Metformin Extended-Release Oral Solution

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Metformin hydrochloride extended-release oral suspension (Riomet ER) is a reformulation of a biguanide that was approved by the U.S. Food and Drug Administration on 29 August 2019 for the treatment of type 2 diabetes (1). The American Diabetes Association's *Standards of Medical Care in Diabetes—2021* recommends metformin as the preferred initial pharmacological agent for treatment of type 2 diabetes (2). These guidelines also recommend that, once initiated, metformin should be continued as tolerated.

Before the approval of Riomet ER, metformin was available as immediate-release tablets, extended-release tablets, and an immediate-release oral solution. Metformin is the only biguanide agent currently available in the United States. According to GoodRx, it was the eighth most commonly prescribed medication in the United States as of August 2020 (3).

Indication

Riomet ER is indicated to be used in combination with diet and exercise to improve glycemic control in both adults and children ≥10 years of age with type 2 diabetes (4). Riomet ER is available as 47.31 g metformin hydrochloride for reconstitution in a 473-mL bottle. Upon reconstitution, the final concentration is 500 mg/5 mL.

The recommended starting dose is 5 mL (500 mg) orally once daily with the evening meal. The dose can be increased in 5-mL increments weekly up to a maximum dose of 20 mL (2,000 mg) once daily with the evening meal. Patients receiving metformin immediate-release can be switched to Riomet ER at the same total daily dose they are currently taking up to 20 mL once daily. Pediatric dose recommendations are the same as for adults (4).

Mechanism of Action

Metformin improves glucose tolerance without directly altering insulin secretion. Specifically, it decreases hepatic glucose production, decreases intestinal absorption of glucose, and increases insulin sensitivity by increasing peripheral glucose uptake (4). This effect ultimately lowers both basal and postprandial plasma glucose levels without directly altering insulin secretion.

Potential Advantages

The package insert for Riomet ER reports the most common side effects for metformin immediate-release tablets to be diarrhea and nausea/vomiting, among others (4). Although the gastrointestinal (GI) side effects tend to resolve with continued use of metformin, it has been reported that diarrhea led to discontinuation of metformin immediate-release tablets in 6% of patients in a U.S. clinical trial (4). Riomet ER is expected to have a lower incidence of diarrhea compared with metformin immediate-release oral solution.

A retrospective chart review of 471 patients showed no significant difference in rates of GI adverse effects between immediate- and extended-release tablets; however, this review also showed that patients who experience GI adverse effects with immediate-release metformin tablets who are switched to extended-release tablets show significant improvement in rates of diarrhea and GI adverse effects (5). Furthermore, manufacturer Sun Pharmaceutical Industries, Inc., conducted a bioequivalence study in which C_{max} (maximum serum concentration) and area under the curve (total exposure to the drug) values of metformin ER tablets and Riomet ER were evaluated. The 90% CI of geometric mean ratios were all within the range of 0.8–1.25, establishing bioequivalence (6).

Therefore, it can be concluded that Riomet ER could potentially offer the same advantage of reduced GI symptoms in patients who experience GI effects with immediate-release metformin tablets. Other advantages of Riomet ER include that it is easier to swallow, has once-daily dosing, and has the low risk of hypoglycemia found with metformin products in general.

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Potential Disadvantages

As previously discussed, GI upset is commonly seen with metformin usage and can lead to poor adherence and discontinuation in some cases.

Riomet ER, along with other metformin products, carries a black box warning for lactic acidosis. The warning states that post-marketing cases of metformin-related lactic acidosis have resulted in death and other serious injuries such as hypotension and bradyarrhythmias (4). Lactic acidosis resulting from metformin usage is more likely to occur in patients with renal impairment, hepatic impairment, excessive alcohol intake, hypoxic states such as congestive heart failure, and age ≥65 years, as well as in patients undergoing surgery or radiographic imaging studies requiring contrast. Because of these risks, Riomet ER is contraindicated in patients with renal disease or acute or chronic metabolic acidosis (including diabetic ketoacidosis) and in patients undergoing radiographic studies involving contrast (4). Riomet ER carries additional warnings for risk of hypoglycemia when taken with insulin or insulin secretagogues, as well as a risk of vitamin B12 deficiency.

In September 2020, Sun Pharmaceuticals Industries issued a voluntary nationwide recall of Riomet ER after the discovery of NMDA (N-nitrosodimethylamine) present in an amount above the acceptable daily intake limit in one lot of the drug. Previous incidents of NMDA contamination in other formulations of metformin have also been reported, and recalls in the future could potentially lead to drug shortages.

Cost

As of December 2020, the cash price to patients for one bottle (about 480 mL) was estimated to cost $635. For a patient taking 1,000 mg (10 mL) per day, this cost would come to $13.23 per day, or $396.88 per month (7). By comparison, using the same metric of 1,000 mg per day, metformin immediate-release oral solution would be expected to cost $10.25 per day. The cost of 1,000-mg immediate-release tablets varies somewhat but in general is less than $1.00 per day, with extended-release tablets costing about the same (8).

Commentary

The Riomet ER package insert shows average changes in A1C and fasting plasma glucose after 16 weeks of metformin ER tablet therapy versus placebo (4). Doses ranging from 500 mg once daily to 1,000 mg twice daily all showed a significant reduction in both A1C (ranging from −0.4 to −1.1%, respectively) and fasting plasma glucose (ranging from −15.2 to −33.6 mg/dL, respectively). Based on the reported bioequivalence of metformin ER tablets and Riomet ER, it can be concluded that Riomet ER will have similar outcomes when taken as directed.

Bottom Line

Metformin is the first-line medication for the treatment of type 2 diabetes and is recommended for prevention or delay of diabetes onset in people at risk for developing type 2 diabetes. Riomet ER will offer patients once-daily dosing of metformin in a formulation that is easier to swallow and less likely to cause GI side effects. Having a convenient and palatable formulation with minimal side effects is crucial for optimal adherence and glycemic control in conjunction with lifestyle modifications; however, the cost of this new formulation may prohibit its use in some patients.

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