PDL NEW DRUG REVIEW

Proprietary Name: Ragwitek®
Common Name: short ragweed pollen allergen extract
PDL Category: Allergenic Extracts

Summary

Indications and Usage: Immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for short ragweed pollen. Ragwitek® is not indicated for the immediate relief of allergic symptoms and is only approved for use in adults 18-65 years of age. This is a pregnancy category C medication. The safety and efficacy of use in children have not been established.

Dosage Forms: Orally Disintegrating Tablet for sublingual use only: 12 Amb a 1-Unit* (Amb a 10U) (*This represents a measure of potency of short ragweed allergen extract; each Amb a 1-unit is roughly equivalent to 1 mcg of the allergen)

Recommended Dosage: Dissolve one table under the tongue once daily. The sublingual tablet should remain under the tongue until it completely dissolves and at least one minute should transpire before swallowing. Do not take with food or beverage, or for up to 5 minutes after haven taken the tablet. The initial dose should be taken in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. The patient should be observed for at least 30 minutes after receiving this first dose, to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the dose is tolerated, subsequent doses may be taken at home.

Treatment should be started at least 12 weeks before the expected onset of ragweed pollen season and continue throughout the season. The safety and efficacy of starting treatment during the season have not been established. Additionally, it is recommended that an auto-injectable epinephrine be prescribed to those taking Ragwitek®, along with proper instructions on how to use the emergency device.

There was no information found regarding the need for dosage adjustments in those with renal or hepatic impairment.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ragwitek®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than placebo.* The most frequently reported adverse events included ear pruritus (9.3%), throat irritation (13.3%), oropharyngeal pain (0.8%), throat tightness (0.8%), oral pruritus (8.9%), paraesthesia oral (6%), mouth edema (5.6%), tongue pruritus (4.6%), lip swelling (2.6%), swollen tongue (2.4%), lip pruritus (1.4%), dry mouth (0.7%), tongue edema (0.8%), nausea (0.8%), palatal edema (1.1%), dysphagia (1%), pruritus (0.5%), and chest discomfort (1%).

Ragwitek® carries a box warning regarding the increased risk of severe allergic reactions, such as anaphylaxis and severe laryngopharyngeal restriction. It should not be given to patients with severe, unstable or uncontrolled asthma. The warning reiterates the need for the first dose to be supervised as outlined above. In addition, the box

warning indicates that Ragwitek® may not be suitable for patients with certain underlying medical conditions that may reduce the ability to survive a serious allergic reaction or for those who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.

Contraindications: Severe unstable or uncontrolled asthma; history of any severe systemic allergic reaction; history of any severe local reaction after taking any SL allergen immunotherapy; history of eosinophil esophagitis; hypersensitivity to any of the inactive ingredients of the product (gelatin, mannitol, and sodium hydroxide).

Manufacturer: Merck Sharp & Dohme Corp

Analysis: Pollen allergen extract from Short Ragweed (*Ambrosia artemisiifolia*), the active ingredient of Ragwitek®, is an allergen immunotherapy. Its exact mechanism of action is not known. Its safety and efficacy for use were assessed in two randomized, double-blind, placebo-control studies in adults ages 18-50 years who had ragweed pollen-induced allergic rhinitis. Treatment was started 12 weeks prior to the start of ragweed pollen season. Efficacy was assessed per the self-reporting of rhinoconjunctivitis daily symptom scores (DSS) and daily medication scores (DMS). In addition, the Total Combined Score (TCS; DSS plus DMS) was also assessed. (The difference relative to placebo was computed as Ragwitek®-placebo, then divided by placebo and multiplied by 100.)

In study 1, a decrease in TCS was seen during the peak and entire ragweed season for Ragwitek® vs placebo. The results of study 1 (N=375) for Ragwitek® vs placebo were as follows: TCS peak season (6.22 vs 8.46, treatment difference -2.24; difference relative to placebo -26%); TCS entire season (5.21 vs 7.01, treatment difference -1.80; difference relative to placebo -26%); DSS peak season (4.65 vs 5.59, treatment difference -0.94; difference relative to placebo -17%); DSS entire season (4.05 vs 4.87, treatment difference -0.82; difference relative to placebo -17%); DMS peak season (1.57 vs 2.87, treatment difference -1.30; difference relative to placebo -45%).

In study 2, a decrease in TCS was seen during the peak and entire ragweed season for Ragwitek® vs placebo. The results of study 2 (N=392) for Ragwitek® vs placebo were as follows: TCS peak season (6.41 vs 8.46, treatment difference -2.04; difference relative to placebo -24%); TCS entire season (5.18 vs 7.09, treatment difference -1.92; difference relative to placebo -27%); DSS peak season (4.43 vs 5.37, treatment difference -0.94; difference relative to placebo -18%); DSS entire season (3.62 vs 4.58, treatment difference -0.96; difference relative to placebo -21%); and DMS peak season (1.99 vs 3.09, treatment difference -1.10; difference relative to placebo -36%).

Although there is limited data directly comparing subcutaneous immunotherapy (SCIT) with sublingual immunotherapy (SLIT), there is a Cochrane review[2] from 2010 that concluded that SLIT had similar efficacy and "a significantly lower risk profile" than injection immunotherapy. It is recommended that Ragwitek® remain non-preferred and require clinical prior authorization to verify diagnosis and appropriate specialty of the prescriber.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Ragwitek [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp, a subsidiary of Merck & Co; 2014.

[2] Radulovic S, Calderon MA, Wilson D, et al. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev*. 2010; 12:CD002893.