Metformin ER Step Therapy Program Summary

This program applies to the Commercial, GenPlus, NetResults F series and Health Insurance Marketplace formularies.

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)[b]
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

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.

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

Both the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) recommend metformin as the optimal non-insulin first-line drug in type II diabetes mellitus.[4,5] Two-drug combinations should be used if metformin fails to achieve A1c target after approximately 3 months.[4,5] The choice of the second agent (sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter 2 inhibitor, basal insulin, glucagon-like peptide 1 agonist) is based upon patient and drug characteristics, with the goal of improving glycemic control while minimizing side effects.[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 Diabetes Mellitus Type 2 (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 mg 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. [1-3]

REFERENCES

1. Fortamet prescribing information. Watson Laboratories. April 2017.
2. Glucophage XR prescribing information. April 2017.
3. Glumetza prescribing information. Depomed, Inc. April 2017.
4. American Diabetes Association. Standards of medical care in diabetes-2016. Diabetes Care 2017. Accessed 10/9/2017. Available at https://professional.diabetes.org/content/clinical-practice-recommendations.
5. Garber AJ, Abrahamson MB, Barzilay J, et al. Consensus statement by the American association of clinical endocrinologists and American college of endocrinology on the comprehensive type 2 diabetes management algorithm – 2017 executive summary. Accessed 10/9/2017. Available at https://www.aace.com/publications/guidelines.

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