Grastek
(Timothy grass pollen allergen extract)

STRENGTH	DOSAGE FORM	ROUTE	GPID
2800 BAU	Tablet	Sublingual	35777

MANUFACTURER

Merck Sharp & Dohme Corp

INDICATION(S)

Immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens, in people ages 5 through 65 years

DRUG CLASS
ALLERGY; ALLERGENIC EXTRACTS, THERAPEUTICS

PLACE IN THERAPY

Grastek is one of the newest FDA-approved sublingual immunotherapy (SLIT) products for the treatment of pollen-induced allergic rhinitis (AR) in the United States (US), specifically Timothy grass pollen. For over a century, allergen immunotherapy has been administered subcutaneously (commonly known as allergy shots), and in recent years the administration of these allergen serums via sublingual drops has grown in popularity. However, this method is considered off-label and generally not covered by insurance companies. Grastek, on the other hand, is an oral tablet that is approved for dissolution under the tongue.

The treatment of AR typically consists of patient education, allergen avoidance, and pharmacotherapy. Immunotherapy is reserved for patients with demonstrable specific IgE antibodies to relevant allergens who continue to have moderate to severe AR symptoms despite pharmacotherapy. Other factors that would justify consideration of immunotherapy include intolerable side effects to medications, the patient's desire to limit cost burden associated with chronic medication use, and the presence of comorbid conditions. Unlike pharmacotherapy, the clinical benefits of immunotherapy may be sustained for years after discontinuation of treatment for some patients. Immunotherapy can potentially modify the disease such that the immune system no longer reacts to the allergen.

Grastek provides an alternative to subcutaneous immunotherapy with minimal risk for systemic allergic reactions, decreased burden of office visits, and elimination of injection site discomfort. Grastek has been shown to be effective in reducing allergic symptoms and the use of allergy medications. Currently there are only two other immunotherapy agents with FDA-approval for sublingual use, Oralair and Ragwitek. Unfortunately, patients who exhibit an allergic response to allergens not specified in these novel products will still need to rely on customary allergy shots.

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EFFICACY

The efficacy of Grastek was evaluated in three randomized, double-blind, parallel group, multi-center clinical trials (Studies P05239, P08067, and GT-08). Subjects ranged from 5 to 65 years of age with a history of grass pollen induced rhinoconjunctivitis, with or without asthma. In all three trials, subjects initiated Grastek or placebo approximately 12 weeks prior to the pollen season. The primary efficacy endpoints of these studies were the average rhinoconjunctivitis Daily Symptom Score (DSS), the average rhinoconjunctivitis Daily Medication Score (DMS), or the average combined rhinoconjunctivitis DSS and DMS (Total Combined Score, TCS) over the entire pollen season. The DSS is the sum of six individual rhinoconjunctivitis symptom scores with possible values of 0 (absent) to 3 (severe); the maximum DSS is 18. The six symptoms that were scored include: runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes. The DMS is the sum of scores that are assigned to the following medications: loratadine syrup, loratadine RediTabs, olopatadine hydrochloride ophthalmic solution, mometasone furoate nasal spray, and prednisone tablet. The maximum DMS is 36.

Study P05239 involved 344 pediatric subjects (ages 5-17 years) randomized to Grastek or placebo for 24 weeks. Pediatric subjects treated with Grastek had a decrease in TCS by 26% throughout the grass pollen season compared to the placebo group. Similarly, the DSS and DMS were decreased in the treatment group compared to placebo. Study P08067 consisted of 1,501 subjects 5-65 years of age randomized to Grastek or placebo for 24 weeks. Results of the TCS, DSS and DMS were similar to the pediatric study (see Table 1). Trial GT-08 was a 5-year study which measured the sustained efficacy of Grastek. It included 634 adult subjects (18-65 years of age) randomized to receive Grastek or placebo for 3 consecutive years, followed by a treatment-free, observational period of 2 years. Subjects treated with Grastek had a decrease in TCS throughout the first three grass pollen seasons. The effect was sustained during the grass pollen season in the first year after discontinuation of Grastek, but not in the second year. There was no statistically significant difference in DMS between Grastek and placebo groups during the second year of the treatment-free period (year 5). See Table 2 for a summary of the efficacy endpoint results.

Table 1. Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Grass Pollen Seasons in Studies P05239 and P08067

Treatment	Number of Subjects	% change in DSS relative to placebo (95% CI)	% change in DMS relative to placebo (95% CI)	% change in TCS relative to placebo (95% CI)
Study P05239 (Pediactric study)				
Grastek	149	-24% (-36.4, -9.1)	-32% (-57.7, 4.0)	-26% (-38.2, -10.1)
Placebo	158			
Study P08067				
Grastek	629	-20% (-32.0, -10.0)	-35% (-49.3, -20.8)	-23% (-36.0%, -13.0%)
Placebo	672			

Obtained from Grastek package insert

Table 2. GT-08: Analyses of Grastek Efficacy During the Entire Pollen Season

Trial Endpoint	MK-7243 (N) Mean	Placebo (N) Mean	Treatment Difference (MK-7243 – Placebo)			Difference Relative to Placebo (%)[a]	
			Estimate	95% CI	p-value	Estimate	95% CI
GT08 (Year 1)							
TCS	(282) 4.46	(286) 6.78	-2.32	(-2.98, -1.67)	<0.0010	-34.2	(-42.0, -26.3)
DSS	(282) 2.85	(286) 4.14	-1.29	(-1.68, -0.90)	<0.0001	-31.2	(-38.8, -23.4)
DMS	(282) 1.65	(286) 2.68	-1.03	(-1.44, -0.63)	<0.0001	-38.4	(-49.8, -26.5)
GT08 (Year 2)							
TCS	(172) 4.10	(144) 6.94	-2.84	(-3.88, -1.79)	<0.0001	-40.9	(-51.8, -29.5)
DSS	(172) 2.40	(144) 3.76	-1.36	(-1.86, -0.86)	<0.0001	-36.2	(-46.5, -26.2)
DMS	(172) 1.74	(144) 3.19	-1.45	(-2.16, -0.75)	<0.0001	-45.5	(-60.4, -28.2)
GT08 (Year 3)							
TCS	(160) 4.39	(127) 6.64	-2.26	(-3.26, -1.25)	<0.0001	-34.0	(-45.5, -21.4)
DSS	(160) 2.56	(127) 3.59	-1.04	(-1.56, -0.52)	0.0001	-29.0	(-40.3, -16.3)
DMS	(160) 1.82	(127) 3.04	-1.22	(-1.92, -0.52)	0.0007	-40.1	(-55.4, -21.2)
GT08 (Year 4)							
TCS	(142) 4.96	(115) 6.81	-1.85	(-2.97, -0.73)	0.0014	-27.2	(-39.9, -12.4)
DSS	(142) 2.68	(115) 3.63	-0.95	(-1.50, -0.40)	0.0007	-26.2	(-37.6, -12.2)
DMS	(142) 2.32	(115) 3.25	-0.93	(-1.72, -0.14)	0.0215	-28.6	(-46.3, -6.0)
GT08 (Year 5)							
TCS	(137)4.96	(104) 6.42	-1.46	(-2.61, -0.31)	0.0128	-22.7	(-37.1, -6.3)
DSS	(137) 2.56	(104) 3.40	-0.84	(-1.41, -0.28)	0.0037	-24.7	(-37.7, -9.7)
DMS	(137) 2.42	(104) 3.04	-0.62	(-1.38, 0.15)	0.1136	-20.4	(-39.8, 4.3)

TCS = Total combined score (DSS + DMS); DSS = Rhinoconjunctivitis Daily Symptom Score; DMS = Rhinoconjunctivitis Daily Medication Score; CI = Confidence Interval.

Note: All trials compared MK-7243 (2800 BAU) with placebo; all scores presented are for the entire GPS.

a: Percent reduction in the MK-7243 (2800 BAU) group compared to placebo: (MK-7243 -placebo)/placebo X 100%. Confidence intervals were obtained using the bootstrap method.

Obtained from the Grastek FDA briefing Dec 12, 2013

SAFETY

Grastek carries the following black box warnings:

- Grastek can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction
- Do not administer Grastek to patients with severe, unstable or uncontrolled asthma
- Observe patients in the office for at least 30 minutes following the initial dose
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use
- Grastek may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction
- Grastek may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers

In the adult pooled analysis, discontinuation rates were 4.9% in the Grastek group and 0.9% in the placebo group. Treatment emergent adverse events (TEAEs) leading to withdrawal in the Grastek group included oral pruritus, mouth edema, and swollen tongue, eye pruritus, dyspepsia, dysphagia, lip swelling, nausea, oral mucosal blistering, salivary gland enlargement, stomatitis, chest discomfort, chest pain, hypersensitivity, headache, asthma, cough, dysphonia, dyspnea, pharyngeal erythema, pharyngeal edema, throat irritation, throat tightness, angioedema, pruritus, swelling face, and urticaria. The most commonly reported TEAEs were oral pruritus (26.7% Grastek, 3.5% placebo), throat irritation (22.6% Grastek, 2.8% placebo), ear pruritus (12.5% Grastek, 1.1% placebo), and mouth edema (11.1% Grastek, 0.8% placebo).

In the children/adolescents pooled analysis, 6.3% of the Grastek group and 0.7% of the placebo group discontinued the study. TEAEs that led to withdrawal in the Grastek group included throat irritation, mouth edema, dyspepsia, dysphagia, lip swelling, oral discomfort, oral pruritus, swollen tongue, chest discomfort, cough, and dyspnea. The most commonly reported TEAEs were oral pruritus (24.4% Grastek, 2.1% placebo), throat irritation (21.3% Grastek, 2.5% placebo), mouth edema (9.8% Grastek, 0.2% placebo), and tongue pruritus (9.2% Grastek, 0.9% placebo).

Grastek is Pregnancy Category B. However, Grastek should be used during pregnancy only if clearly needed, since systemic and local adverse reactions with immunotherapy may be poorly tolerated during pregnancy.

DOSAGE

The recommended dosage of Grastek is 2800 BAU (1 tablet) daily for children and adults 5-65 years of age.

Grastek should be initiated 12 weeks prior to the expected onset of each grass pollen season and continued throughout the season.

COST

Drug	**Cost/unit**	**Maximum Cost per 30 Days**
Grastek 2800 BAU	AWP $9.90	$297
Oralair 300 IR	AWP $12	$360
Ragwitek*	AWP $9.90	$297

*For the treatment of ragweed pollen-induced allergic rhinitis

FORMULARY PLACEMENT RECOMMENDATIONS

Based on this initial assessment of available clinical and financial information, consider NOT ADDING Grastek to the formulary pending complete review by the appropriate oversight committee for the plan.

REFERENCES

- Grastek [Prescribing Information]. Whitehouse Station, NJ, Merck Sharp & Dohme Corp., Apr 2014.
- Sur DK, Scandale S. Treatment of Allergic Rhinitis. Am Fam Physician, 2010 Jun; 81(12):1440-6.
- Wallace DV, Dykewicz MS, et al. The diagnosis and management of rhinitis: An updated practice parameter. J Allergy Clin Immunol, 2008 Aug; 122:S1-84.
- FDA Briefing Document - Biologic License Application (BLA) for Timothy Grass Pollen Extract Tablets. Accessed on April 2014 at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/AllergenicProductsAdvisoryCommittee/UCM378093.pdf