



FINAL CDEC RECOMMENDATION

GRASS POLLEN ALLERGEN EXTRACT

(Oralair – Paladin Labs Inc.)

Indication: Allergic Rhinitis (Grass Pollen)

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that 5-grass pollen allergen extract (5-GPAE) be listed for the seasonal treatment of grass pollen allergic rhinitis, if all of the following clinical criteria and conditions are met:

Clinical Criteria:

1. Patients have not adequately responded to, or tolerated, conventional pharmacotherapy.
2. Treatment with 5-GPAE should be initiated by an allergist.

Condition: Reduced Price

The cost of seasonal treatment for allergic rhinitis with 5-GPAE should be no more than the cost of treatment with subcutaneous immunotherapy (SCIT).

Reasons for the Recommendation:

1. 5-GPAE was shown to be superior to placebo for the management of allergic rhinitis in four, double-blind, randomized controlled trials (RCTs). However, there was no evidence from RCTs to establish the comparative efficacy of 5-GPAE relative to SCIT.
2. At the submitted price, seasonal treatment with 5-GPAE is more costly than SCIT for allergic rhinitis. Given the insufficient evidence to support the comparative efficacy of 5-GPAE relative to SCIT, the Committee concluded that the cost of treatment with 5-GPAE should not exceed that of SCIT.

Of Note:

The Committee noted that for the Common Drug Review (CDR) participating drug plans that currently fund treatment with SCIT for allergic rhinitis, 5-GPAE could be listed in a manner similar to SCIT, provided the cost of treatment with 5-GPAE does not exceed that of SCIT.

Background:

5-GPAE has a Health Canada indication for the treatment of symptoms of moderate to severe seasonal grass pollen allergic rhinitis with or without conjunctivitis in patients five to 50 years of age, confirmed by clinically relevant symptoms, a positive cutaneous test and a positive titre of

the specific IgE to *Poaceae* grass pollen, who have suffered from allergic rhinitis with or without conjunctivitis for at least two pollen seasons and have not adequately responded to, or tolerated, conventional pharmacotherapy. 5-GPAE is available as sublingual 100 or 300 index of reactivity (IR) tablets. 5-GPAE tablets contain standardized allergen extract of pollens of five grasses that are native or naturalized across Canada. The product monograph states that treatment should be initiated four months before the expected onset of the pollen season and must be maintained throughout the pollen season. The recommended maintenance dose is one 300 IR tablet per day.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the CDR: a systematic review of RCTs of 5-GPAE and a critique of the manufacturer's pharmacoeconomic evaluation. The manufacturer submitted a confidential price for 5-GPAE.

Patient Input Information

No patient input was received for this submission.

Clinical Trials

The systematic review included four manufacturer-sponsored, double-blind, placebo-controlled RCTs:

- Study VO53.06 (N = 633) was a three-arm trial comparing 5-GPAE 300 IR once daily, started four months before the pollen season; 5-GPAE 300 IR once daily started two months before the pollen season; and placebo, all used for three consecutive pollen seasons in adults with moderate to severe allergic rhinitis. Treatment-free follow-up continued for an additional two years.
- Study VO34.04 (N = 628) was a four-arm trial comparing three doses of 5-GPAE started four months before the season (100 IR once daily, 300 IR once daily, and 500 IR once daily) with placebo for one pollen season in adults with moderate to severe allergic rhinitis.
- Study VO61.08 (N = 473) compared 5-GPAE 300 IR once daily started four months before the season with placebo for one pollen season in adults with moderate to severe allergic rhinitis.
- Study VO52.06 (N = 278) compared 5-GPAE 300 IR once daily (started four months before to the season) with placebo for one pollen season in children and adolescents aged five to 17 years old with moderate to severe allergic rhinitis.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following:

- Average Rhinoconjunctivitis Total Symptom Score (ARTSS) – assesses six symptoms of rhinoconjunctivitis on a scale from 0 to 3 (higher scores indicate worse symptoms), and then sums these scores for a total score ranging between 0 and 18.
- Average adjusted Symptom Score (AASS) – a variation of the ARTSS which adjusts for the confounding effects of rescue medication use.
- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) – a self-administered questionnaire that contains 28 questions in seven domains: activities limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems, and emotional function.

- Daily Combined Score – combines Rhinoconjunctivitis Symptom Score and the Rescue Medication Score. The Rescue Medication Score (RMS) measures the types of rescue medication used during the pollen season: 0 (none), 1 (antihistamine), 2 (intranasal corticosteroid), and 3 (oral corticosteroid).
- Rescue medication usage.
- Total adverse events, serious adverse events, and withdrawals due to adverse events.

The primary outcomes were ARTSS in two trials (VO34.04 and VO52.06), AASS in one trial (VO53.06), and Daily Combined Score in one trial (VO61.08). Outcomes were reported after one pollen season in VO34.04, VO61.08, and VO52.06 and after three pollen seasons in VO53.06.

Results

Based on the Health Canada-recommended dosing, the Committee focused their discussion on the results reported for one 300 IR tablet per day.

Efficacy

- 5-GPAE 300 IR was statistically superior to placebo for ARTSS in VO53.06 (mean difference [MD] [95% CI], -1.37 [-2.03 to -0.71]), VO34.04 (MD [95% CI], -1.39 [-2.09 to -0.69]), VO61.08 (MD [95% CI], -0.94 [-1.58 to -0.30]), and VO52.06 (MD [95% CI], -1.13 [-1.18 to -0.46]).
- In VO53.06, 5-GPAE 300 IR was statistically superior to placebo for AASS (MD [95% CI], -1.81 [-2.61 to -1.02]).
- In VO61.08, there was a statistically significant difference in the Daily Combined Score favouring 5-GPAE compared with placebo (MD [95% CI], -0.13 [-0.19 to -0.06]).
- Patients treated with 5-GPAE 300 IR had significantly fewer days with rescue medication use compared with placebo in VO53.06 (19.6% versus 29.4%), VO34.04 (19.7% versus 27.9%), VO61.08 (9.1% versus 16.1%), and VO52.06 (35.4% versus 46.5%).
- 5-GPAE 300 IR was associated with a statistically significant improvement in the RQLQ compared with placebo in VO53.06 (MD [95% CI], -0.41 [-0.64 to -0.19]), VO34.04 (MD [95% CI], -0.11 [-0.19 to -0.04]), and VO61.08 (MD [95% CI], -0.32 [-0.55 to -0.10]).

Harms (Safety and Tolerability)

- The proportion of patients with at least one adverse event was greater with 5-GPAE compared with placebo in VO53.06 (62.9% versus 46.4%), VO34.04 (62.6% versus 48.7%), and VO61.08 (82.0% versus 76.7%). In the pediatric population (VO52.06), the proportion of patients with at least one adverse event was similar between 5-GPAE and placebo (84.9% versus 82.0%). Most adverse events were mild or moderate in severity. Oral pruritus, throat irritation, and mouth edema were reported more frequently in the 5-GPAE groups compared with placebo.
- Serious adverse events were rare in the included trials. Compared with placebo, a larger proportion of patients treated with 5-GPAE experienced at least one serious adverse event during the first year of VO53.06 (3.4% versus 0.5%). The proportion of patients with at least one serious adverse event was similar between 5-GPAE and placebo in VO34.04 (0.6% versus 0%), VO52.06 (1.4% versus 1.4%), and VO61.08 (0.9% versus 1.7%). There were no reports of severe anaphylactic shock or anaphylaxis, autoimmune disorders, or deaths in the 5-GPAE treatment groups.

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- Withdrawals due to adverse events were more common with 5-GPAE than placebo in VO34.04 (3.9% versus 0%), VO61.08 (6.4% versus 0.8%), and VO52.06 (5.0% versus 1.4%). No patients withdrew from VO53.06 as a result of adverse events.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing 5-GPAE with SCIT allergenic extracts, administered seasonally and perennially. As there were no head-to-head trials comparing 5-GPAE with SCIT, the manufacturer conducted an indirect comparison to support the assumption of similar clinical efficacy and safety between 5-GPAE and SCIT. In the first year of treatment, the manufacturer estimated that the total cost (treatment, dispensing fees, physician visits, and treatment of adverse events) for 5-GPAE ([*confidential price removed at manufacturer's request*]) was less than perennial SCIT (\$1,583) and similar to seasonal SCIT (\$946). For subsequent years of treatment, the costs of 5-GPAE and seasonal SCIT were similar, while costs of perennial SCIT decreased (\$716).

CDR noted the following limitations with the manufacturer's analysis:

- There are no head-to-head randomized trials comparing 5-GPAE with SCIT. The indirect comparison submitted by the manufacturer did not consider the same parameter estimates and the minimal clinically important difference (MCID) associated with the symptom scale was not reported. Consequently the clinical efficacy of 5-GPAE compared with SCIT remains uncertain.
- Coverage for SCIT varies by participating public drug plans. For drug plans that do not reimburse SCIT, the appropriate comparator for the treatment of patients who have not adequately tolerated or responded to conventional pharmacotherapy would be no treatment, as 5-GPAE would be the first disease-modifying agent for grass pollen allergic rhinitis. This analysis was not considered by the manufacturer.

The cost of 5-GPAE ([*confidential price removed at manufacturer's request*]) is dependent on the duration of therapy: ranging from [*confidential price removed at manufacturer's request*] for six months to [*confidential price removed at manufacturer's request*] for 10 months. The cost of SCIT varies from \$83 (for nine weeks of seasonal treatment) to \$333 (for the first year of perennial treatment).

Other Discussion Points:

The Committee noted the following:

- The Health Canada indication for 5-GPAE is restricted to patients who have not adequately responded to, or tolerated, conventional pharmacotherapy; however, the trials included in the CDR submission were not restricted to these patients.
- In the data provided in the CDR submission, there was uncertainty regarding the comparative efficacy of initiating therapy with 5-GPAE two months before the predicted pollen season versus four months before the predicted pollen season.
- The product monograph for 5-GPAE recommends that the first tablet of 5-GPAE be taken under medical supervision and that the patient should be monitored for 30 minutes. Subsequent dosing of 5-GPAE can be done in the absence of a physician. In contrast, each session of SCIT can require a 20 to 30 minute observation in a physician's office. The Committee considered that a potential benefit of 5-GPAE is the reduced need for physician services; however, they noted that there is uncertainty regarding the longer-term

safety of 5-GPAE, as [confidential data removed at manufacturer's request] have been reported with this treatment.

Research Gaps:

The Committee noted that there is no direct comparison between 5-GPAE and SCIT for grass pollen allergic rhinitis.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

February 20, 2013 Meeting

Regrets:

Two CDEC members did not attend the meeting.

Conflicts of Interest:

None

About this Document:

CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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