Policy Number	**RX501.183**
Policy Effective Date	**05/15/2026**
Policy End Date	**07/31/2026**

Zopapogene imadenovec-drba

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as

generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

EXCEPTION: For members residing in the state of Arkansas, § 23-79-147 relating to off-label prescription drug coverage, requires any plan that covers prescription drugs to provide for the coverage of any anticancer chemotherapeutic regimen ("drug") approved by the U.S. Food and Drug Administration (FDA) when that drug has been recognized as safe and effective for treatment of that specific type of cancer in standard reference compendia, (the American Hospital Formulary Service Drug Information, the National Comprehensive Cancer Network Drugs and Biologics Compendium, The Elsevier Gold Standard's Clinical Pharmacology), or has been recognized as safe and effective for treatment of that specific type of cancer in two [2] articles from medical literature that have not had their recognition of the drug's safety and effectiveness contradicted by clear and convincing evidence presented in another article from medical literature, or other authoritative compendia as identified by the Secretary of the United States Department of Health and Human Services. This coverage must include medically necessary services associated with the administration of the drug, provided that such services are covered by the insurance policy. However, coverage is never required where the FDA has recognized a use to be contraindicated. This applies to the following: Fully Insured Group, Student, Small Group, Mid-Market, Large Group, HMO, EPO, PPO, POS. Unless indicated by the group, this mandate or coverage will not apply to ASO groups.

Coverage

Zopapogene imadenovec-drba (Papzimeos™) **may be considered medically necessary** when all the following criteria are met:

- Adults with recurrent respiratory papillomatosis (RRP);
- The individual has undergone 3 or more debulking procedures to remove laryngotracheal papillomas during the previous 12 months;
- Surgical debulking has left the individual with minimal residual disease.

Zopapogene imadenovec-drba (Papzimeos™) **is considered experimental, investigational and/or unproven** for all other non-U.S. Food and Drug Administration (FDA) approved indications.

Policy Guidelines

Dosage and Administration (1)
NOTE: Papzimeos™ is a prescription medication that must be administered by a healthcare provider via subcutaneous injection.

The recommended dosage of Papzimeos is $5x10^{11}$ particle units (PU) per injection administered as subcutaneous injection four times over a 12-week period. The recommended dosing schedule is shown in Table PG1.

Table PG1. Recommended Treatment Schedule for Papzimeos™

Administration	Administration Interval
Initial	-
Second	2 weeks after initial administration[1]
Third	6 weeks after initial administration
Fourth	12 weeks after initial administration

[1] The second administration should occur no less than 11 days after the initial administration.

Prior to the initial administration of Papzimeos, perform a surgical debulking of visible papilloma to establish minimal residual disease. To maintain minimal residual disease during treatment with Papzimeos, remove visible papilloma, if present, prior to the third and fourth administration of Papzimeos.

Description

Recurrent Respiratory Papillomatosis

Recurrent respiratory papillomatosis (RRP) is a rare disorder characterized by the development of small, wart-like growths (papillomas) in the respiratory tract, which includes the nose, mouth, throat (pharynx), voice box (larynx), windpipe (trachea), various airway passages (bronchi) and lungs. Papillomas can develop anywhere along the respiratory tract, but most often affect the larynx and the vocal cords (laryngeal papillomatosis). Less often, the disorder affects the area within the mouth (oral cavity), trachea and bronchi. Only in rare cases do these growths spread to affect the lungs. Papillomas are benign but in extremely rare cases can become malignant. They can cause severe, even life-threatening airway obstruction and respiratory complications. In RRP, papillomas tend to grow back even after they have been removed. (3)

RRP affects all ages and is caused by an infection with human papillomavirus (HPV), although exposure to the virus alone may not be sufficient to cause the disease. Two specific subtypes of HPV, HPV 6 and HPV 11, account for more than 90% of cases of RRP. These two subtypes are the same HPV subtypes most often identified in genital warts (anogenital condyloma). HPV subtypes 16 and 18 account for most of the remaining cases. In children, the most likely cause of the transmission of HPV is passage from an affected mother to the child during labor as the child passes through the birth canal; however, some cases appear to have developed before birth (in utero). In adults, the mode of transmission is less clear. Some cases may represent infection during infancy as described above, but that remains latent until being triggered for unknown reasons in adulthood. Some circumstantial evidence suggests that RRP can develop after HPV is transmitted through oral sexual contact. (3)

In the United States, the incidence of RRP was previously estimated to be approximately 2 per 100,000 adults and 4 per 100,000 children with approximately 1,000 new pediatric cases in the United States each year. With the increased uptake of the HPV vaccine, these numbers are dropping abruptly. (3)

Treatment is directed toward removing papillomas as there is no cure. The basis of treatment is surgical removal of papillomas. However, like warts on the hands and feet, these growths often return necessitating more surgery. The recurrence of papillomas is unpredictable. Some individuals may require surgery every few weeks while others may only require surgery twice a year or only a few times during their life. Surgical techniques used to treat individuals with RRP include "cold" excision, microdebridement, various pulsed dye lasers, or carbon dioxide lasers. Cold excision, sometimes referred to as "cold steel," is the use of sharp surgical equipment to remove papillomas. Cold excision may be beneficial for the initial removal (debulking) of papillomas and for papillomas located in certain areas. Microdebridement is an increasingly popular procedure for use in children with RRP in which suction is applied to affected tissue which is then cut away (debrided) by miniature shavers. Pulsed dye lasers use various light frequencies focused into a single beam to destroy the blood vessels that supply the papillomas. Laser ablation generates a laser beam by passing electricity through a mixture of several different gases including carbon dioxide (CO_2). The CO_2 laser is used to directly destroy papillomas in the larynx and can also be used through a bronchoscope to effectively remove papillomas in the trachea. In severe cases where tumor growth is aggressive, an affected individual may need a tracheostomy to keep the breathing airways open. A tracheostomy is used only as a method of last resort because the procedure may allow for spread of the disease further into the respiratory tract. (3)

Zopapogene imadenovec-drba (Papzimeos™)
Papzimeos is a non-replicating adenoviral vector-based immunotherapy. It uses a modified virus to train the immune system to attack the HPV types 6 and 11 causing the growths. (4) It is given subcutaneously four times over a 12-week period by a healthcare provider. Prior to the initial administration, a surgical debulking of visible papillomas should be performed to establish minimal residual disease. To maintain minimal residual disease during treatment visible papilloma should be removed, if present, prior to the third and fourth administration of Papzimeos. (1)

Regulatory Status
The U.S. Food and Drug Administration (FDA) approved zopapogene imadenovec-drba (Papzimeos™; Precigen Inc., Germantown, MD) for the treatment of adults with recurrent respiratory papillomatosis. (1, 2)

Rationale

This policy is based on the United States (U.S.) Food and Drug Administration (FDA) approved labeled indications for zopapogene imadenovec-drba (Papzimeos™).

Zopapogene imadenovec-drba (Papzimeos™) (1)
The efficacy of Papzimeos was evaluated in an open-label, single-arm study in adults with recurrent respiratory papillomatosis (PRGN-2012-201; NCT04724980). The study enrolled adults who had histological and clinically diagnosed recurrent respiratory papillomatosis and had 3 or more debulking procedures to remove laryngotracheal papillomas in the 12 months prior to treatment with Papzimeos.

A total of 38 patients received subcutaneous injections of Papzimeos on days 1, 15, 43, and 85. Prior to initiation of treatment with Papzimeos (Day 1), patients underwent a standard-of-care surgical debulking procedure to remove laryngotracheal papillomas. Physicians also had the option to remove any visible papillomas during the treatment interval. Of the 38 patients, 3 patients were treated with Papzimeos at a dose of 1×10^{11} particle units (PU) per injection. Thirty-five patients were treated at a dose of 5×10^{11} PU per injection and were included in the efficacy evaluation.

The demographic characteristics of the population were as follows: the median age was 50 years (range 20 to 88 years), 15 patients (39%) were female, 33 patients (87%) were White, 1 patient (3%) was Asian, 1 patient (3%) was African American, 1 patient (3%) was of "other" race, 2 patients (5%) were of unknown race, and 32 patients (84%) were non-Hispanic or Latino. The mean (SD: standard deviation) body mass index (BMI) was 28 (6) kg/m^2. The median number of baseline surgical procedures performed in the 12 months prior to treatment was 4 (range 3 to 10). This included the protocol mandated debulking surgery on Day 1 to establish minimal residual disease.

The primary efficacy endpoint was the percentage of patients with a complete response to Papzimeos treatment, defined as no requirement for surgical intervention in the 12 months after treatment.

At a dose of 5×10^{11} PU per injection, 18 out of 35 patients achieved a complete response at 12 months resulting in a complete response rate of 51% [95% confidence interval (CI) 34 to 69%]. Of the 18 patients with a complete response in the ongoing study, 15 demonstrated continued complete response at 24 months yielding a complete response rate of 43% (95% CI 26 to 61%) at 2 years for the 35 patients in the efficacy population.

At a dose of 1×10^{11} PU per injection, no patient (0 out of 3) achieved a complete response.

According to the FDA label, the safety and effectiveness of Papzimeos have not been established in pediatric patients.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J3404

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U..S. Food and Drug Administration Label

1. FDA. Highlights of prescribing information Papzimeos™ (zopapogene imadenovec-drba). U.S. Food and Drug Administration (8/2025). Available at: <https://www.accessdata.fda.gov> (accessed January 6, 2026).

Other:

2. Papzimeos. Papzimeos: Uses, Dosage, Side Effects, Warnings. September 4, 2025. Available at: <https://www.drugs.com> (accessed January 6, 2026).
3. NORD. Recurrent Respiratory Papillomatosis. June 8, 2023. Available at: <https://www.rarediseases.org> (accessed January 6, 2026).
4. Talavera F. Papzimeos: First Approved Immunotherapy for Recurrent Respiratory Papillomatosis in Adults. Available at: <https://www.webmd.com> (accessed January 6, 2026).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
05/15/2026	New medical document. Zopapogene imadenovec-drba (Papzimeos™) may be considered medically necessary when all the following criteria are met:

	Adults with recurrent respiratory papillomatosis (RRP); The individual has undergone 3 or more debulking procedures to remove laryngotracheal papillomas during the previous 12 months; Surgical debulking has left the individual with minimal residual disease. Zopapogene imadenovec-drba (Papzimeos™) is considered experimental, investigational and/or unproven for all other non-U.S. Food and Drug Administration (FDA) approved indications.