VENTURA COUNTY
HEALTH CARE PLAN

Prior Authorization DRUG Guidelines

AVANDAMET (rosiglitazone and metformin)

Effective Date: 1/28/14

Date Developed: 1/28/14 by Catherine Sanders, MD

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Note: Rosiglitazone has been discontinued in the United States

Avandamet is a combination of rosiglitazone and metformin. Rosiglitazone is a thiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin, without increasing pancreatic insulin secretion. It has a mechanism of action that is dependent on the presence of insulin for activity. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity (increases peripheral glucose uptake and utilization).

Authorization Criteria:

NOTE: there are FDA restrictions on medications containing rosiglitazone due to data that has suggested an elevated risk of heart attacks. Healthcare providers and patients must be enrolled in the Avandia-Rosiglitazone Medicines Access Program in order to prescribe and receive rosiglitazone medicines. Providers should determine whether their patients are appropriate candidates to receive treatment with rosiglitazone medicines based on the risks and benefits of taking rosiglitazone medicines versus other therapies.

1) adjunct to diet and exercise in adults with type 2 diabetes mellitus (noninsulin dependent, NIDDM) in whom dual therapy is appropriate, especially if other therapies are ineffective or associated with intolerable side effects (e.g. metformin, GLP-1, DPP-4, AGI, insulin)

2) Not to be used in patients with renal failure (creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females.

3) Therapy is not to be initiated in patients with active liver disease or ALT >2.5 times the upper limit of normal.

4) Contraindicated in patients with NYHA Class III-IV CHF and not recommended in patients with symptomatic CHF.

5) Not to be used concomitantly with insulin due to an increased risk of edema, congestive heart failure, and myocardial ischemic events.

6) Not recommended for use in type 1 diabetes (insulin-dependent) as the mechanism of rosiglitazone requires the presence of insulin.

Prescribing and Access Restrictions:
As a requirement of the REMS program, the prescribing and dispensing of any rosiglitazone-containing medication in the U.S. requires physician and patient enrollment in the Avandia-Rosiglitazone Medicines Access Program™. Complete program details are available at www.avandia.com or by calling the program Coordinating Center at 800-282-6342.

Medication Guide:
An FDA-approved patient medication guide, which is available with the product information and at http://www.fda.gov/downloads/Drugs/DrugSafety/UCM143419.pdf, must be dispensed with this medication.

Dosing: Adult:
Type 2 diabetes mellitus: Oral:
First-line therapy (drug-naive patients): Initial: Rosiglitazone 2 mg and metformin 500 mg once or twice daily; may increase by 2 mg/500 mg per day after 4 weeks to a maximum of 8 mg/2000 mg per day.
Second-line therapy:
Patients inadequately controlled on metformin alone: Initial dose: Rosiglitazone 4 mg/day plus current dose of metformin
Patients inadequately controlled on rosiglitazone alone: Initial dose: Metformin 1000 mg/day plus current dose of rosiglitazone
Note: When switching from combination rosiglitazone and metformin as separate tablets: Use current dose
Dose adjustment: Doses may be increased as increments of rosiglitazone 4 mg and/or metformin 500 mg, up to the maximum dose; doses should be titrated gradually.
After a change in the metformin dosage, titration can be done after 1-2 weeks
After a change in the rosiglitazone dosage, titration can be done after 8-12 weeks
Maximum dose: Rosiglitazone 8 mg/metformin 2000 mg daily

Dosing: Pediatric:
Pediatric dosing is currently unavailable or not applicable for this drug.

Dosing: Geriatric:
The initial and maintenance dosing should be conservative, due to the potential for decreased renal function (monitor). Generally, elderly patients should not be titrated to the maximum. Do not use in patients ≥80 years unless normal renal function has been established.

Dosing: Renal Impairment:
Do not use with renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females or abnormal clearance).

Dosing: Hepatic Impairment:
Do not initiate therapy with active liver disease or ALT >2.5 times the upper limit of normal.

Dosage Forms: U.S.:
Excipient information presented when available (limited, particularly for generics); consult specific product labeling.
Tablet:
Avandamet®: 2/500: Rosiglitazone 2 mg and metformin hydrochloride 500 mg

Avandamet®: 4/500: Rosiglitazone 4 mg and metformin hydrochloride 500 mg
Avandamet®: 2/1000: Rosiglitazone 2 mg and metformin hydrochloride 1000 mg
Avandamet®: 4/1000: Rosiglitazone 4 mg and metformin hydrochloride 1000 mg

Generic Equivalent Available: U.S.-No

Administration
Administer with meals. Patients who are NPO may need to have their dose held to avoid hypoglycemia.

Contraindications:
Note: Temporarily discontinue in patients undergoing radiologic studies in which intravascular iodinated contrast media are utilized.
NYHA Class III/IV heart failure (initiation of therapy); renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL [males] or ≥1.4 mg/dL [females], or abnormal creatinine clearance which may also result from conditions such as cardiovascular collapse, acute myocardial infarction, and septicemia); acute or chronic metabolic acidosis, including diabetic ketoacidosis (with or without coma)

Adverse Reactions:
>10%: headache, nausea/vomiting, diarrhea, upper respiratory tract infection
Other Serious ~~Less Common~~ Reactions: fractures, hypoglycemia, CHF, MI, angina, pulmonary edema, pleural effusion, hepatotoxicity, diabetic macular edema, anaphylaxis, angioedema, Stevens-Johnson syndrome, megaloblastic anemia, lactic acidosis

U.S. BOXED WARNING:
Thiazolidinediones cause or exacerbate CHF; observe patients closely after treatment initiation or dose increase for signs and/or symptoms including excessive, rapid weight gain, dyspnea, and/or edema; manage CHF based on current care standards if signs and/or symptoms develop and consider discontinuation or dose reduction; contraindicated in patients with NYHA Class III-IV CHF and not recommended in patients with symptomatic CHF.
Meta-analysis of 52 studies showed statistically *significant increased risk of myocardial infarction*; three other studies showed statistically non-significant increased risk of myocardial infarction and statistically non-significant decreased risk of death; no studies directly comparing cardiovascular risk with pioglitazone, but separate placebo-controlled study of pioglitazone did not show increased risk of myocardial infarction or death.
Lactic acidosis can occur due to metformin accumulation; increased risk with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, acute CHF; symptoms including malaise, myalgias, respiratory distress, increased somnolence, nonspecific abdominal distress; lab findings including low pH, increased anion gap, increased blood lactate; discontinue metformin and hospitalize patient immediately if lactic acidosis suspected.

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Controlled Trial. DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication)Trial Investigators," *Lancet*, 2006,368(9541):2096-105. [PubMed 16997664]
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