DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

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Dear Doctor,

Beginning on July 8, 1998, non-standardized extracts of eight grass pollen allergens will no longer be available for sale in the United States. These eight non-standardized grass pollen extracts have been replaced by standardized grass pollen extracts, which include Kentucky (June) Bluegrass (*Poa pratensis*), Meadow Fescue (*Festuca elatior*), Orchard (*Dactylis glomerata*), Perennial Rye (*Lolium perenne*), Redtop (*Agrostis alba*), Sweet Vernal (*Anthoxanthum odoratum*), Timothy (*Phleum pratense*), and Bermuda (*Cynodon dactylon*) grass. The Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER), has licensed nine allergenic extract product manufacturers to manufacture and distribute the new standardized extracts. A complete listing of allergenic extract manufacturers licensed to manufacture and distribute standardized grass pollen extracts may be obtained from the FDA CBER Internet web site (http://www.fda.gov/cber/appr1997/1997grass.htm)

Standardized grass pollen extracts are expected to improve the safety of diagnosing and treating grass allergy. This improvement to safety will occur because standardized extracts define the level of potency and narrow the range of variability from one lot to the next. In addition, the standardized extracts have demonstrated stability in real time studies. The benefits to patients include enhanced safety when switching from an old vial to a new one and a more reliable response to immunotherapy, since each lot has an established potency. In addition, since each manufacturer measures potency based on the same CBER reference standard, health care professionals will have a greater choice of extracts.

The new units of standardization, Bioequivalent Allergy Units (BAU), are based on two assays originally developed at CBER, FDA. The potency of the FDA reference standard was initially determined by skin testing a cohort of allergic subjects using the $ID_{50}EAL$ method Subsequently, all manufactured lots are tested using an *in vitro* IgE-based ELISA and are assigned BAU units based on their potency relative to the FDA reference standard. Potency values of manufactured lots may also be checked by the Allergenics Testing Lab of CBER. By

combining these *in vivo* and *in vitro* approaches, one can be sure that each lot is of equivalent potency to others and contains the relevant major allergens.

Each grass extract will be available in potencies of 100,000 BAU/ml and 10,000 BAU/ml, except for Bermuda grass, which will only be available at 10,000 BAU/ml. The 10,000 BAU/ml dose is indicated for diagnosis and immunotherapy. The 100,000 BAU/ml dose is intended primarily for preparation of mixtures with final concentrations appropriate for immunotherapy. The package insert contains tables describing the percutaneous and intracutaneous reactivity of a group of highly allergic subjects to each 10,000 BAU/ml standardized grass pollen extract. The insert also contains directions on how to perform skin testing with these extracts in order to make a diagnosis of grass pollen allergy, how to select a safe dose when switching from nonstandardized to standardized extracts, and how to initiate immunotherapy.

Stock mixtures containing the standardized grass pollen extracts also will be available. The label will specify the potency of each grass in the mix, as well as the total potency of the mixture. In a patient allergic to multiple grass allergens, these potencies may be additive. The package insert contains full prescribing information.

Standardized grass pollen extracts labeled in BAUs are not directly interchangeable with grass pollen extracts labeled in Allergy Units (AU/ml) or with non-standardized extracts labeled in PNU/ml or the extraction ratio (e.g., 1:10 weight by volume). However, the package insert does show the potency of the previously available non-standardized extracts, for comparison with the standardized lots currently available. It also provides guidance for switching patients to the new standardized extracts.

Allergenic extracts carry a risk of inducing life-threatening reactions, such as anaphylaxis, or even death. Therefore, they should be used by physicians experienced in administering the extracts, as well as in the emergency care of anaphylactic reactions. Emergency measures and personnel trained in their use should be immediately available in the event of such a reaction.

Appropriate caution must be exercised in treating patients with steroid-dependent or labile asthma. Physicians who administer immunotherapy to asthmatics with either significant irreversible obstruction or who require continuous systemic corticosteroids should carefully weigh the benefit versus the risk of provoking increased bronchospasm.

In the event of a serious adverse reaction (systemic reactions including anaphylaxis, angioedema, or bronchospasm, disability, hospitalization, or death) associated with the use of allergenic extracts, FDA requests that physicians report the event using the Med Watch form or by calling (1-800) FDA-1088. Reports should include pertinent information such as history of asthma or prior systemic reactions, clinical status at the time of injection, concomitant medications, degree of patient sensitivity, manufacturer and dose of each allergen given, allergen dose compared to the previous injected dose, and any predisposing factors.

In summary, standardized grass pollen extracts are now available for use in diagnosing and treating grass-allergic patients. These products have a more accurate potency determination, greater lot to lot consistency, and better defined stability than was available previously. They will benefit patients by reducing dose variability, permitting a more consistent response to immuno-therapy, while decreasing the risk of adverse reactions due to incorrect dosing. They must be used with great care in treating highly sensitive grass-allergic patients.

Sincerely yours,

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