Molina Clinical Policy
Papzimeos (zopapogene-imadenovec)
Policy No. 474

Last Approval: 10/08/2025
Next Review Due By: October 2026

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy covers the use of Papzimeos (zopapogene imadenovec) for the treatment of adult recurrent respiratory papillomatosis (RRP).

Recurrent respiratory papillomatosis is an acquired condition due to HPV infection (Human Papilloma Virus) along the respiratory tract. Papillomatous (wart-like) tumors at the larynx and vocal cords can lead to hoarseness, voice change, wheezing, chronic dyspnea, post obstructive pneumonia and airway obstruction. Rarely RRP can lead to squamous cell cancer of the respiratory tract. There are approximately 2,000 individuals affected by RRP in the United States with an annual incidence of 2-4 per one hundred thousand. The primary treatment for problematic RRP is surgical excision or laser ablation although papillomas can recur. Severe RRP may require dozens or even 100s of interventions to maintain airway patency & vocal function. Repeat surgeries can lead to significant morbidities. Curative therapies do not exist. There are adjunct therapies, but they do not typically address the underlying HPV infection (Fortes et al 2017; Hayes 2025).

Papzimeos is an *in vivo* gene therapy that induces HPV specific T cell responses focused on HPV infected cells. Papzimeos uses an adenoviral vector to deliver a gene that is translated into a fusion antigen of selected regions of human papillomavirus (HPV) proteins in HPV 6- and HPV 11-infected cells. It's administered in a series of 4 doses after initial debulking of papillomatous tissue from the larynx, trachea or lungs (Papzimeos prescribing information, 2025).

COVERAGE POLICY

Papzimeos (zopapogene Imadenovec) for the treatment of adult recurrent respiratory papillomatosis (RRP) may be **considered medically necessary** when ALL the following criteria are met:

1. Age 18 years and older

2. Clinical diagnosis of RRP (Recurrent Respiratory Papillomatosis)
   a. Histological diagnosis of papilloma confirmed by pathology report from a CLIA-certified laboratory
   b. Presence of laryngotracheal papillomas with or without pulmonary RRP
   c. A history of 3 or more interventions in the last 12 months for control of RRP
   d. Clinical performance status of ECOG of 0-1

3. Members must have adequate organ and marrow function as defined below:
   a. Bone marrow:
      i. absolute neutrophil count) ≥1500 cells/mm^3
      ii. platelets ≥ 100,000/mm^3
      iii. hemoglobin ≥9 g/dL

b. Hepatic:
   i. total serum bilirubin ≤ 1.5 × upper limit of normal (ULN)
   ii. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 2.5 × ULN
c. Renal function: serum creatinine ≤ 1.5 × ULN

4. Sexually active subjects (men and women) of reproductive potential must agree to use contraception throughout treatment and for at least 120 days after treatment

5. Seronegative for hepatitis B antigen. Positive hepatitis B testing can be further evaluated by confirmatory tests (Hep B DNA quant, HBV viral load). Confirmatory tests must be negative to proceed with therapy

6. Seronegative for hepatitis C antibody unless antigen negative. If the hepatitis C antibody test is positive, the presence of antigen by hepatitis C RNA quantitative testing, hepatitis C viral load, and hepatitis C RNA are negative

7. No History of significant (i.e., active) cardiovascular disease, cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (greater than or equal to New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication

8. No history of severe acute or chronic medical conditions including liver disease, lung disease (with the exception of RRP), or laboratory abnormalities that may increase the risk associated with the administration or efficacy of Papzimeos. Members with mild to moderate asthma or chronic obstructive pulmonary disease (COPD) well controlled with oral or inhaled medications are permitted

9. No history of a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of Papzimeos administration. Inhaled, topical intranasal or intra-ocular steroids, and adrenal replacement doses <10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease

10. There should be no ongoing side effects from previous treatments that are worse than Grade 1 (mild), based on NCI-CTCAE v5.0. However, hair loss, mild sensory nerve issues (Grade 2 or less), or other mild side effects (Grade 2 or less) that don't pose a safety risk are allowed.

11. Absent substance use disorder (alcohol or drugs)

12. Not currently pregnant or breastfeeding

Limitations and Exclusions

QUANTITY LIMITATIONS: FDA approved dosing with one-time set of 4 doses administered over a 12 week period per lifetime. Additional infusions will not be authorized.

CONTINUATION OF THERAPY: Repeat treatment or re-administration of a dose is not supported by labeling or compendia and is not considered medically necessary as of August 2025.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Papzimeos (PRGN-2012) FDA approval was supported by a phase 1/2 clinical trial, NCT04724980. This was a single arm, non-randomized trial. This trial initially enrolled 15 individuals. Three were at the low dose and 12 at the high dose (5 x 10 11 particle units) that eventually became the FDA approved dose.

The primary outcome was the number of surgical interventions post therapy as compared to the number of interventions pre-therapy. Complete response was defined as no interventions during the study follow-up period of 12 months. Partial response was defined as 50% or less surgical interventions post treatment as compared to baseline. Overall response was the combined complete and partial response (Norberg et al 2025).

There were no grade 3 or 4 adverse events in the phase 1 trial. There were 2 patients with grade 2 fatigue & myalgia. The phase 1 trial showed therapeutic safety, and suggested efficacy with a 58% overall response rate in the high dose group.

The phase 2 trial added 23 new patients to the 12 participants carried over from the phase 1 trial (Norberg, 2025). Median age of the study group was 49. There was a total of 35 participants, 25 of them had prior preventative HPV vaccine. Participants had a median of 40 prior surgical procedures.

Primary outcome was the percentage of complete responders within a 12-month follow-up period. Fifty one percent of participants in the phase 2 trial did not require an intervention during the 12-month trial period. Extended follow up of the complete responders (median duration of 22 months) showed no surgical interventions.

Secondary outcomes were overall response which included both complete and partial responders as defined above. The overall response was 66%. Interventions among partial responders were reduced from baseline of 2 to a median of 1 & for complete responders the median interventions dropped from 3 in the prior 6 months to 0.

Other secondary outcomes were change in Derkay score (a measure of papillomatous disease burden) and the change in vocal cord handicap 10 index (VHI-10). Complete responder's Derkay score (disease burden) was reduced by 90% and their VHI-10 score was reduced by 95%. Partial responders Derkay and VHI-10 scores were reduced by 32% and 14% respectively. There were 4 patients with evaluable pulmonary RRP. Assessment of pulmonary response rate was with CT scans & RECIST version 1.1 criteria (Response Evaluations Criteria in Solid tumors). Four participants with pulmonary RRP had no significant change in lung lesions. There was no difference in adverse response rates as compared to the phase 1 study. There was a participant death, however the death was unrelated to the therapy. That individual had a myocardial infarction (MI) and passed. The MI was attributed to coronary artery disease and severe aortic stenosis.

A phase 3 trial (NCT06538480) is underway.

National and Specialty Organizations
As of August 2025, No guidelines have recommendations for Papzimeos at this time.

SUPPLEMENTAL INFORMATION

Staging System for Assessing Severity of Disease and Response to Therapy in Recurrent Respiratory Papillomatosis
Derkay et al (1998).

STAGING ASSESSMENT FOR RECURRENT LARYNGEAL PAPILLOMATOSIS

PATIENT INITIALS:_____ DATE OF SURGERY_____ SURGEON_____
PATIENT ID #_____ INSTITUTION_____

1. How long since the last papilloma surgery? _____days, ____weeks, ____months,
   ____years,____ don't know,
   _____this is the child's first surgery
2. Counting today's surgery, how many papilloma surgeries in the past 12 months? _____
3. Describe the patient's voice today:
   normal__(0), abnormal__(1), aphonic__(2)
4. Describe the patient's stridor today:
   absent__(0), present with activity__(1), present at rest__(2)
5. Describe the urgency of today's intervention:
   scheduled__(0),elective__(1),urgent__(2),emergent(3)
6. Describe today's level of respiratory distress:
   none__(0), mild__(1), Mod__(2), severe__(3), extreme__(4)

Total score for questions 3-6=_____

FOR EACH SITE, SCORE AS: 0= NONE, 1= SURFACE LESION, 2=RAISED LESION, 3=BULKY LESION

LARYNX:
- Epiglottis
  - Lingual surface_____ Laryngeal surface_____
- Aryepiglottic folds: Right____ Left_____
- False vocal cords: Right____ Left_____
- True vocal cords: Right____ Left_____
- Arytenoids: Right_____ Left_____
- Anterior commissure_____
- Posterior commissure_____
- Subglottis _____

TRACHEA:
- Upper one-third_____
- Middle one-third_____
- Lower one-third_____
- Bronchi: Right____ Left_____
- Tracheotomy stoma_____

OTHER:
- Nose_____
- Palate_____
- Pharynx_____
- Esophagus_____
- Lungs_____
- Other_____

CODING & BILLING INFORMATION

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
C9399	Unclassified drugs or biologicals [when specified as Papzimeos (Zopapogene-imadenovec)]
J3590	Unclassified biologics [when specified as Papzimeos (Zopapogene-imadenovec)]

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

10/08/2025 New policy. IRO Peer Review on September 28, 2025), by a practicing physician board-certified in Otolaryngology-Head and Neck Surgery

REFERENCES

1. ClinicalTrials.gov. NCT04724980. Adjuvant PRGN-2012 in Adult Patients With Recurrent Respiratory Papillomatosis. Accessed August 24 2025. Last updated June 11, 2025. https://clinicaltrials.gov/study/NCT04724980?term=PRGN-2012&rank=2
2. Derkay CS, Malis DJ, Zalzal G, et al. A staging system for assessing severity of disease and response to therapy in recurrent respiratory papillomatosis. Laryngoscope. 1998 Jun;108(6):935-7. doi: 10.1097/00005537-199806000-00026. PMID: 9628513.
3. Fortes HR, von Ranke FM, Escuissato DL, et al. Recurrent respiratory papillomatosis: A state-of-the-art review. Respir Med. 2017 May;126:116-121. doi: 10.1016/j.rmed.2017.03.030. Epub 2017 Apr 1. PMID: 28427542.
4. Hayes. Zopapogene Imadenovec -drba (Papzimeos; Precigen Inc.) for Recurrent Respiratory papillomatosis. Published August 20, 2025, https://evidence.hayesinc.com/.
5. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: No guidelines for papzimeos. https://www.nccn.org/guidelines/category_1
6. Norberg SM, Valdez J, Napier S, et al. PRGN-2012 gene therapy in adults with recurrent respiratory papillomatosis: a pivotal phase 1/2 clinical trial. Lancet Respir Med. 2025 Apr;13(4):318-326. doi: 10.1016/S2213-2600(24)00368-0. Epub 2025 Jan 21. Erratum in: Lancet Respir Med. 2025 Apr;13(4):e22. doi: 10.1016/S2213-2600(25)00078-5. PMID: 39855244; PMCID: PMC11968209.
7. United States Food and Drug Administration (FDA). Prescribing information Papzimeos (Zopapogene imadenovec). Published August 2025. Accessed August 2025. https://www.fda.gov/media/188264/download

APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

This policy contains prior authorization requirements.