CDEC FINAL RECOMMENDATION

TIMOTHY GRASS STANDARDIZED ALLERGENIC EXTRACT
(Grastek — Merck Canada Inc.)
Indication: Allergic Rhinitis (Grass pollen)

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that Timothy grass (*phleum pratense*) standardized allergenic extract (PPAE) not be listed.

Reason for the Recommendation:
CDEC considered the comparative clinical benefit of PPAE to be uncertain due to the variability of efficacy results across the included randomized controlled trials (RCTs) and the small magnitude of the absolute differences between PPAE and placebo.

Background:
PPAE is indicated for reducing the signs and symptoms of moderate to severe seasonal Timothy and related grass pollen-induced allergic rhinitis, with or without conjunctivitis, in adults and children ≥ 5 years of age, as confirmed by clinically relevant symptoms for at least two pollen seasons, a positive skin prick test, and/or a positive titre to *phleum pratense* specific immunoglobulin E; and who have responded inadequately, or are intolerant to, conventional pharmacotherapy.

PPAE is available as a sublingual tablet containing 2,800 bioequivalent allergy units (BAU), which is equivalent to 75,000 standardized quality units (SQ-U). The recommended dosage is 2,800 BAU sublingually once daily starting at least eight weeks before the grass pollen season (GPS), and continuing through the entire GPS.

Summary of CDEC Considerations
CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of PPAE, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals living with seasonal allergies.

Patient Input Information
The following is a summary of key information provided by one patient group that responded to the CDR call for patient input:

- Patients report a variety of symptoms from their seasonal allergies, including breathing difficulties, throat, eye and nose irritation, poor sleep and the fatigue that results, and depressed mood.
- Respiratory allergies may negatively impact the following aspects of an individual's life: ability to work, leisure activities, physical activities, emotional well-being, ability to travel, ability to socialize, independence, financial situation, and family/friend relationships.
- Many surveyed patients expressed concerns about a range of treatment-related adverse events and the financial burden imposed by the condition and the associated treatments.
- Most surveyed patients with experience receiving subcutaneous immunotherapy (SCIT) for allergic rhinitis would prefer an oral treatment.

Clinical Trials

The CDR systematic review included eight double-blind, placebo-controlled RCTs of patients with allergic rhinitis: GT-02 (N = 855), GT-07 (N = 114), GT-08 (N = 634), GT-14 (N = 329) and P05238 (N = 439) involved adult patients; GT-12 (N = 253) and P05239 (N = 345) involved pediatric patients; and P08067 (N = 1,501) involved a mixed population of adult and pediatric patients. All studies, with the exception of GT-02, randomized patients to PPAE 2,800 BAU daily or placebo. GT-02 was a multi-arm trial that compared three doses of PPAE (2,500 SQ-U, 25,000 SQ-U, or 75,000 SQ-U) against placebo, with additional randomization based on rescue medication (loratadine or placebo).

Pre-seasonal treatment durations ranged from 8 to 16 weeks across studies GT-02, GT-07, GT-12, GT-14, P05238, P05239, and P08067, for a total treatment duration of approximately 24 weeks. In GT-08, the pre-seasonal treatment duration ranged from 16 to 35 weeks. All study protocols (except GT-02, as noted above) allowed for the use of concomitant rescue medications as required, either for allergic rhinitis or asthma symptoms.

Outcomes

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

- Rhinoconjunctivitis daily symptom score (DSS) — a 4-point severity rating scale from 0 (no symptoms) to 3 (severe symptoms) used to assess the severity of four nasal symptoms (runny nose, blocked nose, sneezing, and itchy nose) and two ocular symptoms (gritty feeling/red/itchy eyes, and watery eyes).
- Daily Medication Scores (DMS) — a scoring system used to measure rescue medication usage (scoring varied across the studies, with maximum possible scores ranging from 12 to 38).
- Total combined score (TCS) — the sum of the DSS and DMS.
- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) — a self-administered questionnaire that contains 28 questions in 7 domains: activities limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems, and emotional function.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

DSS and DMS during the entire GPS were the co-primary outcomes in GT-02, GT-08, and GT-12. DSS during the entire GPS was the primary outcome in GT-14. TCS during the entire GPS was the primary outcome in P05238, P05239, and P08067. In GT-07, which specifically

enrolled patients with asthma, the primary outcome was the asthma medication score (AMS) during the entire GPS. Outcomes in all studies, except GT-08, were assessed during one GPS. GT-08 assessed outcomes in each GPS over five years (seasonal treatment for three years and two non-treatment years).

Efficacy

- PPAE was statistically superior to placebo for DMS in four studies (GT-02, GT-08, GT-12 and P08067) and not statistically significantly different from placebo in four studies (GT-07, GT-14, P05238 and P05239).The mean difference in DMS score for PPAE versus placebo was reported as follows:
  - Adults: –1.03 (95% CI: –1.44 to –0.63) in GT-08, –0.40 (95% CI: –0.85 to 0.05) in GT-14, –0.45 (95% CI: –0.96 to 0.06) in P05238, –0.58 (95% CI: –1.16 to –0.01) in GT-02, and –1.21 (*P* = 0.136) in GT-07.
  - Children: –0.41 (95% CI: –0.68 to –0.01) in GT-12 and –0.42 (95% CI: –0.88 to 0.03) in P05239.
  - Mixed: –0.40 (95% CI: –0.65 to –0.15) in P08067.
- The mean difference in total DSS score for those receiving PPAE versus placebo was reported as follows:
  - Adults: –1.29 (95% CI: –1.68 to –0.90) in GT-08, –0.37 (95% CI: –1.16 to 0.41) in GT-14, and –0.86 (95% CI: –1.46 to –0.26) in P05238.
  - Children: –0.62 (95% CI: –1.15 to –0.10) in GT-12 and –1.20 (95% CI: –1.95 to –0.45) in P05239.
  - Mixed: –0.47 (95% CI: –0.79 to –0.16) in P08067.
- PPAE was statistically superior to placebo for TCS in five studies (GT-08, P05238, GT-12, P05239, and P08067) and there was no statistically significant difference in GT-14.
- PPAE was statistically superior to placebo for RQLQ scores in five studies (GT-02, GT-08, P05238, P05239, and P08067) and there was no statistically significant difference in GT-14.

Harms (Safety and Tolerability)

- The proportion of patients with at least one adverse event was greater with PPAE (range: 74% to 95%) compared with placebo (range: 61% to 90%). Adverse events were reported as being mild or moderate in severity. The most frequently reported adverse events were those associated with the mouth or throat. Longer term data (seasonal treatment over three years), available from an extension phase of GT-08, did not reveal additional safety concerns.
- The proportion of patients who experienced at least one serious adverse event was similar in the PPAE (range: 0 to 2%) and placebo groups (range: 0 to 2.4%).
- The proportion of patients who withdrew due to adverse events was numerically higher with PPAE (range: 3% to 7.2%) compared with placebo (range: 0 to 4%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis in patients with moderate to severe seasonal allergic rhinitis to grass pollen, considering a three-year time horizon. The analysis was primarily based on inputs from the manufacturer's network meta-analysis, and it estimated the cost differences between PPAE, perennial SCIT, seasonal SCIT, and sublingual five-grass pollen allergen extract (5-GPAE). The manufacturer reported three-year cost savings with PPAE

of $1,391 per patient compared with perennial SCIT, $862 per patient compared with seasonal SCIT, and $756 per patient compared with 5-GPAE.

The key limitation with the manufacturer's cost-minimization analysis was that the cost of treatment was based on a pollen season of three months with eight weeks of pre-season treatment. In Canada, the pollen season ranges from two to six months. Accounting for this, CADTH recalculated the costs of treatment for a pollen season that ranges from two to six months and pre-seasonal use of PPAE that ranges from 8 to 16 weeks.

The submitted price for PPAE is $3.80 per 2,800 BAU sublingual tablet. At the recommended dose of 2,800 BAU per day, PPAE costs $555 to $897 per patient per year when used for at least eight weeks before the GPS and throughout the season. 5-GPAE (100 index of reactivity [IR] on day 1 and 2, and 300 IR per day thereafter) costs from $862 to $1,233 per patient per year when used for four months before the onset of GPS and maintained throughout the season. Seasonal SCIT (100,000 BAU/mL diluted according to patient reactivity) costs $80 per year when used as nine injections per-pollen season. Perennial SCIT (100,000 BAU/mL diluted according to patient reactivity) costs from $248 to $346 for the first year and $106 for the subsequent years when administered as weekly injections for five to eight months, and monthly injections in the maintenance phase.

Other Discussion Points:
CDEC noted the following:

- The DSS, DMS, and TCS have not been validated and the clinical significance of the observed differences is uncertain.
- Only one study examined the effects of PPAE during multiple GPS and this trial was limited by the high proportion of patients who discontinued the study (approximately 50%) and the differential rate of withdrawals between the PPAE and placebo groups.
- Improvements in RQLQ scores with PPAE compared to placebo were statistically significant in five RCTs; however, the absolute differences ranged from 0.08 to 0.37, all of which are below the minimal clinically important difference.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- There are no studies directly comparing PPAE with SCIT or other available sublingual immunotherapy products.

September 17, 2014 Meeting:

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani

Regrets: None

Conflicts of Interest: None

June 18, 2014 Meeting:

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. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets: None

Conflicts of Interest: None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. 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 not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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