C by another0.74%.

- There are no clinical trials that have demonstrated a superior benefit of sitagliptin over first line therapies such as metformin or sulfonylureas (see Appendix 1). [9]

- The recommended dose of sitagliptin (in patients with an estimated creatinine clearance ≥ 50 mL/min) is 100 mg once daily, either as monotherapy or combined with metformin or pioglitazone. There is no clinical advantage to using a higher dose. [1]

    * In moderate renal insufficiency (CrCl ≥ 30 mL/min and ≤ 50 mL/min), the dose of sitagliptin should be 50 mg once daily. [1]

    * In severe renal insufficiency (CrCl ≤ 30 mL/min), or with ESRD requiring hemodialysis or peritoneal dialysis, the dose of sitagliptin should be 25 mg once daily. [1]

Safety

- The most common adverse reactions (reported in ≥ 5% of patients treated with sitagliptin and more commonly than in patients treated with placebo) are: upper respiratory tract infection, nasopharyngitis, and headache. [1]

- The incidence of hypoglycemia in the clinical trials in patients receiving sitagliptin was generally similar to patients receiving placebo (1.2% vs. 0.9%). [1]

Investigational Conditions

- Prediabetes / Prevention of Diabetes / Metabolic Syndrome

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* There are no clinical trials that have demonstrated that sitagliptin can prevent or delay the development of type 2 diabetes. [9]

* Sitagliptin has not been proven to improve health outcomes in the treatment of "metabolic syndrome".

- Weight Loss

  * In the two monotherapy studies, weight did not increase in the group of patients receiving sitagliptin, compared to a modest decrease in weight in the patients receiving placebo. [1, 5-6]

- Type 1 diabetes

  * There are no well designed, randomized controlled trials that demonstrate a benefit to using sitagliptin in type 1 diabetes.

Appendix 1: Comparison Of Product Information Reported Reductions In A1C (Monotherapy Only) [1, 10-15]

Drug	Baseline A1C (%)	Duration of Trial	Mean change from baseline (%)	Placebo Corrected change in A1C (%)
metformin (Glucophage®) up to 2550 mg per day	8.4	29 weeks	-1.4	-1.8
pioglitazone (Actos®) 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®) 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®) up to 4 mg daily (titration trial)	8.5	12 weeks	-0.6	-1.7
exenatide (Byetta®) 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®, generic)	unknown	14 weeks	unknown	-2.0
sitagliptin (Januvia®) 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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Cross References
Actos®, pioglitazone – containing medications dru131
Avandia®, rosiglitazone - containing medications dru132
Symlin®, pramlintide, dru121
Byetta®, exenatide, dru120

Codes	**Number**	**Description**
N/A		

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