

PRODUCT MONOGRAPH

POLLINEX<sup>®</sup>-R

MODIFIED RAGWEED TYROSINE ADSORBATE VACCINE

Professed

VACCINE

Allergy Therapeutics (UK) Limited  
Worthing, BN14 8SA, UK  
CONTROL # 063362

Date of Preparation:  
March 20, 1998  
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April 3, 2005

NAME OF DRUG

POLLINEX-R  
Modified Ragweed Tyrosine Adsorbate

THERAPEUTIC CLASSIFICATION

Vaccine

Standard

Professed

ACTION AND CLINICAL PHARMACOLOGY

The exact mode of therapeutic action of POLLINEX-R (modified ragweed tyrosine adsorbate), as with other allergy vaccines, is unknown. It has been proposed that elevations of IgG blocking antibodies may interfere with the immediate hypersensitivity reaction of patients exposed to ragweed pollen. In addition, patients receiving POLLINEX-R have lesser post-seasonal increase in ragweed specific IgE antibody compared to placebo treated patients. It is possible that suppression of IgE antibody by POLLINEX-R during the ragweed season could influence the response of ragweed allergic patients to the pollen in their environment.

INDICATIONS AND CLINICAL USE

POLLINEX-R (modified ragweed tyrosine adsorbate) is indicated for the pre-seasonal immunotherapy of adults and children, over the age of 8 years, who have demonstrated ragweed allergic rhinitis by careful patient history and physical examination, supplemented by skin testing and/or immunological assay.

POLLINEX-R is generally not expected to completely eliminate the various allergic symptoms but should reduce their severity. POLLINEX-R should also be expected in many patients to reduce their dependence on other medication, such as antihistamines and other cough/cold over-the-counter medications that are taken during the season to alleviate rhinitis symptoms. There is also evidence that the use of more potent therapy, such as nasal and oral steroids, is reduced in patients who have received a course of POLLINEX-R.

CONTRAINDICATIONS

POLLINEX-R (modified ragweed tyrosine adsorbate) should not be administered to a patient who has experienced a previous severe anaphylactic reaction to ragweed vaccine immunotherapy.

Immunotherapy with Pollinex R is contraindicated in those individuals who do not exhibit skin test reactions and clinical sensitivity to ragweed.

Any injections, including immunotherapy with Pollinex R, should be avoided in patients with diseases characterized by a bleeding diathesis.

### WARNINGS

Patients suffering from febrile conditions or an acute attack of asthma should not be given POLLINEX-R (modified ragweed tyrosine adsorbate) until twenty-four (24) hours after their condition has returned to normal. Acute immediate anaphylactic reactions characterized by difficulty in breathing, cyanosis and shock have rarely occurred with POLLINEX-R treatment, but if such should occur, standard emergency measures must be adopted with the use of a tourniquet above the injection site, epinephrine, oxygen, intravenous steroids and airway management including intubation if required. Similarly, delayed anaphylactic reaction have rarely been reported with POLLINEX-R, however, the patient should be advised to report to their physician immediately if symptoms of such a reaction should be manifested.

Recent evidence suggests that patients on beta-blockers may be more prone to anaphylaxis during immunotherapy and in such patients, anaphylaxis may be less responsive to conventional treatment.

Hence, in such patients, the need for continued immunotherapy and/or continued beta-blocker use should be carefully reviewed.

Do not administer POLLINEX-R during the ragweed season, which usually starts in mid-August through to the end of September or until the first killing frost.

As routine immunizations may exacerbate autoimmune diseases, Pollinex R immunotherapy should be given cautiously to such patients.

Patients with unstable asthma or steroid dependant asthma and patients with underlying cardiovascular disease are at additional risk during a systemic reaction. The risk must be weighted against the benefit.

### PRECAUTIONS

All administrations of POLLINEX-R (modified ragweed tyrosine adsorbate) must be given by the subcutaneous route, by or under the supervision of a physician. Care must be taken never to inject POLLINEX-R directly into a blood vessel.

All patients should remain under observation in the doctor's office or clinic for 20 to 30 minutes after each vaccine injection and then should avoid strenuous physical exercise for at least twenty-four (24) hours.

Patients should be advised not to eat a heavy meal immediately before receiving their injection of POLLINEX-R. It is advisable to administer an antihistamine about one hour prior to an injection of POLLINEX-R. Epinephrine hydrochloride 1:1000 solution should always be kept on hand for use in the very unlikely event of a severe immediate reaction.

It is extremely important to shake the syringe containing the vaccine prior to injection, thus greatly reducing the possibility of needle blockage.

Use in Pregnancy: Safety for the use of POLLINEX-R in pregnancy has not been established.

Use in Nursing Mothers: Safety for the use of POLLINEX-R in nursing mothers has not been established.

Use in Geriatric populations: Safety for the use of POLLINEX-R in geriatric populations has not been established. Patients over 60 years of age may have an increased risk of impaired cardiovascular or pulmonary function.

Use in Pediatric Populations: Safety for the use of POLLINEX-R in pediatric populations has not been established, POLLINEX-R should not be used to treat patients under 8 years of age.

Safety for the use of POLLINEX-R in combination with other allergens has not been established.

POLLINEX-R administration should not be instituted unless other ragweed pollen extract therapy has been discontinued.

### ADVERSE REACTIONS

The following adverse reactions may occur during therapy with POLLINEX-R:

Hypersensitivity Reactions: Erythema, swelling, pruritis, wheal, papule, mild hives, anaphylactoid reaction.

Other: Local reactions, such as pain accompanied by induration at the site of injection have been reported; wheezing, stuffy and/or runny nose, chest tightness.

### SYMPTOMS AND TREATMENT OF OVERDOSAGE

It is not possible to administer to a patient an overdosage of POLLINEX-R, as long as no more than 0.5 mL of the vaccine is administered starting with either syringe or vial number 1, followed in sequence by syringe or vial 2, 3 and lastly 4.

In patients with severe allergic reactions, general supportive measures (if the patient is in shock) or symptomatic therapy similar to that applied in all cases of hypersensitivity, are recommended. Agents such as pressor amines, antihistamines and corticosteroids should be readily available. POLLINEX-R is not suitable for such patients with severe allergic reactions.

### DOSAGE AND ADMINISTRATION

POLLINEX-R (modified ragweed tyrosine adsorbate) must be given prior to the ragweed season which usually starts in mid-August. The course of vaccine therapy should start toward the end of June and be given such that the last injection is received about the first week in August.

#### Pre-filled Syringes

The dosage regimen is outlined below. Each course of POLLINEX-R consists of a patient treatment pack of four sterile pre-filled syringes clearly labeled 1,2,3 and 4 containing the following POLLINEX-R strengths each in a volume of 0.5 mL.

<u>Syringe Number</u>	<u>Strength in Protein Nitrogen Units/0.5 mL</u>	<u>Strength in Noon Units/0.5 mL</u>
1	105	300
2	250	700
3	700	2000
4	2150	6000

The vaccine treatment regimen consists of the administration of POLLINEX-R by subcutaneous injection. On the first occasion, the contents of No. 1 syringe are given, followed in order by syringe numbers 2, 3 and 4 at a recommended interval of approximately 7 days between injections.

The operation of the syringe is as follows:

1. Withdraw the syringe from the cold storage condition well before time of administration and allow to attain room temperature. Do not heat.
2. DO NOT REMOVE THE NEEDLE GUARD UNTIL READY FOR USE.
3. Withdraw syringe plunger slightly and shake the syringe thoroughly to ensure a homogeneous suspension.
4. Release the pressure in the syringe by withdrawing the plunger slightly.
5. Shake the syringe thoroughly again, remove needle guard, then carefully express the air from the syringe with the needle held upwards, to minimize loss of contents.
6. Slowly inject the suspension deep subcutaneously.
7. DO NOT INJECT INTO A BLOOD VESSEL.

### Vials

Each patient treatment pack consists of four sterile vials clearly labeled 1, 2, 3 and 4 containing the following POLLINEX-R strengths each in a volume of 1.0 mL.

<u>Vial Number</u>	<u>Strength in Protein Nitrogen Units/1.0 mL</u>	<u>Strength in Noon Units/1.0 mL</u>
1	210	600
2	500	1400
3	1400	4000
4	4300	12000

The vaccine treatment regimen consists of the administration of POLLINEX-R by subcutaneous injection. On the first occasion, 0.5 mL of the contents of No.1 vial are given, followed in order by 0.5 mL of vial numbers 2, 3 and 4 at a recommended interval of approximately 7 days between injections.

Procedure

1. Withdraw the vial from the cold storage condition well before time of administration and allow to attain room temperature. Do not heat.
2. Shake vial thoroughly to ensure a homogeneous suspension.
3. Using a sterile disposable syringe, withdraw 0.5 mL of suspension.
4. Carefully express the air from the syringe with the needle held upwards to minimize loss of contents.
5. Slowly inject the suspension deep subcutaneously.
6. DO NOT INJECT INTO A BLOOD VESSEL.

PHARMACEUTICAL INFORMATIONDrug Substance

Proper Name: Modified Ragweed Tyrosine Adsorbate

Composition:

POLLINEX-R (modified ragweed tyrosine adsorbate) is an aqueous extract of short ragweed pollen (*Ambrosia elatior*) chemically modified with glutaraldehyde adsorbed onto tyrosine and then suspended in saline. Pre-filled syringes (0.5 mL) and vials (1 mL) contain phenol 0.5% (w/v) as preservative.

Stability and Storage Recommendations:

POLLINEX-R should be stored at 2EC - 8EC.

AVAILABILITY OF DOSAGE FORMSPre-filled Syringes

Each patient treatment package consists of four pre-filled sterile syringes each containing 0.5 mL of suspension. Each syringe is clearly labeled as to syringe number and strength in total Protein Nitrogen Units. The syringe number and dosage are shown below:

<u>Syringe Number</u>	<u>Dosage in Protein Nitrogen Units</u>
1	105
2	250
3	700
4	2150

Vials

Each patient treatment package consists of four sterile vials each containing 1.0 mL of suspension. Each vial is clearly labeled as to vial number and strength in total Protein Nitrogen Units. The vial number and strength are shown below:

<u>Vial Number</u>	<u>Total Protein Nitrogen Units/Vial</u>
1	210
2	500
3	1400
4	4300

PHARMACOLOGY

Modified ragweed tyrosine adsorbate embodies two principles designed to reduce the immediate bioavailability of allergen on injection, and hence to increase safety:

1. Chemical modification with glutaraldehyde
2. Adsorbed to tyrosine suspension

The resultant tyrosine adsorbate of glutaraldehyde-treated ragweed pollen extract shows characteristics of a depot preparation; tyrosine persists at the site of injection for several days, so that the adsorbed modified allergen is released slowly. The antibody induced by the injected adsorbate retains specificity for unmodified allergen.

1. Persistence of tyrosine at the site of injection  
Tyrosine injected subcutaneously into guinea pigs in aliquots of 40, 20 or 10 mg has been shown to be substantially removed from the injection site over a period of seven days.
2. Slow release of adsorbed antigen  
Ragweed extract injected subcutaneously into guinea pigs previously sensitized by intradermal injection of guinea pig anti-ragweed pollen antiserum, induces a passive cutaneous anaphylactic response: a dose response relationship can be demonstrated. Tyrosine adsorbed ragweed extract gave a response not greater than that of unadsorbed material with 4% of its normal potency.
3. Adjuvant effect of tyrosine  
In rats, the immune response to grass pollen extracts was found to be enhanced by adsorption to tyrosine to levels intermediate between that shown in aqueous extracts and that given by extracts in Freund's Complete Adjuvant. In guinea pigs, enhanced antibody responses were given by the ragweed extract which was adsorbed to tyrosine.
4. Effect of glutaraldehyde on allergenicity  
On treatment with glutaraldehyde, the reactivity of ragweed extract in skin test in allergic subjects falls to a level dependant on the glutaraldehyde concentration used. This fall is approximately paralleled by a fall in primary amino group content.

5. Allergenicity of adsorbate  
The modified tyrosine adsorbate ragweed extract has low allergenicity relative to its nominal potency as assessed by skin testing in ragweed atopic volunteers.
6. Antibody response  
In guinea pigs, injection of the tyrosine adsorbate modified ragweed pollen extract induces antibodies with specificity for unmodified extract.

## TOXICOLOGY

### Acute Toxicity

The acute toxicity and median lethal dose of L-tyrosine and modified ragweed pollen tyrosine adsorbate was determined in mice dosed by the subcutaneous and intramuscular routes, and in rats following subcutaneous and intramuscular administration. LD<sub>50</sub>'s are show in tables 1 and 2.

TABLE 1  
L-tyrosine

Route of Administration	Mice	LD <sub>50</sub> (mg/kg)	Rats
s.c.	>5000		>5000
i.m.	>5000		>5000

TABLE 2  
Modified Ragweed Tyrosine Adsorbate

Route of Administration	Mice	LD <sub>50</sub> (NU/kg)	Rats
s.c.	>280,000		>280,000

### Subacute Animal Toxicity

#### Toxicity of Tyrosine Base

Four-week studies of parenteral toxicity were performed in rats and beagle dogs. Dosages of 10, 25 and 50 mg/kg/day, (each divided equally between the subcutaneous and intramuscular routes) were administered to groups of twenty rats, each group equally composed of males and females. Also, three groups, (2 males and 2 females per group), of beagle dogs, were given dosages of 10 or 25 mg/kg/day or diluent by parenteral injection. (0.5 or 1.0 mL was given by the intramuscular route, while the remainder was given by the subcutaneous route).

Apart from local reactions, there were no morphological changes suggesting tissue damage with a drug induced etiology.

20-Day repeat dose study in the rat (Modified ragweed pollen tyrosine adsorbate)

The systemic toxicity was studied in 2 groups of 24 rats, (12 males and 12 females per group). A dose of 0.2 mL/rat of a solution of modified ragweed tyrosine adsorbate containing 14,000 Noon Units/mL was given by intramuscular injection on alternate days using left and right thigh muscles alternately. Control animals were similarly dosed with normal sterile saline.

There were no deaths. Initial loss or arrest of body weight was rapidly replaced by normal body weight gains. Overall body weight gain was slightly lower than control in male rats dosed with modified ragweed tyrosine adsorbate.

Slightly reduced food intake was observed in female rats dosed with modified ragweed tyrosine adsorbate. Food conversion efficiency initially was poorer in rats dosed with modified ragweed tyrosine adsorbate but thereafter became similar or even better than in the controls.

Clinical chemistry and urinalysis values showed no adverse changes, all results being considered within normal limits.

Terminal studies were carried out on the rats. At macroscopic and microscopic examination the only lesions considered to be related to treatment concerned the injection sites.

Macroscopic post-mortem findings revealed a few small foci of white material within the musculature of rats dosed with modified ragweed tyrosine adsorbate and only slight reddening of the muscle in control animals. Organ weights were all considered within normal limits.

Histopathology revealed moderate reactive changes – focal necrosis accompanied by oedema being frequently seen – at sites injected with modified ragweed tyrosine adsorbate. No changes were seen at sites injected with saline.

20-Day repeat dose toxicity in the dog (Modified ragweed pollen tyrosine adsorbate)

The systemic toxicity was studied in beagle dogs. Eight beagle dogs were divided into two groups, each of two males and two females. The compound, (0.5 mL of solution containing 14,000 Noon Units/mL), was administered by subcutaneous injection to the first group of animals and normal sterile saline (used as control) given to the second group. Single 0.5 mL injections were given on alternate days to separate sites over a dosing period of 20 days.

There were no deaths. Small subcutaneous swellings lasting up to 48 hours were seen following injections of modified ragweed tyrosine adsorbate. Brief minimal swelling followed injection of saline. There were no differences in body weight gain between dogs which had received modified ragweed tyrosine adsorbate or saline. Food consumption was not adversely affected by dosing.

Slight lower water intake in dogs dosed with modified ragweed tyrosine adsorbate was observed. No other changes were observed which could be attributed to dosing with modified ragweed tyrosine adsorbate.

Terminal studies were carried out on the dogs. Gross findings were limited to injection sites. Localized thickening and lamination of subcutaneous tissue with associated diffuse hemorrhage were seen up to five days after injection. In addition, foci of white material (probably the test compound) were seen up to three days after injection. Occasional subcutaneous hemorrhage was seen up to three days after saline injection. All organ weights were within normal limits.

The main histopathology findings were as follows:

Moderate to marked oedema, inflammation and foci of necrosis were seen within the subcutaneous connective tissue up to three days after injection of modified ragweed tyrosine adsorbate. Rapid regeneration occurred thereafter.

Occasional hemorrhage and minimal inflammatory foci were seen up to 5 days after saline injections.

No other abnormalities were seen that could be attributed to dosing with modified ragweed tyrosine adsorbate.

#### 20-Day local irritancy study in the rat (modified tyrosine adsorbate)

This study was designed to assess the degree of local irritancy of modified ragweed tyrosine adsorbate when injected intramuscularly in the rat, (6 groups of 3 males and 3 females each and one group of 9 males and 9 females rats). Rats were given either single or multiple injections, (0.2 mL of solution containing 14,000 Noon Units/mL), up to a maximum of 10, followed by differing recovery periods ranging from 24 hours to 14 days. Examinations of these animals was restricted to clinical examination and gross and microscopic examination of injection sites.

Single injections produced mild acute inflammation in the musculature at the site of injection.

Multiple injections into the muscle at the same site produced focal necrosis particularly in the intermuscular connective tissue. Chronic inflammation rapidly developed but true abscesses were not produced. The chronic inflammation was not progressive and resolution was complete 7-14 days after the last injection.

#### 20-Day local irritancy study in the dog (modified ragweed tyrosine adsorbate)

The local irritancy was investigated in beagle dogs. Four beagle dogs were divided into two groups, each of one male and one female. The compound, (0.5 mL of solution containing 14,000 Noon Units/mL), was administered by subcutaneous injection; normal sterile saline being used as a control. Single or multiple injections were made at each site over a dosing period of up to 20 days. The dosing regimen allowed local irritancy to be assessed up to 13 days after multiple injections.

There were no deaths. Small subcutaneous swelling lasting up to 48 hours were seen following single or multiple doses. Brief minimal swelling followed injection of saline. No differences in body weight gain were observed between dogs which had received either single or multiple injections.

No adverse changes in food consumption or water consumption were observed.

Terminal studies were carried out on the dogs. Gross finding were limited to injection sites. Localized thickening and lamination of subcutaneous tissues with associated diffuse hemorrhage were seen one day after injection and up to three days following multiple injections. In addition, foci of white material (probably the test compound) were also seen within the thickened tissues one day following single or multiple doses. Occasional subcutaneous hemorrhage was seen one day after saline injections.

The main histopathology finding noted were as follows:

Moderate to marked oedema, inflammation and foci of necrosis were seen within the subcutaneous connective tissue up to three days after injection of single or multiple doses of modified ragweed tyrosine adsorbate. Rapid tissue regeneration occurred thereafter. Occasional hemorrhage and minimal inflammatory foci were seen up to 5 days after saline injections.

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