

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
Regence BlueCross BlueShield of Utah • Regence BlueShield of Idaho
Independent licensees of the Blue Cross and Blue Shield Association**

Medication Policy Manual

Policy No: dru132

Topic: Avandia[®], rosiglitazone – containing medications (Avandia, Avandamet[®], Avandaryl[®])

Date of Origin: March 10, 2006

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

Rosiglitazone (Avandia[®]), a thiazolidinedione, is an oral medication used alone or in combination with metformin, a sulfonylurea, or insulin for the treatment of type 2 diabetes. Rosiglitazone/metformin (Avandamet[®]) and rosiglitazone/glimepiride (Avandaryl[®]) are oral combination products used for the treatment of type 2 diabetes.

Policy/Criteria

- I. Most contracts require prior authorization approval of rosiglitazone prior to coverage. Rosiglitazone may be considered medically necessary when one of the criteria A, B or C below is met.

- A. **Type 2 Diabetes:** Initial authorization for rosiglitazone may be considered medically necessary for patients with type 2 diabetes when the following criteria under 1 and 2 are met:

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

AND

- 2. 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.

OR

- B. **Nonalcoholic Steatohepatitis:** Initial authorization for rosiglitazone may be considered medically necessary for patients with nonalcoholic steatohepatitis when metformin was ineffective, contraindicated, or not tolerated.

OR

- C. **Polycystic Ovary Syndrome:** Initial authorization for rosiglitazone may be considered medically necessary for patients with polycystic ovary syndrome when metformin was ineffective, contraindicated, or not tolerated.

II. Administration and Authorization Period

- A. Regence considers rosiglitazone to be a self-administered medication.
 - B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

- III.** Rosiglitazone is considered investigational when used for all other conditions, including, but not limited to:
- A.** Advanced melanoma
 - B.** Alzheimer's disease
 - C.** Atopic dermatitis
 - D.** Crohn's disease
 - E.** Gliomas
 - F.** HIV-related lipoatrophy
 - G.** Metabolic syndrome
 - H.** Pre-diabetes
 - I.** Type 1 diabetes

Position Statement

Background

- The American Diabetes Association has established a treatment algorithm for type 2 diabetes. ^[28, 69]
 - * 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.
 - * If a goal A1C of $\leq 7\%$ 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 \pm a thiazolidinedione is

recommended, if needed, to achieve the goal A1C level.

- * 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.^[10]

Goal of Treatment

- The American Diabetes Association has set an A1C treatment goal for patients with diabetes to not exceed 7%.^[28]
 - Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes.^[28]
- * 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.^[28, 70-72]
- * Intensive glycemic control (A1C goals less than 6.5%) may increase mortality in some patients.^[70]

Thiazolidinedione Overview

- Pioglitazone and rosiglitazone can lower A1C by up to 1.6 percentage points compared to placebo over 6 months.^[11-12]
- Thiazolidinedione therapy has demonstrated a clinical benefit in reduction of A1C as monotherapy compared to placebo and as adjunctive therapy.^[3, 5-6, 9, 11-16, 22-27, 34-36]
- Clinical trials have not demonstrated a superior benefit of thiazolidinediones over first line therapies such as metformin.^[1-9, 15-16, 73]
- Thiazolidinedione therapy generally results in similar glycemic control when compared with sulfonylureas. Thiazolidinedione therapy generally results in lowered insulin resistance, whereas sulfonylureas generally result in lower serum cholesterol, compared with each other.^[37-40]
- When compared head-to-head, pioglitazone and rosiglitazone demonstrated similar effects on reduction in HgA_{1c} in type 2 diabetic patients.^[15]
- The value of rosiglitazone in the treatment of "metabolic syndrome" is unclear since there are many other options with established benefit in treating the individual components

associated with this syndrome.

Clinical Efficacy

- A large-scale, reliable trial (PROactive) with pioglitazone failed to achieve its primary endpoint of reducing the total mortality and macrovascular morbidity in type 2 diabetic patients. [17-18]
 - * The composite endpoint was made up of death, non-fatal myocardial infarction (MI), silent MI, stroke, major leg amputation, acute coronary syndrome, coronary revascularization, and leg revascularization.
 - * Statistical significance was only demonstrated when several secondary endpoints were combined.
 - * Caution is urged when using pioglitazone in patients with a history of a previous MI.
- A published subgroup analysis suggests that patients with a history of MI, pioglitazone may reduce the risk of another MI (53 patients needed to be treated to prevent one additional MI). However, patients were more likely to have worsening heart failure that required hospitalization (only 43 patients needed to be treated to result in one additional serious case of heart failure). [58]

Other Uses

I. NONALCOHOLIC STEATOHEPATITIS

- Metformin, pioglitazone, and rosiglitazone have been evaluated in small, preliminary trials to evaluate their usefulness in the management of nonalcoholic steatohepatitis (NASH). [30, 43-47]
- In an open-label, randomized, placebo-controlled fashion, **metformin** 850 mg twice daily + calorie restricted diet was evaluated against calorie-restricted diet alone in 36 patients with laboratory-confirmed NASH. At the end of 6 months, patients receiving metformin had significant improvements in serum AST, insulin, C-peptide and insulin-resistance. [42]
- **Rosiglitazone** has been evaluated in non-controlled and controlled studies in adult patients with biopsy-confirmed NASH. In studies lasting up to 1 year, patients treated with rosiglitazone had statistically significant improvements in transaminase levels, and

histological features, though no long-term benefits were noted. Though these were small studies, they all generally point to an overall improvement in clinical status in patients with NASH. [43-45]

- **Pioglitazone** has been evaluated in randomized, placebo-controlled, single-blind, and double-blind trials in adult patients with biopsy proven NASH. Significant improvements were noted in ALT, GGT, hepatocellular injury and fibrosis. [30, 73] Though these studies were small (less than 100 patients per trial), these findings are consistent with previous studies. [46, 47]

II. POLYCYSTIC OVARY SYNDROME (PCOS):

- The initial treatment of PCOS should involve lifestyle modification with an emphasis on controlled eating patterns, regular aerobic exercise and management of blood pressure and lipid abnormalities. [48,49]
- Metformin should be considered as an initial intervention in most women with PCOS, especially in those women who are overweight or obese. Metformin improves many metabolic abnormalities in PCOS and may improve menstrual cyclicality and the potential for pregnancy. [48,49]
- Pioglitazone and rosiglitazone have been evaluated in small, preliminary trials to evaluate their usefulness in the management of PCOS. [19-21, 50-55]
 - * In aggregate, these trials have generally shown that the thiazolidinediones improve insulin resistance, hyperglycemia and glucose intolerance related to PCOS.
 - * Major deficiencies in these trials, including lack of ITT analyses, lack of blinding, lack of control groups and small study size, make the validity and usefulness of these trials uncertain.
 - * Nevertheless, there appears to be a consensus that thiazolidinedione therapy may be useful in patients who either do not respond to, or cannot tolerate, metformin. [48,49]

III. INVESTIGATIONAL USES

- **Advanced melanoma** – a phase II randomized, open-label, active controlled trial in 76 patients with advanced melanoma suggested that pioglitazone +_rofecoxib added to

trofosamide may have a modest effect on progression free survival. Larger, well designed trials are needed to establish safety and efficacy. ^[64]

- **Atopic dermatitis** – a published retrospective case series suggests that rosiglitazone may offer a modest benefit in the treatment of atopic dermatitis. A well designed, randomized controlled trial is needed to establish safety and efficacy. ^[60]
- **Crohn’s disease** – a small, randomized, blinded, controlled trial suggests that rosiglitazone may offer a modest benefit in the treatment of patients with Crohn’s disease. Larger, well designed, randomized controlled trials are needed to establish safety and efficacy for this indication. ^[59]
- **Gliomas** – a small, randomized controlled trial evaluated pioglitazone + rofecoxib when added to chemotherapy in 14 patients with high-grade gliomas. There was a modest effect noted, but larger, well designed randomized controlled trials are needed to establish safety and efficacy for this indication. ^[63]
- **HIV-related lipoatrophy** – A randomized placebo-controlled trial failed to show a significant benefit from rosiglitazone in lipoatrophy or metabolic parameters in patients with HIV-related lipoatrophy. ^[62]
- **Type 1 diabetes** – The FDA approved package insert warns that both rosiglitazone and pioglitazone exerts their antihyperglycemic effect only in the presence of insulin. Therefore, neither agent should be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Small randomized trials have suggested a possible benefit of TZDs administered with insulin in patients with type 1 diabetes, but larger, well-designed, randomized, controlled trials are needed to establish safety and efficacy. ^[11-14, 27, 57, 61]
- **Pre-diabetes** – A large randomized, double-blind, placebo-controlled trial (DREAM) evaluated rosiglitazone in 5,269 adults with impaired glucose tolerance or impaired fasting glucose (pre-diabetes).^[32,33] Limitations to the validity and usefulness of this study include:
 - * High number of patient drop-outs (~23%), which erodes randomization creates uncertainty as to whether the treatment groups were comparable by the end of the study.
 - * The clinical relevance of the co-primary endpoint is uncertain as rosiglitazone resulted in no significant improvement in the incidence of any cardiovascular

endpoint or in the incidence of death during the trial.

- * Rosiglitazone resulted in a statistically significant increase in heart failure (0.5% vs. 0.1%, HR 7.03, P=0.01) compared to placebo, despite having excluded patients with significant pre-existing CV disease.

Safety

- The FDA approved package insert for both pioglitazone and rosiglitazone contains a black box warning advising that thiazolidinediones cause or exacerbate congestive heart failure in some patients. Patients should be observed for signs and symptoms of heart failure after initiation.^[11-14, 27, 57]
 - * Administration of pioglitazone to patients with NYHA functional class II/III heart failure was associated with a statistically significant increase in the composite primary endpoint of cardiovascular mortality and hospitalization or ER visits for heart failure.^[74]
- The FDA approved package insert for rosiglitazone warns that a meta-analysis of 42 clinical trials showed that rosiglitazone was associated for an increased risk of myocardial ischemic events such as angina and myocardial infarction. Other trials have not confirmed this association.^[11-14, 27, 57, 65-68]
- Dose related weight gain has been observed for both rosiglitazone and pioglitazone, alone and in combination with other hypoglycemic agents.^[11,12]
- Common thiazolidinedione adverse reactions include headache, upper respiratory tract infection, sinusitis, edema, hypoglycemia (especially when combined with other agents) and diarrhea.^[11,12]
- Rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. Pioglitazone may be a weak inducer of CYP450 isoform 3A4 substrate and may interact with other drugs metabolized by the same enzyme.^[11,12]
- Rosiglitazone and pioglitazone may increase the rate of upper arm, hand and foot fractures in female patients with type 2 diabetes.^[31,56]
 - * The hazard ratio for fractures in women at 5 years was 1.81 to 2.13 for rosiglitazone compared to women taking metformin or glyburide, respectively. There was no apparent increase in fracture risk for men.^[78]

Appendix 1: Comparison Of Product Information Reported Reductions In A1C (Monotherapy Only) ^[11, 12, 79-82]

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

References

1. Mayerson AB, Hundal RS, Dufour S, et al. "The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes." *Diabetes*. 2002;51(3):797-802.
2. Nakamura T, Funahashi T, Yamasita S. "Thiazolidinedione derivative improves fat distribution and multiple risk factors in subjects with visceral fat accumulation-double blind placebo-controlled trial." *Diabetes Res Clin Prac*. 2001;54(3):181-90.
3. Miyazaki Y, Mahankali A, Matsuda M, et al. "Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone." *Diabetes Care*. 2001;24(4):710-9.
4. Kelly I, Han TS, Walsh K, Lean MEJ. "Effects of a thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes." *Diabetes Care*. 1999;22(2):288-93.
5. Raskin R, Rendell M, Riddle MC, "A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes." *Diabetes Care*. 2001;24(7):1226-32.
6. Lawrence SP, Grunberger G, Miller E, et al. "Once and twice daily dosing with rosiglitazone improved glycemic control in patients with type 2 diabetes." *Diabetes Care*. 2001;24(2):308-15.
7. Bloomgarden ZT. "American diabetes association 60th scientific sessions, 2000." *Diabetes Care*. 2001;24(1):162-6.
8. Pavo I, Jermendy G, Varkonyi TT, et al. "Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes." *J Clin Endocrinol Metab*. 2003;88:1637-1645.
9. Hanefeld M, Brunetti P, Schernthaner GH, Matthews DR, Charbonnel BH; QUARTET Study Group. "One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes." *Diabetes Care*. 2004 Jan;27(1):141-7.

10. Rodbard HW, Blonde L, Braithwaite SS, et al.; AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract.* 2007 May-Jun;13 Suppl 1:1-68.
11. Actos[®] [package insert]. Lincolnshire, IL: Takeda Pharmaceuticals America, Inc.; September 2007
12. Avandia[®] [package insert]. Research Triangle Park, NC: GlaxoSmithKline; February 2008
13. Avandamet[®] [package insert]. Research Triangle Park, NC: GlaxoSmithKline; September 2007
14. ActoPlus MET[®] [package insert]. Lincolnshire, IL: Takeda Pharmaceuticals America, Inc.; September 2007
15. Goldberg RB, Kendall DM, Deeg MA, et al. "A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia." *Diabetes Care.* 2005;7:1547-54.
16. Schernthaner G, Matthews DR, Charbonnel B, et al. "Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial." *J Clin Endocrinol Metab.* 2004;89:6068-76.
17. Charbonnel B, Dormandy J, Erdmann E, et al. "The prospective pioglitazone clinical trial in macrovascular events (PROactive). Can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5,238 patients." *Diabetes Care.* 2004;7:1647-53.
18. Results from the "Prospective Actos clinical trial in macrovascular events (PROactive)." Available at: <http://www.proactive-results.com>. Accessed on 9/29/2005.
19. Ortega-Gonzalez C, Luna S, Hernandez L, et al. "Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome." *J Clin Endocrinol Metab.* 2005;90:1360-5.
20. Brettenthaler N, De Geyter C, Huber PR, et al. "Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunction in women with polycystic ovary syndrome." *J Clin Endocrinol Metab.* 2004;89:3835-40.
21. Baillargeon JP, Jakubowicz DJ, Iuorno MJ, et al. "Effects of metformin and rosiglitazone,

- alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity." *Fertil Steril*. 2004;82(4):893-902.
22. Fonseca V, Rosenstock J, Ratwardhan R, Salzman A. "Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus, a randomized controlled trial." *JAMA*. 2000;283(13):1695-1702.
 23. Gomez-Perez, FJ, et al. "Efficacy and safety of rosiglitazone plus metformin in Mexicans with type 2 diabetes." *Diabetes Metab Res Rev*. 2002;18:127-34.
 24. Ballary C, Desi A. "Efficacy and safety of a combination of metformin and rosiglitazone in patients with type 2 diabetes mellitus-a post-marketing study." *J Indian Med Assoc*. 2003;101(2):113-4, 123.
 25. Dailey GE 3rd, Noor MA, Park JS, et al. "Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial." *Am J Med*. 2004;116(4):223-9.
 26. Einhorn D, Rendell M, Rosenzweig J, et al. "Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The pioglitazone 027 Study group." *Clin Ther*. 2000;22(12):1395-1409.
 27. Avandaryl[®] [package insert]. Research Triangle Park, NC: GlaxoSmithKline; September 2007
 28. American Diabetes Association. Standards of Medical Care in Diabetes--2007. *Diabetes Care*. 2007 Jan;30 Suppl 1:S4-41. Available at: http://care.diabetesjournals.org/content/vol30/suppl_1/. Accessed: 1/12/2007
 29. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. ; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006 Dec 7;355(23):2427-43.
 30. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med*. 2006 Nov 30;355(22):2297-307.
 31. Avandia Safety Warning, Food and Drug Administration "MedWatch". <http://www.fda.gov/medwatch/safety/2007/safety07.htm#rosiglitazone> Accessed: 2/26/07
 32. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators; Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, et al. Effect

- of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet*. 2006 Sep 23;368(9541):1096-105. Erratum in: *Lancet*. 2006 Nov 18;368(9549):1770.
33. Gerstein HC, Yusuf S, Holman R, Bosch J, Pogue J; The DREAM Trial Investigators. Rationale, design and recruitment characteristics of a large, simple international trial of diabetes prevention: the DREAM trial. *Diabetologia*. 2004 Sep;47(9):1519-27.
 34. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. *Diabetes Care*. 2006 Mar;29(3):554-9.
 35. Derosa G, D'Angelo A, Ragonesi PD, Ciccarelli L, Piccinni MN, Pricolo F, et al. Metformin-pioglitazone and metformin-rosiglitazone effects on non-conventional cardiovascular risk factors plasma level in type 2 diabetic patients with metabolic syndrome. *J Clin Pharm Ther*. 2006 Aug;31(4):375-83.
 36. Davidson JA, Perez A, Zhang J; The Pioglitazone 343 Study Group. Addition of pioglitazone to stable insulin therapy in patients with poorly controlled type 2 diabetes: results of a double-blind, multicentre, randomized study. *Diabetes Obes Metab*. 2006 Mar;8(2):164-74.
 37. Umpierrez G, Issa M, Vlahjic A. Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial. *Curr Med Res Opin*. 2006 Apr;22(4):751-9.
 38. Hanefeld M, Patwardhan R, Jones NP; Rosiglitazone Clinical Trials Study Group. A one-year study comparing the efficacy and safety of rosiglitazone and glibenclamide in the treatment of type 2 diabetes. *Nutr Metab Cardiovasc Dis*. 2007 Jan;17(1):13-23.
 39. Derosa G, Gaddi AV, Piccinni MN, Salvadeo S, Ciccarelli L, Fogari E, et al. Differential effect of glimepiride and rosiglitazone on metabolic control of type 2 diabetic patients treated with metformin: a randomized, double-blind, clinical trial. *Diabetes Obes Metab*. 2006 Mar;8(2):197-205.
 40. Perriello G, Pampanelli S, Di Pietro C, Brunetti P; Italian Pioglitazone Study Group. Comparison of glycaemic control over 1 year with pioglitazone or gliclazide in patients with Type 2 diabetes. *Diabet Med*. 2006 Mar;23(3):246-52.
 41. Risner ME, Saunders AM, Altman JF, Ormandy GC, Craft S, Foley IM, et al. Rosiglitazone in Alzheimer's Disease Study Group. Efficacy of rosiglitazone in a genetically defined

- population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics J*. 2006 Jul-Aug;6(4):246-54. Epub 2006 Jan 31.
42. Uygun A, Kadayifci A, Isik AT, Ozgurtas T, Deveci S, Tuzun A, et al. Metformin in the treatment of patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2004 Mar 1;19(5):537-44.
 43. Brunt EM, Neuschwander-Tetri BA, Oliver D, Wehmeier KR, Bacon BR. Nonalcoholic steatohepatitis: histologic features and clinical correlations with 30 blinded biopsy specimens. *Hum Pathol*. 2004 Sep;35(9):1070-82.
 44. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Oliver D, Bacon BR. Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. *Hepatology*. 2003 Oct;38(4):1008-17.
 45. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Sponseller CA, Hampton K, et al. Interim results of a pilot study demonstrating the early effects of the PPAR-gamma ligand rosiglitazone on insulin sensitivity, aminotransferases, hepatic steatosis and body weight in patients with non-alcoholic steatohepatitis. *J Hepatol*. 2003 Apr;38(4):434-40.
 46. Promrat K, Lutchman G, Uwaifo GI, Freedman RJ, Soza A, Heller T, et al. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. *Hepatology*. 2004 Jan;39(1):188-96.
 47. Lutchman G, Promrat K, Kleiner DE, Heller T, Ghany MG, Yanovski JA, et al. Changes in serum adipokine levels during pioglitazone treatment for nonalcoholic steatohepatitis: relationship to histological improvement. *Clin Gastroenterol Hepatol*. 2006 Aug;4(8):1048-52.
 48. American Association of Clinical Endocrinologists Polycystic Ovary Syndrome Writing Committee. American Association of Clinical Endocrinologists Position Statement on Metabolic and Cardiovascular Consequences of Polycystic Ovary Syndrome. *Endocr Pract*. 2005 Mar-Apr;11(2):126-34.

49. American College of Obstetricians and Gynecologists (ACOG). Polycystic ovary syndrome. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2002 Dec. 14 p. (ACOG practice bulletin; no. 41). Available at: http://www.guidelines.gov/summary/summary.aspx?ss=15&doc_id=3989&nbr=003128&string=polycystic+AND+ovary+AND+syndrome. Accessed: 2/26/07
50. Glintborg D, Hermann AP, Andersen M, Hagen C, Beck-Nielsen H, et al. Effect of pioglitazone on glucose metabolism and luteinizing hormone secretion in women with polycystic ovary syndrome. *Fertil Steril*. 2006 Aug;86(2):385-97.
51. Rouzi AA, Ardawi MS. A randomized controlled trial of the efficacy of rosiglitazone and clomiphene citrate versus metformin and clomiphene citrate in women with clomiphene citrate-resistant polycystic ovary syndrome. *Fertil Steril*. 2006 Feb;85(2):428-35.
52. Lemay A, Dodin S, Turcot L, Dechene F, Forest JC. Rosiglitazone and ethinyl estradiol/cyproterone acetate as single and combined treatment of overweight women with polycystic ovary syndrome and insulin resistance. *Hum Reprod*. 2006 Jan;21(1):121-8. Epub 2005 Sep 30.
53. Rautio K, Tapanainen JS, Ruokonen A, Morin-Papunen LC. Rosiglitazone treatment alleviates inflammation and improves liver function in overweight women with polycystic ovary syndrome: a randomized placebo-controlled study. *Fertil Steril*. 2007 Jan;87(1):202-6.
54. Rautio K, Tapanainen JS, Ruokonen A, Morin-Papunen LC. Endocrine and metabolic effects of rosiglitazone in overweight women with PCOS: a randomized placebo-controlled study. *Hum Reprod*. 2006 Jun;21(6):1400-7.
55. Cataldo NA, Abbasi F, McLaughlin TL, Basina M, Fechner PY, Giudice LC, et al. Metabolic and ovarian effects of rosiglitazone treatment for 12 weeks in insulin-resistant women with polycystic ovary syndrome. *Hum Reprod*. 2006 Jan;21(1):109-20.
56. Actos Safety Warning, Food and Drug Administration “MedWatch”. <http://www.fda.gov/medwatch/safety/2007/safety07.htm#actos> Accessed: 3/14/07
57. Duetact[®] [package insert]. Lincolnshire, IL: Takeda Pharmaceuticals America, Inc.; October 2007
58. Erdmann E, Charbonnel B, Wilcox RG, et al.; PROactive investigators. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). *Diabetes Care*. 2007 Nov;30(11):2773-8.

59. Lewis JD, Lichtenstein GR, Deren JJ, et al.; Rosiglitazone for Ulcerative Colitis Study Group. Rosiglitazone for active ulcerative colitis: a randomized placebo-controlled trial. *Gastroenterology*. 2008 Mar;134(3):688-95.
60. Behshad R, Cooper KD, Korman NJ. A retrospective case series review of the peroxisome proliferator-activated receptor ligand rosiglitazone in the treatment of atopic dermatitis. *Arch Dermatol*. 2008 Jan;144(1):84-8.
61. Bhat R, Bhansali A, Bhadada S, Sialy R. Effect of pioglitazone therapy in lean type 1 diabetes mellitus. *Diabetes Res Clin Pract*. 2007 Dec;78(3):349-54.
62. Cavalcanti RB, Raboud J, Shen S, Kain KC, Cheung A, Walmsley S. A randomized, placebo-controlled trial of rosiglitazone for HIV-related lipodystrophy. *J Infect Dis*. 2007 Jun 15;195(12):1754-61.
63. Hau P, Kunz-Schughart L, Bogdahn U, et al. Low-dose chemotherapy in combination with COX-2 inhibitors and PPAR-gamma agonists in recurrent high-grade gliomas - a phase II study. *Oncology*. 2007;73(1-2):21-5.
64. Reichle A, Vogt T, Coras B, et al. Targeted combined anti-inflammatory and angiostatic therapy in advanced melanoma: a randomized phase II trial. *Melanoma Res*. 2007 Dec;17(6):360-4.
65. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007 Jun 14;356(24):2457-71. Epub 2007 May 21.
66. Psaty BM, Furberg CD. Rosiglitazone and cardiovascular risk. *N Engl J Med*. 2007 Jun 14;356(24):2522-4. Epub 2007 May 21.
67. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, et al. Rosiglitazone Evaluated for Cardiovascular Outcomes -- An Interim Analysis. *N Engl J Med*. 2007 Jun 5; [Epub ahead of print]
68. McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM. Coronary heart disease outcomes in patients receiving antidiabetic agents. *Pharmacoepidemiol Drug Saf*. 2007 Jun 6; [Epub ahead of print]
69. Nathan DM, Buse JB, Davidson MB, et al. American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009 Jan;32(1):193-203.
70. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358:2545–2559, 2008

71. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 358:2560–2572, 2008
72. Duckworth W, Abraira C, Moritz T, et al. ; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009 Jan 8;360(2):129-39.
73. Aithal GP, Thomas JA, Kaye PV, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology*. 2008 Oct;135(4):1176-84.
74. Giles TD, Miller AB, Elkayam U, Bhattacharya M, Perez A. Pioglitazone and heart failure: results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction. *J Card Fail*. 2008 Aug;14(6):445-52.
75. Comaschi M, Corsi A, Di Pietro C, Bellatreccia A, Mariz S; COM06 Study Investigators. The effect of pioglitazone as add-on therapy to metformin or sulphonylurea compared to a fixed-dose combination of metformin and glibenclamide on diabetic dyslipidaemia. *Nutr Metab Cardiovasc Dis*. 2008 Jun;18(5):373-9.
76. Ratziu V, Giral P, Jacqueminet S, et al. L, et al . LIDO Study Group. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology*. 2008 Jul;135(1):100-10.
77. Idilman R, Mizrak D, Corapcioglu D, et al. Clinical trial: insulin-sensitizing agents may reduce consequences of insulin resistance in individuals with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2008 Jul;28(2):200-8.
78. Kahn SE, Zinman B, Lachin JM, et al. ; Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care*. 2008 May;31(5):845-51.
79. Glucophage[®] [package insert]. Princeton, NJ: Bristol-Myers Squibb Company., Inc.; June 2006
80. Prandin[®] [package insert]. Princeton, NJ: Novo Nordisk, Inc.; December 2004
81. Byetta[®] [package insert]. San Diego, CA: Amylin Pharmaceuticals, Inc.; October 2006
82. Amaryl[®] [package insert]. Bridgewater, NJ: Aventis Pharmaceuticals Inc.; October 2005

Cross References
Actos [®] , pioglitazone-containing medications dru131
Januvia [®] , sitagliptin-containing medications (Januvia, Janumet [®]) dru140
Symlin [®] , pramlintide, dru121
Byetta [®] , exenatide, dru120

Codes	Number	Description
N/A		