Drug Use Research & Management Program
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New Drug Evaluation: zopapogene imadenovec-drba (PAPZIMEOS)

Date of Review: December 2025
Generic Name: zopapogene imadenovec-drba

End Date of Literature Search: 10/14/25
Brand Name (Manufacturer): Papzimeos (Precigen, Inc.)

Dossier Received: No

Plain Language Summary:

- Recurrent respiratory papillomatosis (RRP) is a rare disease caused by the human papillomavirus (HPV). RRP causes wart-like growths (papillomas) in the airways, such as the windpipe and vocal cords. Most of the growths do not cause cancer but can block the airway.
- Symptoms of RRP are hoarseness, trouble breathing, and voice changes.
- There are two forms of RRP, juvenile-onset and adult-onset. The juvenile-onset occurs in childhood and is often passed from the mother to the baby during childbirth. Adult-onset occurs later and is usually associated with milder symptoms but is often reoccurring.
- The main treatment is surgery to remove the growths. Surgery often needs to be repeated because growths return. Until recently, there were no medications specifically approved by the Food and Drug Administration (FDA) for RRP.
- The FDA approved a new therapy called zopapogene imadenovec, or PAPZIMEOS, for adults with RRP. It is given as 4 injections given under the skin, spaced over 12 weeks.
- Evidence from one small study in 38 patients shows that zopapogene imadenovec decreased the number of surgeries needed for patients with RRP.
- The most common side effects were pain related to the injection, fever and chills.
- The Drug Use Research and Management Group recommends that the Oregon Health Authority pay for zopapogene imadenovec in patients with RRP who need repeated surgeries after their provider documents medical appropriateness through a process called prior authorization.

Research Questions:

1. What is the evidence for efficacy of the zopapogene imadenovec in the treatment of RRP?
2. What is the evidence for the safety of zopapogene imadenovec in the treatment of RRP?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender, disease severity), for whom zopapogene is more effective or associated with less harm?

Conclusions:

- Zopapogene imadenovec is an orphan drug approved for the treatment of RRP. FDA approval was based on one phase 1/2 trial.
- There is low quality evidence that zopapogene imadenovec reduces the number of interventions (i.e., surgical resection or laser ablation) to remove recurrent papillomas in patients with RRP.[1]

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- Zopapogene imadenovec was studied in 38 adults diagnosed with RRP who required 3 or more interventions in the year before treatment .[1] Patients received 4 doses of zopapogene imadenovec over 12 weeks after receiving a debulking procedure prior to administration. The primary outcome was complete response rate, defined as patients who did not require an intervention (i.e., surgery or laser ablation) to control RRP symptoms in the 12 months following treatment. Eighteen of 35 patients (51%) had a complete response.[1] Recurrent respiratory papillomatosis is a very heterogenous disease and there is not a predictable disease course following surgery to remove papillomas. The median number of interventions required in patients in the study in the previous 12 months prior to treatment was 4.
- Zopapogene imadenovec was well tolerated with no discontinuations due to adverse effects. Injection site reactions were the most common adverse event occurring in 97% of patients.[1] Fatigue, chills and fever were also common adverse events.
- There is insufficient evidence to evaluate efficacy or safety of zopapogene imadenovec in specific subgroups based upon age, gender, or disease severity.

Recommendations:
- Make zopapogene imadenovec nonpreferred on the preferred drug list (PDL).
- Implement prior authorization (PA) to allow coverage for adult patients when other RRP treatments have failed.

Background:
Recurrent respiratory papillomatosis is a chronic, variable disease with an incidence of 4.3 per 100,000 children and 1.8 per 100,000 adults in the United States.[2] It is rare disease caused by HPV type 6 or 11 which results in recurrent growth of papillomas in the upper and lower respiratory tracts. The most common sites of infection are the larynx, trachea, and lungs.[1] Adult onset is usually occurs between 20 and 40 years and is typically transmitted through sexual contact. Disease patterns are variable from spontaneous remission to aggressive persistent disease.[3] Presentation in those under 5 years of age can occur and is usually acquired via transmission from mother to child during birth. HPV acquired during birth is the most common benign laryngeal tumor in children.[4] Infection in younger populations is decreasing due to increased rates of preventative HPV vaccination.[1] The clinical symptoms of RRP are dysphonia, stridor, dyspnea, chronic cough and airway occlusion.[5] Recurrent airway lesions can lead to loss of lung volume, post-obstructive pneumonia or respiratory failure and occasionally can cause malignant disease.[6]

Until recently, there were no approved medical therapies for treatment of RRP. Vaccination is effective for prevention but does not consistently provide benefit in those already infected with RRP.[1] Low quality evidence suggests vaccination may decrease the rates of papillomas and need for surgery. The current standard of care for RRP is repeated endoscopic debulking of lesions by ablation or surgical excision.[6] However, debulking surgery does not address the underlying HPV infection, and papillomas can reoccur. Adjuvant treatment is recommended for patients requiring 3 or more surgical removals of papilloma in a year, rapid recurrence of the papilloma with airway compromise, or distal multisite spread.[6] Up to 20% of patients may require adjuvant treatments. Adjuvant treatments studied for RRP include off-label use of immunomodulators (e.g., imiquimod), disruption of HPV replication (e.g., cidofovir), inflammation control (e.g., celecoxib) or prevention of angiogenesis (e.g., bevacizumab).[6] Adverse reactions and variable effectiveness prevent routine use of adjuvant therapies for RRP. Bevacizumab has the most evidence for reducing requirement for surgeries but requires chronic use which can be associated with toxicity.[6]

Due to the rarity of RRP there are no outcome measures or biomarker of disease to reliably track treatment efficacy. The Derkay score is a staging system used for RRP with scores that range from 0-30.[7] Higher scores indicate severe disease. Scoring is based on the number of sites and bulkiness of papillomas in the pharynx, larynx and trachea as well as subjective clinical symptoms (i.e., voice and breathing symptoms).[1] There is no official minimal clinically important difference (MCID), but reductions of 50% or more are considered clinically meaningful .[7] The Voice Handicap Index-10 (VHI-10) is a validated patient-reported

tool to measure the extent that a voice disorder interferes with a patient's daily life.[8] Scores range from 0 to 40 with higher scores suggestive of greater handicap. Scores above 11 are considered abnormal. The MCID is a 6 point or more decrease in scoring.[8]

In 2025, the FDA approved zopapogene imadenovec for treatment of RRP in adults.

Beginning in January 2026, the Oregon Health Authority is proposing that high cost, rarely used medications be carved out of Coordinated Care Organization (CCO) payments and billed directly to fee-for-service (FFS). Medications can be included in this carve-out if they meet the following criteria:

1. Estimated acquisition cost of more than $500,000 per member over a 12-month period
2. Are indicated for rare conditions, and
3. Have few alternatives, as determined by the Oregon Health Authority

Zopapogene imadenovec is currently included in the list of medications proposed to be carved-out of CCO budgets. Zopapogene imadenovec is a one-time treatment course with an estimated cost of $460,000.

Zopapogene imadenovec is a non-replicating adenoviral vector-based immunotherapy that enhances T-cell responses to detect and reduce cells infected with HPV.[9] The dose of zopapogene imadenovec is $5x10^{11}$ particles (1 mL) injected subcutaneously four times over a 12-week time period (at weeks 0, 2, 6 and 12).[9] Surgical debulking of visible papilloma is recommended prior to the initial dose of zopapogene. Removal of additional papilloma is recommended prior to the third and fourth doses if present. Zopapogene imadenovec is supplied as a frozen suspension that must be thawed prior to injection. The thawing process should not exceed 5 minutes, with injection required immediately once thawed.[9] Patients should be monitored for 30 minutes post-injection after initial treatment for local injection site reactions.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 2**.

Clinical Efficacy:

Zopapogene imadenovec was studied in a 12-week single-center, single-arm phase 1/2 study in patients that were 18 years and older with a diagnosis of RRP.[1] Diagnosis was defined as histological diagnosis of papillomas, presence of laryngotracheal papillomas, and history of three or more clinically indicated interventions in the 12 months before treatment. A 30-day washout was required for patients prescribed systemic bevacizumab or any other systemic, adjuvant RRP therapy.[1] The use of corticosteroids or other immunosuppressants was held for 14 days prior to administration of zopapogene imadenovec. HPV vaccine within one year of zopapogene imadenovec was not permitted.[1] Patients received zopapogene as 4 subcutaneous doses at day 1, 15, 43 and 85 following a debulking procedure.[1] Patients with visible papilloma growth underwent additional surgery to maintain residual disease if present at days 43 and 85. Patients had to have an Eastern Cooperative Oncology Group performance score of 0 or 1 which indicates patients were fully active and ambulatory with the ability to carry out light work and are able to tolerate surgery. Higher scores on this scale indicate diminished ability to complete daily activities without assistance. The median age was 49 years, age diagnosis was 35 years, 43% were female and HPV 6 was the primary genotype (69% of patients).[1] The number of lifetime interventions (i.e., surgery) for RRP was 40 and the median number of interventions done in the previous 12 months was 4. The baseline Derkay score was 8, indicating mild disease with limited airway involvement and manageable symptoms. The baseline VHI-10 score was 24, suggestive of moderate handicap, in which the patient experiences significant limitations in daily activities due to their voice.[1] The primary outcome was complete response rate, which was the

percentage of patients with no clinically indicated interventions (i.e., surgical resection or laser ablation) during the 12 months after treatment. Clinically indicated interventions were based on documentation from patient's home care team.

For the primary outcome, 51% of patents had a complete response at 12 months after treatment with zopapogene imadenovec.[1] This response was maintained in 83% of patients up to 33 months after completing treatment.[1] A median of one debulking surgery was required to maintain residual disease in patients that were complete responders during treatment and a median of 2 debulking procedures were required in the non-complete responder group. An objective response (i.e., defined as patients with at least 50% decrease in the number of interventions in the 12 months after treatment compared to the 12 months before treatment) was achieved in 66% (n=23) of patients (95% CI, 48 to 81%).[1] The number of interventions 12 months after treatment was less in complete responders (median of 0) compared to non-complete responders, median of 2 (P<0.001).[1] Time to first intervention was not met because an intervention was not needed by those that had a complete response with follow up of 22 months. Subgroup analysis by the FDA found results to be consistent regardless of HPV type, number of surgeries prior to treatment, and age of disease onset.[6] Additional data analyses on complete responders demonstrated no surgical interventions in 15/18 patients studied out to 2 years and 6/6 patients evaluated at 3 years.[6]

The study had several limitations. Results were presented based on a complete response versus a non-complete response which increases the risk of reporting bias as some outcomes appear more improved compared to reporting results as a whole. There was a high risk of selection and performance bias since there was no randomization and a single-arm, open-label study design. Assessment of RRP was done by patient's home care team which could introduce significant variability in outcome evaluation and increase risk of detection bias. The study was conducted at a single center which reduces external validity. Since RRP is a heterogenous disease with fluctuations in disease severity over time, having a primary outcome evaluated over 12 months may not necessarily predict long-term durability or additional need for surgery.

Clinical Safety:
The most common adverse reactions associated with zopapogene imadenovec were injection-site reactions, fatigue, chills, fever and myalgia.[1,9] These common adverse events are due to the non-replicating adenovector-based immunotherapy mechanism of action which activates an immune response. No serious side effects were reported in the study. There were no discontinuations due to treatment related adverse reactions.[1] There is a risk of thrombosis with adenoviral vector-based therapies which may be caused by cytokine mediated coagulation, endothelial activation and platelet activation.[9]

There are no long-term studies to provide evidence on the chronic use of zopapogene imadenovec. The safety and efficacy of repeated doses, beyond the recommended 4 doses, has not been studied. Zopapogene imadenovec has not been studied in pregnant women. There are unknown safety effects in patients with more severe RRP disease and when the drug is given to a wider population.

Look-alike / Sound-alike Error Risk Potential: none identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Prevention of recurring papillomas
2) Number of interventions to remove papillomas
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Complete response rate (i.e., no need for interventions to remove papillomas for 12 months following treatment)

Table 1. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Norberg, et al SA, SC, OL, Phase 1/2	1. Zopapogene imadenovec $5x10^{11}$ particle units subcutaneously on day 1, 15, 43, and 85* Treatment course: 12 weeks Study duration: 12 months	Demographics: Median age: 49 years Median age at diagnosis: 35 years Juvenile-onset RRP: 12 (34%) Adult-onset RRP: 23 (66%) Female: 15 (43%) Number of lifetime interventions for RRP: 40 HPV 6: 24 (69%) HPV 11: 11 (31%) Median Derkay score: 8 Median VHI-10 score: 24 Key Inclusion Criteria: - Ages 18 years and older - RRP diagnosis - Three or more interventions in the previous year - Eastern Cooperative Oncology Group performance score of 0 or 1. Key Exclusion Criteria: - Immunosuppressant use - History of previous systemic therapy for RRP within 3 half-lives from the previous drug	ITT: 35 PP: 35 Attrition: 0	Primary Endpoint: Complete Response Rate†: 1. 18 (51%) (95% CI, 34% to 69%) Secondary Endpoint: Objective Response Rate‡: 1. 23 (66%) Fewer number of interventions 12 months after treatment compared to 12 months before treatment: 1. 30 patients (86%) (95% CI 70% to 95%) Number of patients with a decrease in Derkay score after treatment compared to baseline: Complete responders: 90% Non-complete responders: 32% Number of patients with a decrease in VHI-10 score changes compared to baseline: Complete responders: 95% Non-complete responders: 14% Median number of clinically indicated interventions during treatment: Responders: 1 Non-complete responders: 2	NA for all	Injection-site Reaction: 34 (97%) Fatigue: 28 (80%) Chills: 25 (71%) Fever: 24 (69%) Serious AE: 0 Discontinuations due to AE: 0	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (High) Trial not randomized. Performance Bias: (High) Trial was open label with no comparison group. Detection Bias: (High) Assessments of primary outcome was based on patient's home care team (otolaryngologist, independent of study team1) which could vary between clinics and providers. Attrition Bias: (Low) None observed. Reporting Bias: (High) Timeframe of measurement of Derkay score and VHI-10 score was not prespecified. Other Bias: (Unclear) Trial was funded by manufacturer. **Applicability**: Patient: Patients Derkay scores indicative of mild impairment and VHI-10 scores indicating severe dysphonia. Patients required debulking surgeries prior to treatment. Intervention: Dose was based on phase 1 phase of the study which demonstrated efficacy and safety. Comparator: None which makes it difficult to determine if zopapogene imadenovec results in fewer interventions compared to standard of care. Outcomes: Number of interventions for papillomas is a clinically appropriate and relevant outcome. Setting: Single-center at National Institutes of Health.

Key: * Treatment started on day 1 following surgical debulking; † Complete response rate was defined as percentage of patients who did not require an intervention to control RRP in the 12 months after treatment; ‡ Percentage of patients with a complete response or partial response (defined as patients with at least 50% decrease in the number of interventions in the 12 months after treatment compared to the 12 months before treatment).
Abbreviations: AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; HPV = human papillomavirus; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; PP = per protocol; RRP = SA = single-arm; SC = single-center; VHI = Vocal Handicap Index 10.

References:

1. Norberg S, 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; 13:318-26.

2. Derkay C, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope. 2008;118(7):1236-47.

3. Fortes H, Ranke F, Escuissato D, 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.

4. Palefsky J. Human papillomavirus infections: Epidemiology and disease associations - UpToDate. Accessed September 18, 2025. https://www.uptodate.com/contents/human-papillomavirus-infections-epidemiology-and-disease-associations?search=recurrent%20respiratory%20papillomatosis&sectionRank=1&usage_type=default&anchor=H15115461&source=machineLearning&selectedTitle=1~13&display_rank=1#H15115461

5. Derkay CS, Wiatrack B. Recurrent respiratory papillomatosis: a review. Laryngoscope. 2008;118:1236-37.

6. Food and Drug Administration. BLA Clinical and Clinical Pharmacology Review Memorandum - Papzimeos. August 2025.

7. 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;108(6):935-937.

8. Rosen CA, Lee AS, Osborne J, et al. Development and validation of the Voice Handicap Index-10. Laryngoscope. 2004;114(9):1549-1556.

9. Papzimeos (zopapogene imadenovec-drba) [prescribing information]. Germantown, MD; Precigen, Inc. August 2025.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PAPZIMEOS™ safely and effectively. See full prescribing information for PAPZIMEOS.

PAPZIMEOS (zopapogene imadenovec-drba) suspension for subcutaneous injection
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------
PAPZIMEOS™ is a non-replicating adenoviral vector-based immunotherapy indicated for the treatment of adults with recurrent respiratory papillomatosis. (1)

----------DOSAGE AND ADMINISTRATION----------
PAPZIMEOS is for subcutaneous injection only. (2.1)

The recommended dose of PAPZIMEOS is 5×10^{11} particle units (PU) per injection administered by subcutaneous injection four (4) times over a 12-week interval. (2.1)

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. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
PAPZIMEOS is supplied in a single-dose vial that contains 5×10^{11} PU in an extractable volume of 1 mL of suspension. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Injection-site reactions: Injection-site reactions, have been observed. Monitor patients for local site reactions for at least 30 minutes after the initial treatment. (5.1)
- Thrombotic events: Thrombotic events may occur following administration of adenoviral vector-based therapies. Monitor patients for signs and symptoms of thrombotic events and treat events according to clinical practice. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥5%) were injection site reactions, fatigue, chills, pyrexia, myalgia, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Precigen Inc. at 855-743-6777 and medinfo@precigen.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2025

Appendix 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Non-replicating adenoviral vector-based immunotherapy
Oral Bioavailability	Not applicable
Distribution and Protein Binding	Not studied
Elimination	Not studied
Half-Life	Not studied
Metabolism	Not studied

Appendix 3: Proposed Prior Authorization Criteria

Papzimeos™ (zopapogene imadenovec-drba)

Goal(s):

- To allow for the adjuvant treatment of recurrent respiratory papillomatosis (RRP) in patients who have persistent disease despite surgical intervention.
- Incorporate 2-step review process for drugs on the high-cost drug carve-out list.

Length of Authorization:

- Up to 12 months

Requires PA:

- All doses of Papzimeos™ (zopapogene imadenovec-drba) require PA

Covered Populations: FFS and CCO patients beginning 1/1/26

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is this an FDA approved age? Note: Papzimeos is currently approved for adults.	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for a patient with recurrent respiratory papillomatosis (RRP)? * Note: Recurrent is defined as a need for 3 or more debulking procedures for papillomas related to RRP in the previous 12 months	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient been previously treated with Papzimeos?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for one treatment course (4 doses over 12 weeks). Approval start and end dates can be extended to accommodate scheduling visits.

P&T/DUR Review: 12/25 (KS)
Implementation: 1/1/26