Clinical Policy: Semaglutide (Rybelsus)
Reference Number: HIM.PA.02
Effective Date: 03.01.20
Last Review Date: 02.20
Line of Business: HIM

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Semaglutide (Rybelsus®) is a synthetic glucagon-like peptide-1 (GLP-1) receptor agonist.

FDA Approved Indication(s)
Rybelsus is indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitation(s) of use:
• Not recommended as a first-line therapy for patients inadequately controlled on diet and exercise.
• Has not been studied in patients with a history of pancreatitis.
• Not indicated for use in patients with type 1 diabetes mellitus or treatment of diabetic ketoacidosis.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Rybelsus is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Type 2 Diabetes Mellitus (must meet all):
      1. Diagnosis of type 2 diabetes mellitus;
      2. Age ≥ 18 years;
      3. Member meets one of the following (a or b):
         a. Failure of ≥ 3 consecutive months of metformin as evidenced by HbA1c ≥ 7%, unless contraindicated or clinically significant adverse effects are experienced;
         b. HbA1c drawn within the past 3 months is ≥ 8.5%, and concurrent use of metformin unless contraindicated or clinically significant adverse effects are experienced;
      4. Failure of a sodium-glucose co-transporter 2 (SGLT2) inhibitor (see Appendix B), unless clinically significant adverse effects are experienced or all are contraindicated;
      5. Dose does not exceed 14 mg (one tablet) per day.

   Approval duration: 12 months

   B. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace.

II. Continued Therapy
A. Type 2 Diabetes Mellitus (must meet all):
   1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   2. Member is responding positively to therapy;
   3. If request is for a dose increase, new dose does not exceed 14 mg (one tablet) per day.
   
   **Approval duration: 12 months**

B. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   
   **Approval duration: Duration of request or 12 months (whichever is less); or**

   2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace.

III. Diagnoses/Indications for which coverage is NOT authorized:
A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – HIM.PHAR.21 for health insurance marketplace.

IV. Appendices/General Information
Appendix A: Abbreviation/Acronym Key
- AACE: American Association of Clinical Endocrinologists
- ACE: American College of Endocrinology
- ADA: American Diabetes Association
- ER: extended-release
- FDA: Food and Drug Administration
- GLP-1: glucagon-like peptide-1
- HbA1c: glycated hemoglobin
- IR: immediate-release

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/ Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformin (Fortamet®, Glucophage®, Glucophage® XR, Glumetza®)</td>
<td>Regular-release (Glucophage): 500 mg PO BID or 850 mg PO QD; increase as needed in increments of 500 mg/week or 850 mg every 2 weeks</td>
<td>Regular-release: 2,550 mg/day</td>
</tr>
<tr>
<td></td>
<td>Extended-release:</td>
<td>Extended-release: 2,000 mg/day</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/Maximum Dose</td>
</tr>
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<td>-----------------------------------</td>
<td>---------------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Fortamet, Glumetza: 1,000 mg PO QD; increase as needed in increments of 500 mg/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week</td>
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<td></td>
</tr>
</tbody>
</table>

**SGLT2 Inhibitors**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farxiga (dapagliflozin)</td>
<td>5 mg PO QD</td>
<td>10 mg/day</td>
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<tr>
<td>To reduce the risk of hospitalization for heart failure, the recommended dose is 10 mg PO QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyxambi (empagliflozin/linagliptin)</td>
<td>One 10/5 mg tablet PO QD</td>
<td>25/5 mg/day</td>
</tr>
<tr>
<td>Invokamet (canagliflozin/metformin)</td>
<td>One 50/500 mg tablet PO BID</td>
<td>300/2,000 mg/day</td>
</tr>
<tr>
<td>Invokamet XR (canagliflozin/metformin)</td>
<td>Two 50/500 mg tablets PO QD</td>
<td>300/2,000 mg/day</td>
</tr>
<tr>
<td>Invokana (canagliflozin)</td>
<td>100 mg PO QD</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>Jardiance (empagliflozin)</td>
<td>10 mg PO QD</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>Qtern (dapagliflozin/saxagliptin)</td>
<td>One 5/5 mg tablet PO QD</td>
<td>10/5 mg/day</td>
</tr>
<tr>
<td>Qternmet XR (dapagliflozin/saxagliptin/metformin)</td>
<td>Individualized dose PO QD</td>
<td>10/5/2,000 mg/day</td>
</tr>
<tr>
<td>Steglujan (ertugliflozin/sitagliptin)</td>
<td>One 5/100 mg tablet PO QD</td>
<td>15/100 mg/day</td>
</tr>
<tr>
<td>Synjardy (empagliflozin/metformin)</td>
<td>Individualized dose PO BID</td>
<td>25/2,000 mg/day</td>
</tr>
<tr>
<td>Synjardy XR (empagliflozin/metformin)</td>
<td>Individualized dose PO QD</td>
<td>25/2,000 mg/day</td>
</tr>
<tr>
<td>Trijardy XR (empagliflozin/linagliptin/metformin)</td>
<td>Individualized dose PO QD</td>
<td>25/5/2,000 mg/day</td>
</tr>
<tr>
<td>Xigduo XR (dapagliflozin/metformin)</td>
<td>Individualized dose PO QD</td>
<td>10/2,000 mg/day</td>
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</tbody>
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*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

**Appendix C: Contraindications/Boxed Warnings**

- Contraindication(s):
  - Hypersensitivity to any product components
  - Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
- Boxed warning(s): thyroid C-cell tumors

Appendix D: General Information
- A double-blind, placebo-controlled dose-response trial by Garber et al. found the maximal efficacy of metformin to occur at doses of 2,000 mg. However, the difference in adjusted mean change in HbA1c between the 1,500 and 2,000 mg doses was 0.3%, suggesting that the improvement in glycemic control provided by the additional 500 mg may be insufficient when HbA1c is > 7%.
- Per the 2019 American Diabetes Association (ADA) and 2019 American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guidelines:
  - Metformin is recommended for all patients with type 2 diabetes. Monotherapy is recommended for most patients; however:
    - Starting with dual therapy (i.e., metformin plus another agent, such as a sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, sodium-glucose co-transporter inhibitor, GLP-1 receptor agonist, or basal insulin) may be considered for patients with baseline HbA1c ≥ 1.5% above their target per the ADA (≥ 7.5% per the AACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is < 7% (≤ 6.5% per the AACE/ACE).
    - Starting with combination injectable therapy (i.e., with GLP-1 receptor agonist or insulin) may be considered for patients with baseline HbA1c ≥ 10% or ≥ 2% above their target per the ADA (> 9% if symptoms are present per the AACE/ACE).
  - If the target HbA1c is not achieved after approximately 3 months of monotherapy, dual therapy should be initiated. If dual therapy is inadequate after 3 months, triple therapy should be initiated. Finally, if triple therapy fails to bring a patient to goal, combination injectable therapy should be initiated. Each non-insulin agent added to initial therapy can lower HbA1c by 0.7-1%.

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rybelsus</td>
<td>Initial dose: 3 mg PO QD. After 30 days on the 3 mg dose, increase to 7 mg PO QD. May increase to 14 mg PO QD if needed after at least 30 days on the 7 mg dose</td>
<td>14 mg/day</td>
</tr>
</tbody>
</table>

VI. Product Availability
- Tablet: 3 mg, 7 mg, 14 mg

VII. References


Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created per SDC and prior clinical guidance.</td>
<td>02.25.20</td>
<td>02.20 (ad hoc)</td>
</tr>
</tbody>
</table>

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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