BlueCross BlueShield of Alabama

Metformin ER Step Therapy Criteria Program Summary

This program applies to the Commercial, GenPlus, NetResults F series and Health Insurance Marketplace formularies.
For GenPlus formulary the only target is generic metformin modified release. All other agents are non-formulary.
This program is implemented with auto-grandfathering.

OBJECTIVE

The intent of the Metformin ER Step Therapy program is to encourage the use of cost-effective generic metformin ER agents over the more expensive brand agents. The program will accommodate for brand metformin ER when generic agents cannot be used due to a documented intolerance, FDA labeled contraindication, or hypersensitivity. The program allows continuation of therapy when there is documentation that the patient is receiving the requested agent.

TARGET DRUGS

Fortamet® (metformin osmotic ER)[a]
Glucophage XR® (metformin ER)[a]
Glumetza® (metformin modified release)[b]

a – generic available and not targeted in program
b – generic available and targeted in program

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Brand Metformin ER Products will be approved when ONE of the following is met:

1. The patient's medication history includes at least one non-targeted generic metformin ER product in the past 90 days
   OR
2. There is documentation that the patient is currently using the requested agent
   OR
3. The prescriber states the patient is currently using the requested agent AND is at risk if therapy is changed
   OR
4. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an available non-targeted generic metformin ER product

Length of approval: 12 months

FDA APPROVED INDICATIONS AND DOSAGE[1-3]

BRAND (Generic)	Indication(s)	Dosage and Administration
Fortamet® (metformin ER)[a] 500, 1000 mg tablet	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	Once daily Maximum recommended dose is 2500 mg
Glucophage XR® (metformin ER)[a] 500, 750 mg tablet	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	Once daily Maximum recommended dose is 2000 mg
Glumetza® (metformin ER)[a] 500, 1000 mg tablet	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	Once daily Maximum recommended dose is 2000 mg

CLINICAL RATIONALE

Guidelines

For prevention or delay of type 2 diabetes, the primary treatment option is lifestyle modification. For prevention, metformin has the strongest evidence base and has demonstrated long-term safety compared to all pharmacological therapies.[4,5]

For the treatment of diabetes mellitus type 2 (DM2), most patients should begin with lifestyle modifications including diet and exercise. When lifestyle modifications alone are insufficient, metformin is the primary pharmacological treatment option for diabetes mellitus type 2. Metformin has a long-standing evidence base for treatment efficacy and safety, is inexpensive, and may reduce risk of cardiovascular events. Metformin should be continued as background therapy when additional pharmacological therapy is needed to achieve glycemic control.[4,5]

Efficacy

The non-inferiority of Fortamet compared to immediate release metformin twice daily was studied in a double-blind, multicenter U.S. clinical study. The study contained 680 DM2 patients who had been taking metformin containing medication at study entry. Fortamet was found to be non-inferior in HbA_{1c}, fasting plasma glucose (FPG), plasma insulin, body weight, and body mass index at the 20 week endpoint.[1]

The efficacy of Glucophage XR was studied in a 24 week, double-blind, placebo controlled study with DM2 patients who had failed to achieve glycemic control with diet and exercise alone. Mean HbA_{1c} at endpoint had increased 0.2% from baseline for placebo patients and decreased 0.6% with Glucophage XR. Glucophage XR was also studied in a 16 week, double-blind, placebo controlled, dose response study in DM2 patients who had failed to achieve glycemic control with diet and exercise. Glucophage XR vs. placebo, showed statistically significant ($p<0.001$) improvements from baseline in HbA_{1c} (-0.4% - -1.1% vs. 0.1%) and FPG (-15.2 mg/dL - -33.6 mg/dL vs. 7.6 mg/dL) at all doses compared to

placebo. Glucophage XR once daily was also studied vs. Glucophage twice daily in a 24 week, double-blind, randomized study with DM 2 patients who had been previously treated with Glucophage 500 mg twice daily for at least 8 weeks prior. At study endpoint, Glucophage XR did not show statistical differences in HbA_{1c} nor FPG compared to Glucophage.[2]

The efficacy of Glumetza 1500 mg once daily, Glumetza 1500 per day in divided doses, and Glumetza 2000 mg once daily vs. metformin immediate release tablets 1500 mg in divided doses was studied in a multicenter, randomized, double-blind, active controlled, dose-ranging, parallel group trial of 388 patients who were newly diagnosed with diabetes, patients treated only with diet and exercise, patients treated with a single anti-diabetic medication, and 368 patients receiving metformin up to 1500 mg/day plus a sulfonylurea at a dose equal to or less than one-half the maximum dose. Glumetza was not inferior to immediate release metformin in HbA_{1c} and FPG at all doses. Glumetza plus glyburide vs. placebo plus glyburide was studied in a multicenter, double-blind, randomized trial of 144 newly diagnosed patients or patient being treated with diet and exercise, and 431 patients who were receiving monotherapy with metformin, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglinitides, or treated with combination therapy consisting of metformin/glyburide at doses up to 1000 mg metformin + 10 mg glyburide per day (or equivalent doses of glipizide or glimepiride up to half the maximum therapeutic dose). The difference in the change from baseline in HbA1c levels between the combined Glumetza + glyburide groups and the glyburide only group (-0.8% - -0.9%) was statistically significant at week 24 ($p<0.001$). The changes in glycemic control across the three Glumetza + glyburide groups were comparable.

Safety

All metformin ER agents are contraindicated in the following scenarios:

- Renal disease or renal dysfunction (e.g. serum creatinine levels ≥1.5 mg/dL for males and ≥1.4 mg/dL for females, or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia
- Known hypersensitivity to metformin
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Additionally, all metformin ER agents contain a black box warning regarding the increased risk of lactic acidosis.

REFERENCES

1. Fortamet prescribing information. Watson Laboratories. July 2008.
2. Glucophage XR prescribing information. August 2008.
3. Glumetza prescribing information. Depomed, Inc. April 2011.
4. American Diabetes Association. Standards of Medical Care in Diabetes – 2015. *Diabetes Care*. January 2015. Vol 38, Supp 1.

5. Garber AJ, Abrahamson MJ, Barzilay J, et al. American Association of clinical endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. *Endocrin Pract.* 2013;19(Suppl 2):1-48.