VENTURA COUNTY
HEALTH CARE PLAN

Prior Authorization DRUG Guidelines

AVANDARYL (Rosiglitazone and glimepiride)

Effective Date: 1/28/14

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

Last Approval Date: 1/26/16, 1/24/17, 1/23/18, 1/22/19, 2/18/20, 2/2/21, 2/1/22, 1/31/23, 2/13/24, ARCHIVED 1/2/25

Note: Rosiglitazone has been discontinued in the United States

Avandaryl is a combination therapy for treatment of Type 2 diabetes mellitus. 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. Glimepiride stimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites.

Authorization Criteria: 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)

Pre-Authorization Criteria:
Avandaryl is covered for the management of type 2 diabetes mellitus (noninsulin dependent) as an adjunct to diet and exercise where dual rosiglitazone and glimepiride therapy is appropriate.

1) In following the American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm 2013 Consensus Statement, thiazolidinediones such as rosiblitazone are to be used only if other first, second- and third-line therapies are ineffective or associated with intolerable side effects. All of the following medications/classes of medications are to be tried prior to Avandaryl or other medications containing a thiazolidinedione are covered:
2) Metformin
3) Glucagon-like peptide-1 (GLP-1)
4) Dipeptidyl-peptidase-4 (DPP-4)
5) Alpha-glucosidase inhibitor (AGI)
6) Insulin (in normal weight patients)
7) Therapy is not to be initiated in patients with active liver disease or ALT >2.5 times the upper limit of normal.
8) Contraindicated in patients with NYHA Class III-IV CHF and not recommended in patients with symptomatic CHF.
9) Not to be used concomitantly with insulin due to an increased risk of edema, congestive heart failure, and myocardial ischemic events.

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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/UCM143421.pdf, must be dispensed with this medication.

Dosing: Adult:
Type 2 diabetes mellitus: Oral: Initial: Rosiglitazone 4 mg and glimepiride 1 mg once daily or rosiglitazone 4 mg and glimepiride 2 mg once daily (for patients previously treated with sulfonylurea or thiazolidinedione monotherapy)
Patients switching from combination rosiglitazone and glimepiride as separate tablets: Use current dose.
Titration:
Dose adjustment in patients previously on sulfonylurea monotherapy: May take 2 weeks to observe decreased blood glucose and 2-3 months to see full effects of rosiglitazone component. If not adequately controlled after 8-12 weeks, increase daily dose of rosiglitazone component.
Dose adjustment in patients previously on thiazolidinedione monotherapy: If not adequately controlled after 1-2 weeks, increase daily dose of glimepiride component in ≤2 mg increments in 1–2-week intervals.
Maximum dose: Rosiglitazone 8 mg and glimepiride 4 mg once daily

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

Dosing: Geriatric:
Rosiglitazone 4 mg and glimepiride 1 mg once daily. Carefully titrate dose.

Dosing: Renal Impairment:
Dose conservatively to avoid hypoglycemia.

Dosing: Hepatic Impairment:
No dosage adjustment provided in manufacturer's labeling. Therapy should not be initiated if the patient exhibits symptoms of active liver disease or increased transaminases (ALT >2.5 times the upper limit of normal) at baseline since clearance is significantly lower in hepatic impairment. Discontinue if ALT >3 times ULN or jaundice occurs.

Dosage Forms: U.S.:
Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:
Avandaryl® 4 mg/1 mg: Rosiglitazone maleate 4 mg and glimepiride 1 mg
Avandaryl® 4 mg/2 mg: Rosiglitazone maleate 4 mg and glimepiride 2 mg
Avandaryl® 4 mg/4 mg: Rosiglitazone maleate 4 mg and glimepiride 4 mg
Avandaryl® 8 mg/2 mg: Rosiglitazone maleate 8 mg and glimepiride 2 mg
Avandaryl® 8 mg/4 mg: Rosiglitazone maleate 8 mg and glimepiride 4 mg

Generic Equivalent Available: U.S.-No

Administration:
Should be administered with the first meal of the day.

Adverse Reactions
Edema, hypertension, headache, hypoglycemia, nasopharyngitis
Other Serious Less Common Reactions: CHF, MI, angina, pulmonary edema, pleural effusion, hepatotoxicity, diabetic macular edema, anaphylaxis, angioedema, leukopenia, agranulocytosis, thrombocytopenia, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, pancytopenia, hypersensitivity vasculitis, photosensitivity, Stevens-Johnson syndrome, porphyria, disulfiram-like reaction, hyponatremia, SIADH, fractures.

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.

References:
1. American Diabetes Association, “Standards of Medical Care in Diabetes -- 2013,” *Diabetes Care*, 2013, 36(Suppl 1):11-66. [PubMed 23264422]
2. Gerstein HC, Yusuf S, Bosch J, et al, “Effect Of Rosiglitazone On The Frequency Of Diabetes In Patients With Impaired Glucose Tolerance or Impaired Fasting Glucose: A Randomized Controlled Trial. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication)Trial Investigators,” *Lancet*, 2006,368(9541):2096-105. [PubMed 16997664]
3. Kahn SE, Haffner SM, Heise MA, et al, “Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy,” *N Engl J Med*, 2006:355(23):2427-43. [PubMed 17145742]
4. Lago RM, Singh PP, and Nesto RW, “Congestive Heart Failure and Cardiovascular Death in Patients With Prediabetes and Type 2 Diabetes Given Thiazolidinediones: A Meta-Analysis of Randomized Clinical Trials,” *Lancet*, 2007, 370(9593):1129-36. [PubMed 17905165]

5. Nissen SE, Wolski K, "Effects Of Rosiglitazone On The Risk of Myocardial Infarction and Death From Cardiovascular Causes," N Engl J Med, 2007. Available at http://content.nejm.org/cgi/content/full/NEJMoa07276117517853
6. Qaseem A, Humphrey LL, Sweet DE, et al,"Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline from the American College of Physicians," *Ann Intern Med*, 2012, 156(3):218-31. [PubMed 22312141]
7. Singh S, Loke YK, and Furberg CD, "Long-Term Risk of Cardiovascular Events With Rosiglitazone," *JAMA*, 2007, 298(10):1189-95. [PubMed 17848653]
8. www.uptodate.com: Rosiglitazone and glimepiride: Drug Information
9. www.epocrates.com: Avandaryl Drug information

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