CBER/FDA update: allergen immunotherapy

Jay E. Slater, MD
Division of Bacterial Parasitic and Allergenic Products
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research

Today's presentation

- Background on allergenic products
- Novel allergen immunotheraputics
  - Oralair
  - Grastek
  - Ragwitek

Allergy statistics

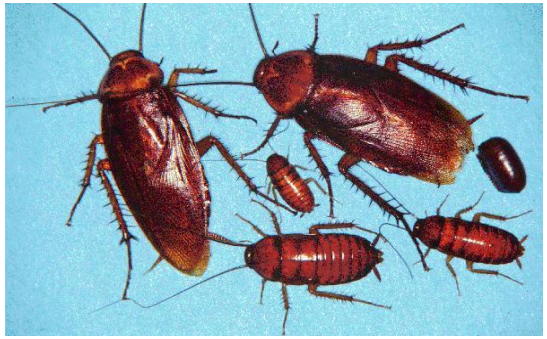
- Allergic diseases
  - affect >20% of the US population
  - are a major cause of chronic disease
  - include allergic rhinitis, allergic conjunctivitis; drug, latex, hymenoptera and food allergy; anaphylaxis; and a subset of asthma and eczema

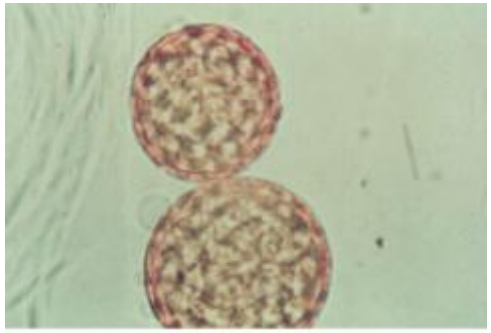
Management of allergic disease

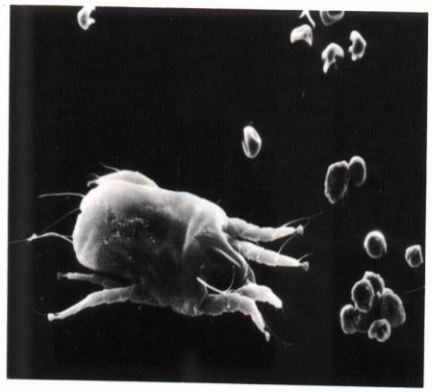
- Identification (skin tests or blood tests)
- Avoidance
- Drugs
  - H1 antagonists, oral and topical
  - topical corticosteroids
  - topical anticholinergic
  - topical mast cell stabilizers
  - leukotriene antagonists
  - topical NSAID
- Allergen immunotherapy

Allergen Extracts

- pollens
- molds
- epidermoids
- insects
- foods







Subcutaneous IT

- Synonyms: desensitization, hyposensitization, allergy shots
- Administration of increasing doses of allergen, subcutaneous route
  - Conventional: weeks to months
  - Rush: days to weeks
- Efficacy is dose-dependent
- Adverse events (all IgE-mediated): local (common), systemic (occasional), fatal (rare)

Adverse reactions to SCIT

- Local
- Systemic : <0.3% per injection (conventional schedule)
- Fatalities: 1 per 2.5 million injections (3-4 deaths/year)

Cox L, et al. *J Allergy Clin Immunol* 2010;125:569-74
Moreno C, et al. *Clin Exp Allergy* 2004;34:527-31
Bernstein DI, et al. *J Allergy Clin Immunol* 2004;113:1129-36
Reid MJ, et al. *J Allergy Clin Immunol* 1993;92: 6-15
Lockey RF, et al. *J Allergy Clin Immunol* 1987;79:660-77

Sublingual IT

- At-home regimen
- Various regimens
- Increasing use in Europe
  - Grazax
  - Oralair
  - “named-patient” products
- Off-label use of SCIT products for SLIT in US
- Local erythema, swelling, pruritus
  - mouth, lips, tongue, upper airway
- Systemic

ORALAIR®

Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergenic Extract Tablet for Sublingual Use

Stallergenes SA

Approved: 1 April 2014

Description

ORALAIR…is a mixed allergen extract of the following five pollens: Sweet Vernal (*Anthoxanthum odoratum L*), Orchard (*Dactylis glomerata L*), Perennial Rye (*Lolium perenne L*), Timothy (*Phleum pratense L)*, and Kentucky Blue Grass (*Poa pratensis L*).

ORALAIR is available as a sublingual tablet in the following strengths:

- 100 IR (equivalent to approximately 3000 BAU (bioequivalent allergy units)
- 300 IR (equivalent to approximately 9000 BAU)

Inactive ingredients: mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate and lactose monohydrate.

Product Description and Unitage

Oralair

- **Tablet for sublingual administration**
- **Potency defined in units of "index of reactivity" (IR)**
- **100 IR elicits wheal size of 7 mm (geometric mean) in 30 sensitive subjects**

Indication and usage

ORALAIR is an allergen extract indicated as 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 any of the five grass species contained in this product. ORALAIR is approved for use in persons 10 through 65 years of age.

ORALAIR is not indicated for the immediate relief of allergy symptoms.

Dose

Oralair

For adults 18 through 65 years of age, the dose is 300 IR (index of reactivity) daily. For children and adolescents 10 through 17 years of age, the dose is increased over the first three days as shown in the table below.

Age	Day 1	Day 2	Day 3 +
10-17	100 IR	2 x 100 IR	300 IR
18-65	300 IR	300 IR	300 IR

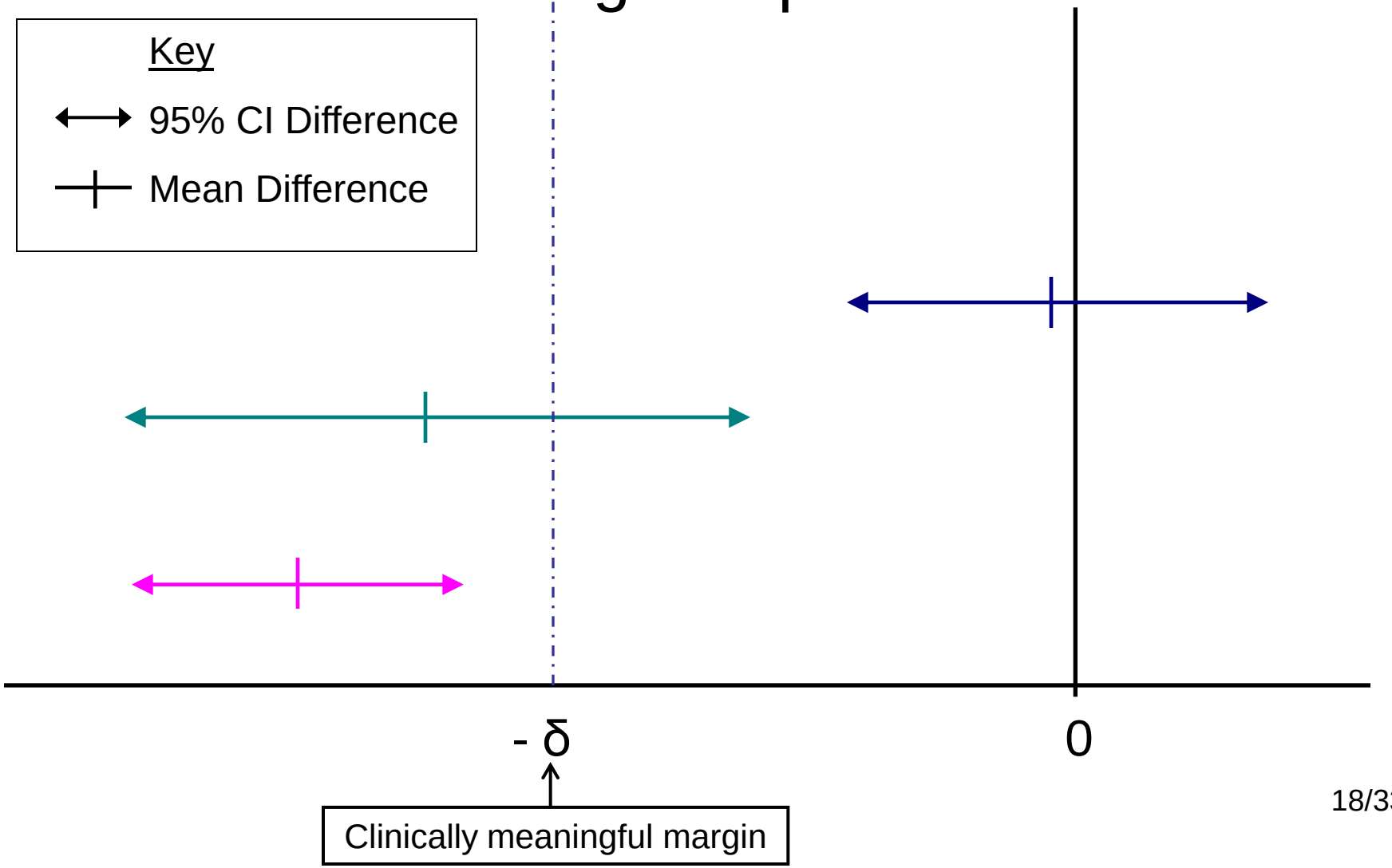
Administration

- Administer the first dose of ORALAIR in a healthcare setting …observe the patient for at least 30 minutes...If the patient tolerates the first dose, the patient may take subsequent doses at home.
- …
- Place the ORALAIR tablet immediately under the tongue until complete dissolution for at least 1 minute before swallowing.
- …
- Initiate treatment 4 months before the expected onset of each grass pollen season and maintain it throughout the grass pollen season.
- …
- It is recommended that auto-injectable epinephrine be made available to patients prescribed ORALAIR. Patients who are prescribed epinephrine while receiving immunotherapy should be instructed in the proper use of emergency self-injection of epinephrine …

ORALAIR Clinical Studies

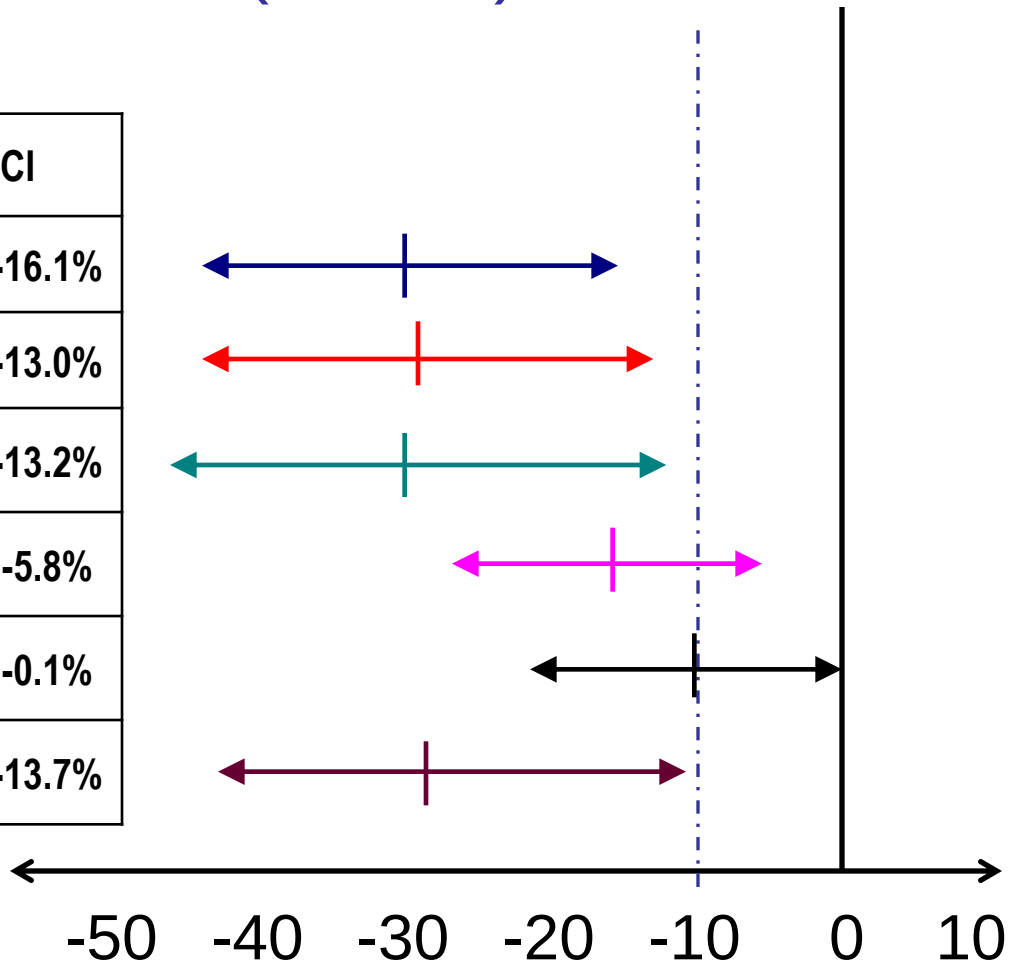
- **Six Phase 3 trials**
  - **EU study of adults 18-45 years of age (VO34.04)**
  - **Pivotal US study of adults (VO61.08)**
  - **EU study of children and adolescents 5-17 years of age (VO52.06)**
  - **EU study of adults with an alternate treatment schedule (VO60.08)**
  - **EU Five-year study of adults (VO53.06)**
    - **first 3 years treatment,**
    - **last 2 years observation**
  - **EU Environmental Exposure Unit study of adults (VO56.07)**

Differences of mean scores (treatment – placebo) over entire grass pollen season



Summary of efficacy data
Combined Scores (Oralair)

Study (VO)	Placebo	300 IR (4M)	% difference	95% CI
34.04	156	155	-29.6%	-43.1%, -16.1%
61.08	240	233	-28.2%	-43.4%, -13.0%
52.06	139	139	-30.1%	-46.9%, -13.2%
53.06	219	207	-16.4%	-27.0%, -5.8%
60.08*	193	188	-10.0%	-19.0%, -0.1%
56.07**	44	45	-28.8%	-43.7%, -13.7%



*2 months pre-season
**EEU study; RTSS, not CS

Contraindications

Oralair

- Severe, unstable or uncontrolled asthma
- History of any severe systemic allergic reaction
- History of any severe local reaction to sublingual allergen immunotherapy
- A history of eosinophilic esophagitis
- Hypersensitivity to any of the inactive ingredients…contained in this product

Warnings and Precautions

Oralair

- Severe allergic reactions
- Epinephrine
- Eosinophilic esophagitis
- Asthma
- Concomitant allergen immunotherapy
- Oral inflammation
- Initiation during grass pollen season

Adverse reactions
Oralair

- Reported in >5% of patients:
  - oral pruritus,
  - throat irritation,
  - ear pruritus,
  - mouth edema,
  - tongue pruritus,
  - cough,
  - oropharyngeal pain.

Approval and post-approval issues (Oralair)

- Approval
  - Medication guide
  - Epinephrine
  - Age
- Post approval
  - Eosinophilic esophagitis

Eosinophilic esophagitis

- "A chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation" [J Allergy Clin Immunol 2011;128:3-20]
- Multiple anecdotal associations with sublingual/oral IT
  - Antico A, Fante R. Esophageal hypereosinophilia induced by grass sublingual immunotherapy. J Allergy Clin Immunol 2014; 133:1482-4
- Systematic review
  - Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2014; [Epub ahead of print]

GRASTEK®: Timothy Grass Pollen Allergen Extract Tablet for Sublingual Use

Merck Sharp and Dohme Corp.

Approval: 14 April 2014

Description

GRASTEK tablets contain pollen allergen extract from Timothy grass (*Phleum pratense*). GRASTEK is a sublingual tablet.

GRASTEK is available as a tablet of 2800 BAU of Timothy grass pollen allergen extract.

Inactive ingredients: gelatin NF (fish source), mannitol USP and sodium hydroxide NF.

Product description and unitage

Grastek

- **Sublingual tablet comprised of extract from Timothy grass (*Phleum pratense*) pollen**
- **Each sublingual tablet contains 2,800 Bioequivalent Allergy Unit (BAU) of the drug substance**
- **The drug substance is an aqueous allergen extract from Timothy grass pollen (*Phleum pratense*) sourced from the US**

Indication and Usage

GRASTEK® is an allergen extract indicated as 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. GRASTEK is approved for use in persons 5 through 65 years of age.

GRASTEK is not indicated for the immediate relief of allergic symptoms.

Dose

One GRASTEK tablet daily.

Administration

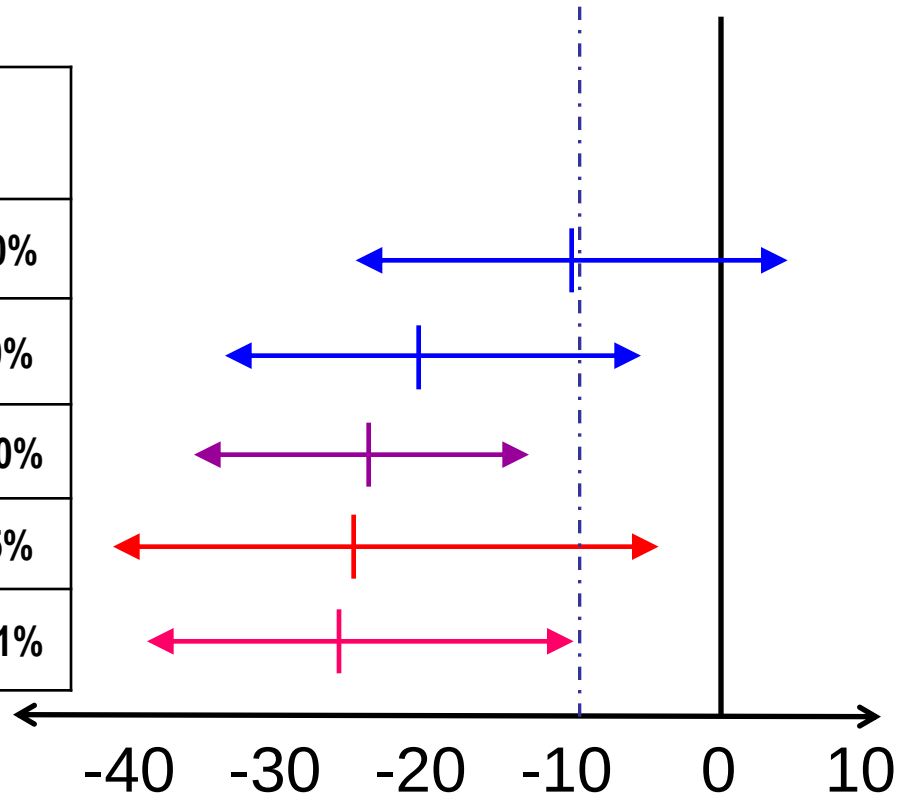
- Administer the first dose of GRASTEK in a healthcare setting…observe the patient for at least 30 …If the patient tolerates the first dose, the patient may take subsequent doses at home.
- …
- Place the tablet immediately under the tongue. Allow it to remain there until completely dissolved. Do not swallow for at least 1 minute.
- …
- Initiate treatment at least 12 weeks before the expected onset of each grass pollen season and continue treatment throughout the season… may be taken daily for three consecutive years (including the intervals between the grass pollen seasons)…
- …
- Prescribe auto-injectable epinephrine to patients prescribed GRASTEK and instruct them in the proper use of emergency self-injection of epinephrine

Grastek Clinical Studies

- **Six Phase 3 trials**
  - **24-36 weeks, one grass pollen season**
    - **US study adults (18-65y)(GT-14)**
  - **24 weeks, one grass pollen season**
    - **US/Canada study of adults (18-65y)(P05238)**
    - **Pivotal US study of adults (18-65y)(P08067)**
    - **Pivotal US study of children/adolescents (5-17 y) (P05239)**
  - **36 weeks, one grass pollen season**
    - **European study of children/adolescents (5-16y)(GT-12)**
  - **Three years of treatment, five-year study**
    - **Pivotal US study of adults (18y and older)(GT-08)**

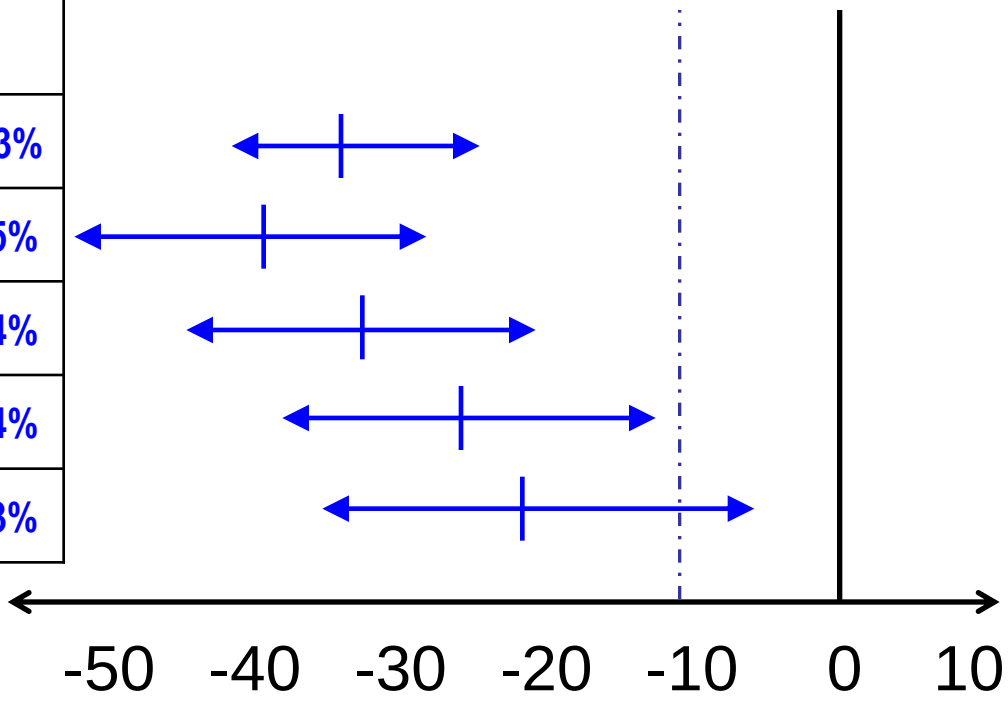
Summary of combined scores from single-year Phase 3 clinical trials (Grastek)

Study	2800 BAU	Placebo	% difference	95% CI
GT-14	139	150	-10.4%	-23.9%, +4.0%
P05238	184	207	-20.5%	-33.0%, -6.0%
P08067	629	672	-23.0%	-36.0%, -13.0%
GT-12	117	121	-24.2%	-41.3%, -4.5%
P05239	149	158	-26.1%	-38.2%, -10.1%



Summary of Total Combined Scores from GT-08 (Grastek)

Year	2800 BAU	Placebo	% difference	95% CI
1	282	286	-34.2%	-42.0%, -26.3%
2	172	144	-40.9%	-51.8%, -29.5%
3	160	127	-34.0%	-45.5%, -21.4%
4	142	115	-27.2%	-39.9%, -12.4%
5	137	104	-22.7%	-37.1%, - 6.3%



Contraindications
Grastek

- Severe, unstable or uncontrolled asthma
- History of any severe systemic allergic reaction
- History of any severe local reaction to sublingual allergen immunotherapy
- History of eosinophilic esophagitis
- Hypersensitivity to any of the inactive ingredients…contained in this product

Warnings and Precautions
Grastek

- Severe allergic reactions
- Epinephrine
- Upper airway compromise
- Eosinophilic esophagitis
- Asthma
- Concomitant allergen immunotherapy
- Oral inflammation

Adverse reactions
Grastek

- Reported in >5% of patients:
  - ear pruritus,
  - oral pruritus,
  - tongue pruritus,
  - mouth edema,
  - throat irritation.

Epinephrine use

- **Adult studies**
  - **Seven adult subjects (7/1669; 0.4%) who received GRASTEK experienced treatment-related systemic allergic reactions that led to discontinuation of GRASTEK in four out of the seven subjects…Five of the seven subjects had reactions on Day 1 of treatment …Three of the five subjects received treatment with epinephrine…**

- **Pediatric studies**
  - **One pediatric subject (1/447; 0.2%) who received GRASTEK experienced a treatment-related systemic allergic reaction consisting of lip angioedema, slight dysphagia due to the sensation of a lump in the throat, and intermittent cough which was of moderate intensity on Day 1. The subject was treated with epinephrine, recovered, and was discontinued from the trial.**

Approval issues (Grastek)

- Med guide
- Epinephrine

RAGWITEK®
Standardized Allergen Extract, Short Ragweed (*Ambrosia artemisiifolia*) sublingual tablet for oral use

Merck Sharp and Dohme Corp.

Approval: 17 April 2014

Description

RAGWITEK tablets contain pollen allergen extract from Short Ragweed (*Ambrosia artemisiifolia*).

RAGWITEK is a sublingual orally disintegrating tablet that dissolves rapidly. RAGWITEK is available as a tablet of 12 Amb a 1-U of short ragweed pollen allergen extract.

Inactive ingredients: gelatin NF (fish source), mannitol USP, and sodium hydroxide NF.

Product description and unitage

Ragwitek

- **Sublingual tablet comprised of extract from short ragweed (*Ambrosia artemisiifolia*) pollen**
- **Each sublingual tablet contains 12 Amb a 1 units of the drug substance**
- **The drug substance is an allergen extract from short ragweed pollen (*Ambrosia artemisiifolia*) sourced from the US**

Indication and Usage

- RAGWITEK is an allergen extract indicated as 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 approved for use in adults 18 through 65 years of age.
- RAGWITEK is not indicated for the immediate relief of allergic symptoms.

Dose

One RAGWITEK tablet daily.

Administration

- Administer the first dose of RAGWITEK in a healthcare setting…observe the patient for at least 30 …If the patient tolerates the first dose, the patient may take subsequent doses at home.
- …
- Place the tablet immediately under the tongue. Allow it to remain there until completely dissolved. Do not swallow for at least 1 minute.
- …
- Initiate treatment at least 12 weeks before the expected onset of ragweed pollen season and continue treatment throughout the season. The safety and efficacy of initiating treatment in season have not been established. …
- …
- Prescribe auto-injectable epinephrine to patients prescribed RAGWITEK and instruct them in the proper use of emergency self-injection of epinephrine

RAGWITEK clinical development: Placebo controlled studies

- **P05233 and P05234, efficacy and safety studies in which subjects were treated for ~52 consecutive weeks beginning about ~16 weeks prior to ragweed pollen season**
- **P06081 and P05151, safety studies in which subjects were treated for 28 consecutive days outside of ragweed pollen season**

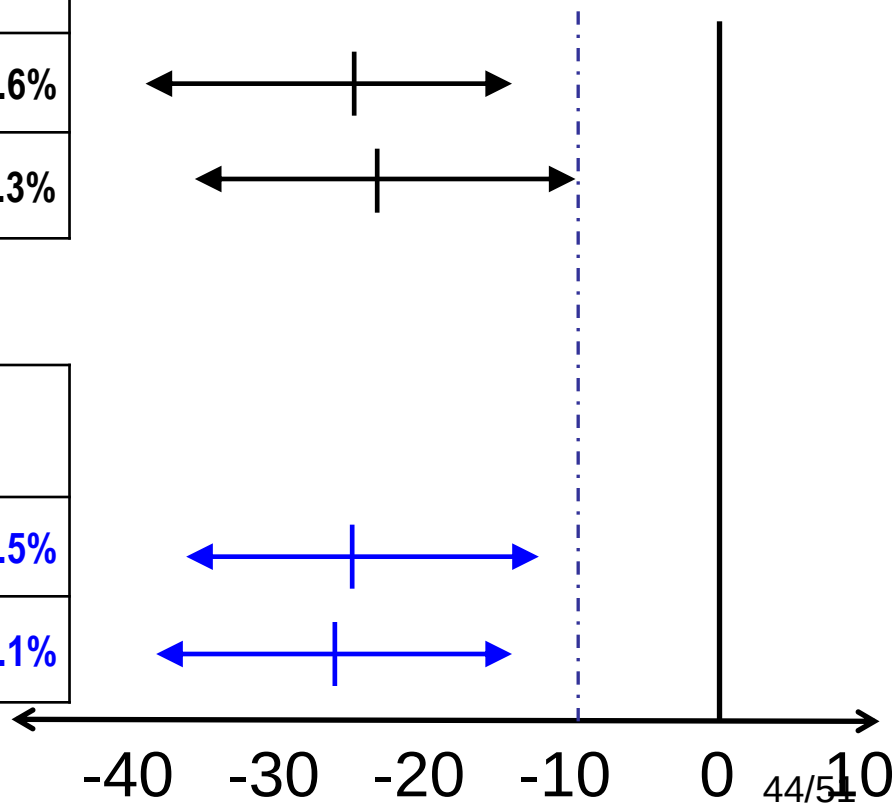
Summary of efficacy trials: Total Combined Score (TCS)

Peak ragweed season

Study	12 Amb a 1-U	Placebo	% difference	95% CI
P05233	159	164	-26.5%	-38.7%, -14.6%
P05234	152	169	-24.2%	-36.5%, -11.3%

Entire ragweed season

Study	12 Amb a 1-U	Placebo	% difference	95% CI
P05233	160	166	-25.7%	-37.6%, -13.5%
P05234	158	174	-27.0%	-38.8%, -14.1%



Contraindications
Ragwitek

- Severe, unstable or uncontrolled asthma
- History of any severe systemic allergic reaction
- History of any severe local reaction to sublingual allergen immunotherapy
- History of eosinophilic esophagitis
- Hypersensitivity to any of the inactive ingredients…contained in this product

Warnings and Precautions
Ragwitek

- Severe allergic reactions
- Epinephrine
- Upper airway compromise
- Eosinophilic esophagitis
- Asthma
- Concomitant allergen immunotherapy
- Oral inflammation

Adverse reactions
Ragwitek

- Reported in >5% of patients:
  - throat irritation,
  - oral pruritus,
  - ear pruritus,
  - oral paresthesia,
  - mouth edema,
  - tongue pruritus.

Epinephrine use

One subject (1/1057; 0.1%) who received RAGWITEK experienced a treatment-related severe systemic allergic reaction that led to discontinuation of RAGWITEK. The subject had local reactions starting on Day 1 of treatment with RAGWITEK. On Day 6 symptoms progressed and included swelling of the throat, dyspnea, nausea, and lightheadedness. The subject fully recovered after treatment with epinephrine (self-administered), antihistamines, and oral corticosteroids.

Approval issues

- Medication guide
- Epinephrine
- Age

Populations not included in the studies under consideration

- Young children (< 5 years)
- Elderly
- Pregnant women
- Persons with
  - poorly-controlled asthma
  - other co-morbid conditions
  - history of anaphylaxis
- Persons taking specified concurrent medications (that enhance the likelihood of a reaction and/or interfere with responses to rescue therapy)

see Cox L, et al. Allergen immunotherapy: A practice parameter third update. *J Allergy Clin Immunol* 2011; 127:S1-S55

Contact information

Jay E. Slater, MD
jay.slater@fda.hhs.gov
240.402.7396