Clinical Policy: Tirzepatide (Zepbound)

Reference Number: CP.PMN.298
Effective Date: 12.20.24
Last Review Date: 02.25
Line of Business: HIM, Medicaid

Coding Implications
Revision Log

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

Description

Tirzepatide (Zepbound®) is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist.

FDA Approved Indication(s)

Zepbound is indicated in combination with a reduced-calorie diet and increased physical activity:

- To reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition
- To treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity

Limitation(s) of use: Coadministration with other tirzepatide-containing products or any GLP-1 receptor agonist is not recommended.

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 Zepbound is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Obstructive Sleep Apnea (must meet all)**:**

1. Diagnosis of moderate to severe OSA confirmed by polysomnography or home sleep apnea test with an apnea-hypopnea index (AHI) ≥ 15 respiratory events per hour;
2. Age ≥ 18 years;
3. Body mass index (BMI) ≥ 30 kg/m^2;
4. Member does not have central or mixed sleep apnea;
5. For members with concurrent type 2 diabetes mellitus, both of the following (a and b):
   a. Failure of ≥ 3 consecutive months of Ozempic® or Rybelsus®, Trulicity®, and Victoza®, unless clinically significant adverse effects are experienced or all are contraindicated;*
      **Prior authorization may be required*
   b. If member is currently receiving a GLP-1 receptor agonist and is requesting to switching to Zepbound, medical justification* supports necessity for Zepbound;
      **Intolerance due to common adverse effects of the GLP-1 receptor agonists class such as gastrointestinal symptoms is not considered acceptable medical justification*

6. Documentation supports member's participation in physician-directed weight loss program that involves a reduced calorie diet, increased physical activity, and behavioral modification that meets both of the following (a and b):
   a. Been actively enrolled in a physician-directed weight loss program for at least 6 months;
   b. Will continue to be actively enrolled in a weight loss program while concomitantly prescribed Zepbound;
7. Member meets one of the following (a or b):
   a. History of non-adherence to positive airway pressure (PAP) therapy;
   b. Zepbound is prescribed concurrently with PAP therapy, unless contraindicated or clinically significant adverse effects are experienced;
8. Zepbound is not prescribed concurrently with other tirzepatide-containing products or any other GLP-1 receptor agonist(s);
9. Documentation of member's baseline body weight in kg;
10. Dose does not exceed the following:
    a. Week 1 through 4: 2.5 mg once weekly;
    b. Week 5 through 8: 5 mg once weekly;
    c. Week 9 through 12: 7.5 mg once weekly;
    d. Week 13 through 16: 10 mg once weekly;
    e. Week 17 through 20: 12.5 mg once weekly;
    f. Week 21 through 24: 15 mg once weekly;
    g. One pen or vial per week.

Approval duration: 6 months

B. Weight Management

1. Use of Zepbound for the treatment of weight management is a benefit exclusion and will not be authorized.

Approval duration: Not applicable

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Obstructive Sleep Apnea (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B)*;
2. Member is responding positively to therapy as evidenced by one of the following (a or b):
   a. If this is the first renewal request, both of the following (i and ii):
      i. Member has lost ≥ 5% of baseline body weight;
      ii. Any of the following parameters (1, 2, or 3):
         1) AHI reduction from baseline;
         2) Improvement from baseline in the sleep apnea-specific hypoxic burden (SASHB) score;
         3) Improvement from baseline in any one of the sleep-related patient reported outcomes scores (e.g., ESS, Calgary SAQLI, FOSQ, PROMIS sleep-related impairment or sleep disturbance; *see Appendix D*);
   b. If this is a second or subsequent renewal request, both of the following (i and ii):
      i. Member has lost weight and/or maintained weight loss on therapy;
      ii. Stabilization or improvement in any of the following parameters (1, 2, or 3):
         1) AHI;
         2) SASHB;
         3) Sleep-related patient reported outcomes scores (e.g., ESS, Calgary SAQLI, FOSQ, PROMIS sleep-related impairment or sleep disturbance);
3. Zepbound is not prescribed concurrently with other tirzepatide-containing products or any other GLP-1 receptor agonist(s);
4. Documentation that member is actively enrolled in a weight loss program that involves a reduced calorie diet, increased physical activity, and behavioral modification adjunct to therapy;
5. Request meets all the following (a, b, and c):
   a. Dose does not exceed 15 mg once weekly;
   b. After the initial dose escalation period (*see Section V*), maintenance dose is ≥ 10 mg once weekly;
   c. Requested quantity does not exceed one pen or vial per week.

Approval duration:
First reauthorization – 6 months
Subsequent reauthorization – 12 months

B. Weight Management
1. Use of Zepbound for the treatment of weight management is a benefit exclusion and will not be authorized.

Approval duration: Not applicable

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AHI: apnea-hypopnea index
BMI: body mass index
ESS: Epworth sleepiness scale
FDA: Food and Drug Administration
FOSQ: functional outcomes of sleep questionnaire
GIP: glucose-dependent insulinotropic polypeptide
GLP-1: glucagon-like peptide-1
MEN 2: multiple endocrine neoplasia syndrome type 2
MTC: medullary thyroid carcinoma
OSA: obstructive sleep apnea
PAP: positive airway pressure
PROMIS: patient-reported outcomes measurement information system
QOL: quality of life
PSG: polysomnography
SAQLI: sleep apnea QOL index
SASHB: sleep apnea-specific hypoxic burden
T2DM: type 2 diabetes mellitus

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2), known serious hypersensitivity to tirzepatide or to any of the excipients in Zepbound
- Boxed warning(s): risk of thyroid C-cell tumors

Appendix D: General Information

- BMI = 703 x [weight (lbs)/height (inches)^2]

- The American Academy of Sleep Medicine (AASM) classifies the severity of OSA based on polysomnography-derived AHI cutoffs:
  - Mild: ≥ 5 to < 15 events per hour
  - Moderate: ≥ 15 to < 30 events per hour
  - Severe: ≥ 30 events per hour
- The American Thoracic Society practice guidelines recommends that patients with OSA who are overweight or obese be treated with comprehensive lifestyle intervention consisting of 1) a reduced-calorie diet, 2) exercise or increased physical activity, and 3) behavioral guidance.
- The American Association of Clinical Endocrinologists and American College of Endocrinology practice guidelines also recommends patients with OSA who are overweight or obese be treated with weight-loss therapy including lifestyle intervention and additional modalities as needed. The weight loss goal should be at least 7 or 11% or more.
- Sleep apnea-specific and sleep-related patient reported scores:

Name	Description	Interpretation
Calgary sleep apnea QOL index (SAQLI)	A 35-item, interview-administered scale, the SAQLI evaluates four domains of quality of life associated with sleep apnea: daily functioning, social interactions, emotional functioning, and symptoms. Optional 5th domain assessing treatment-related symptoms.	Higher scores indicate better quality of life
Epworth sleepiness scale (ESS)	A very short, self-administered questionnaire with 8 questions intended to measure daytime sleepiness. Respondents are asked to rate on a 4-point scale.	A score of 10 or greater indicates excessive (abnormal) daytime sleepiness .
Functional outcomes of sleep questionnaire (FOSQ)	Consisting of 30 questions related to the effects of fatigue on daily activities, evaluating the respondent's quality of life as it relates to disorders of excessive sleepiness. Five domains of day-to-day life are examined: activity levels, vigilance, intimacy and sexual relationships, productivity, and social outcomes.	Lower scores designate more acute issues with sleepiness.
Patient-reported outcomes measurement information system (PROMIS) sleep-related impairment and sleep disturbance	**The PROMIS Short Form v1.0 Sleep-related Impairment 8a** assesses self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments associated with sleep problems or	Higher scores indicating more sleep-related impairment.

Name	Description	Interpretation
	impaired alertness. It consists of 8 items each rated on a 5-point scale. **The PROMIS Short Form v1.0 Sleep Disturbance 8b** assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep, including perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. It consists of 8 items each rated on a 5-point scale.	Higher scores indicating more sleep disturbance.
Sleep apnea-specific hypoxic burden (SASHB)	SASHB is calculated by measuring the area under the oxygen desaturation curve during an overnight sleep study. It considers the frequency, depth, and duration of respiratory events, which are key features of the disease.	Higher values of SASHB are associated with higher risk of cardiovascular events and mortality.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
OSA	The recommended starting dosage is 2.5 mg SC once weekly for 4 weeks and increased by 2.5 mg every 4 weeks until the maximum tolerated recommended maintenance dose of 10 mg or 15 mg is achieved	15 mg/week

VI. Product Availability

- Pre-filled, single-dose pens: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg
- Pre-filled, single-dose vials: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg

VII. References

1. Zepbound Prescribing Information. Indianapolis, IN: Lilly USA, LLC; December 2024. Available at: https://uspl.lilly.com/zepbound/zepbound.html#pi. Accessed January 15, 2024.
2. Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. NEJM. 2024 Jun 21. doi: 10.1056/NEJMoa2404881. Epub ahead of print.
3. Clinicaltrials.gov. Obstructive sleep apnea master protocol GPIF: A study of tirzepatide (LY3298176) in participants with obstructive sleep apnea (SURMOUNT-OSA). Available at: https://clinicaltrials.gov/study/NCT05412004. Accessed September 12, 2024.
4. Epstein LJ, Kristo D, Strollo PJ, et al. Adult obstructive sleep apnea task force of the American Academy of Sleep Medicine: Clinical guideline for the evaluation, management, and long-term care of obstructive sleep apnea in adults. Journal of Clinical Sleep Medicine 2009. 5(3): 263-276.

5. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. Journal of Clinical Sleep Medicine 2017. 13(3):479-504.
6. Patil SP, Ayappa IA, Caples SM, et al. Treatment of adult obstructive sleep apnea with positive airway pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. Journal of Clinical Sleep Medicine 2019. 15(2): 335-343.
7. Mediano O, Gonzalez Mangado N, Montserrat JM, et al. [Translated article] International consensus document on obstructive sleep apnea. Archivos de Bronconeumologia 2022. 58:T52-T68.
8. Hudgel DW, Patel SR, Ahasic AM, et al; The role of weight management in the treatment of adult obstructive sleep apnea. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2018 Sep 15;198(6):e70-e87.
9. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr Pract 2016;22:Suppl 3:1-203.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively for OSA	10.22.24	11.24
RT4: Drug is now FDA approved for OSA – criteria updated per FDA labeling; added option for OSA diagnosis with home sleep apnea test; references reviewed and updated.	01.15.25	02.25
2Q 2025 annual review: added Rybelsus as option for step therapy; for documentation of weight loss program, added member has been actively enrolled for at least 6 months and continues to be actively enrolled while concomitantly prescribed Zepbound; for continued therapy, modified approval duration for first reauthorization as 6 months and subsequent reauthorization as 12 months; references reviewed and updated.	02.07.25	05.25

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.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible 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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

©2024 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.