PRODUCT MONOGRAPH

POLLINEX®-R

Modified Ragweed Pollen Allergen Tyrosine Adsorbate

Pre-filled syringes

105 PNU/0.5 ml, 250 PNU/0.5 ml, 700 PNU/0.5 ml, 2150 PNU/0.5 ml

Vials

210 PNU/ml, 500 PNU/ml, 1400 PNU/ml, 4300 PNU/ml

Suspension for injection

Professed

Allergen Extracts

Allergy Therapeutics (UK) Limited
Dominion Way
Worthing
West Sussex
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

No./ Colour	**Route of Administration**	**Dosage Form / Strength Vials**	**Dosage Form / Strength Pre-filled syringes**	**Clinically Relevant Nonmedicinal Ingredients**
1 Grey 2 Green 3 Yellow 4 Red	Subcutaneous	Suspension for Injection 210 PNU/ml 500 PNU/ml 1400 PNU/ml 4300 PNU/ml	Suspension for Injection 105 PNU/0.5 ml 250 PNU/0.5 ml 700 PNU/ 0.5 ml 2150 PNU/0.5 ml	Disodium Phosphate Dodecahydrate, Glycerol, L-tyrosine, Phenol, Sodium Chloride, Sodium Dihydrogen Phosphate Dihydrate, Water for Injections

DESCRIPTION

POLLINEX-R (modified ragweed pollen allergen tyrosine adsorbate) is an aqueous extract of short ragweed pollen (*Ambrosia elatior*) chemically modified to an allergoid by treatment with glutaraldehyde, adsorbed onto L-tyrosine and then suspended in saline. The pre-filled syringes (0.5 ml) and vials (1 ml) contain phenol 0.5% (w/v) as preservative.

The purified ragweed pollen allergen extract is characterized and standardized (in PNU/ml, Protein Nitrogen Units) by biochemical methods to ensure that the allergoid content and immunogenic potency are consistent.

POLLINEX-R is presented as follows:

No./Colour	**Strength (PNU/ml)**	**Strength (Noon Units/ml)**
1 Grey	210	600
2 Green	500	1400
3 Yellow	1400	4000
4 Red	4300	12000

INDICATIONS AND CLINICAL USE

POLLINEX-R is indicated for:

> The pre-seasonal immunotherapy of ragweed allergic rhinitis in adults and children, over the age of 8 years.

POLLINEX-R is a prescribed treatment indicated for rhinitis, caused by an IgE-mediated allergy to ragweed pollen. This type of treatment is referred to as specific immunotherapy. Careful consideration of the patient's history and diagnosis with a positive skin prick test and/or IgE test need to be conducted prior to treatment.

POLLINEX-R is not expected to completely eliminate the various allergic symptoms but should reduce their severity. POLLINEX-R may also be expected to reduce a patient's dependence on symptomatic medication (antihistamines and other cough/cold over-the-counter products) taken during the ragweed season to alleviate rhinitis symptoms. There is 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.

The product should be administered by or under the supervision of physicians experienced in specific immunotherapy. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.
Epinephrine (1:1000) must always be immediately available.

Geriatrics (≥ 60 years of age):
The safety and efficacy for the use of POLLINEX-R in geriatric populations have not been established.

Paediatrics (≤ 8 years of age):
No data is available.
POLLINEX-R is not approved for use in patients younger than 8 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to any of the excipients in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- POLLINEX-R 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.
- Diseases or conditions preventing the treatment of possible anaphylactic reactions, e.g. chronic heart and lung diseases, severe arterial hypertension.

- Unstable or severe chronic or severe seasonal asthma (FEV1 consistently under 70% of predicted value after adequate pharmacologic treatment).
- Treatment with β-blockers.
- Treatment with tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs)
- Pathologic immune conditions.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Treatment should only be carried out by, or under supervision of physicians experienced in specific immunotherapy.
- Severe systemic reactions, including life-threatening anaphylactic shock, can occur with the use of POLLINEX-R (Ref. ADVERSE REACTIONS).
- Patients with asthma may be more susceptible to severe adverse reactions. (See Contraindications).
- The patient must be under observation for at least 30 minutes (longer in high risk patients) after having received an injection with POLLINEX-R.
- All patients receiving immunotherapy should be instructed in the procedure for emergency self-injection of epinephrine (See WARNINGS AND PRECAUTIONS).
- Avoid intra-vascular injection

Anaphylactic Shock

Severe, immediate systemic reactions including life-threatening anaphylactic shock can occur with the use of POLLINEX-R. Delayed anaphylactic reactions can also occur.

Warning symptoms:
Tingling, itching and burning sensations on and under the tongue, in the throat and particularly on the palms and soles. This may be immediately followed by shock with cyanosis, hypotension, tachycardia, bronchospasm and unconsciousness.

If the patient shows signs of an intense systemic reaction or anaphylactic shock, immediate medical action must be taken, please refer to the Overdosage section for further information.

The product should be administered under the supervision of physicians experienced in specific immunotherapy. Epinephrine (1:1000) must always be immediately available. For further information please refer to Indications and Clinical Use.

General

All administrations of POLLINEX-R (modified ragweed pollen allergen 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.

Patients should be kept under **medical observation for at least thirty minutes** after each injection. This period should be extended even if mild symptoms or signs of hypersensitivity develop and patients should remain under observation until these have completely resolved. A severe and prolonged adverse reaction may necessitate hospital admission. They should then avoid strenuous physical exercise for at least twenty-four (24) hours.

The patient should be informed that he/she must contact their doctor immediately if any signs of adverse reactions occur during the observation period or at any time following the injection. In case of severe systemic reaction, continuation of treatment should be re-evaluated.

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.

Cardiovascular
Concomitant therapy with betablockers while taking POLLINEX-R is contraindicated. Patients on beta blockers may be more prone to anaphylaxis and may not be responsive to conventional treatment such as epinephrine or inhaled bronchodilators.

Anaphylactic reactions may be more severe in patients receiving ACE inhibitors. Concomitant use of POLLINEX-R with ACE inhibitors drugs is not recommended.

The safety of POLLINEX-R in patients with impaired cardiovascular function, or risk factors for cardiovascular disease, has not yet been established.

Immune
There is a risk of reduced efficacy if a viral or bacterial pathogen vaccine is administered in combination with POLLINEX-R. The safety and efficacy of the concomitant use of POLLINEX-R and viral or bacterial pathogen vaccine have not been established.

Psychiatric
Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) potentiate epinephrine and increase the risk of cardiac arrhythmias (with possible fatal consequence). Use of tricyclic antidepressants and monoamine oxidase inhibitors may interfere with the treatment of anaphylaxis: therefore concomitant use of POLLINEX-R with these drugs is contraindicated.

Renal
Anaphylactic reactions may be more severe in patients receiving ACE inhibitors. Concomitant use of POLLINEX-R with ACE inhibitors drugs is not recommended.
Respiratory

If the patient has suffered from an acute infection or fever, POLLINEX-R should not be given until twenty four to forty eight hours after the patient's condition has returned to normal. Patients with unstable asthma or steroid dependant asthma are at additional risk during a systemic reaction. The risk must be weighted against the benefit.

The safety of POLLINEX-R has not been established in patients with impaired pulmonary function.

Concomitant therapy with symptomatic anti-allergic agents (such as antihistamines, corticosteroids or mast cell degranulation inhibitors) may mask the patient's current reactivity status.

Sensitivity/Resistance
High-risk patients (such as patients with an extremely high level of sensitisation) should be monitored more closely.

Local Skin Reactions at Injection Site
Patients may experience one of the following after the administration of the injection: swelling, urticaria, erythema, pruritus, pain, induration, discolouration or warmth.

Special Populations

Pregnant Women: There is no data on the clinical experience for use of POLLINEX-R in pregnant women. Treatment should not be initiated during pregnancy as severe systemic reactions may be detrimental to the foetus.

Nursing Women: No clinical data are available for the use of POLLINEX-R during lactation.

Paediatrics (≤8 years of age): POLLINEX-R is not indicated in children under 8 years of age.

Geriatrics (≥ 60 years of age): The safety and efficacy 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 and/or pulmonary function.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Spontaneously reported adverse reactions include mainly local reactions at the injection site (such as swelling, pruritus, pain, erythema, haematoma, discolouration). Further adverse drug reactions to occur are respiratory disorders (dyspnoea, throat tightness, throat irritation, sinus congestion, nasal congestion, rhinorrhoea), gastrointestinal disorders (diarrhoea, nausea, abdominal discomfort, abdominal pain), skin disorders (urticaria, pruritus), eye disorders (eye swelling) and general disorders (chest discomfort, chills, body temperature increased).

The reactions are commonly mild to moderate in intensity and self-limiting.

There is the potential risk of severe allergic reactions up to anaphylactic shock. However, so far no such cases have been reported for POLLINEX-R.

DRUG INTERACTIONS

Overview

No interaction studies have been performed.

Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 1 - Potential Drug-Drug Interactions

Modified Ragweed Pollen Allergen Tyrosine Adsorbate	**Ref**	**Effect**	**Clinical comment**
Betablockers	T	Patients on betablockers who experience anaphylaxis will be less responsive to epinephrine which would be administered to potentially save their life.	Concomitant use is contraindicated.
Immunosuppressant regime	T	Due to the immune system being suppressed the body will not react in the anticipated way and may result in less efficacy.	Concomitant use is contraindicated.
Hyposensitisation therapy	T	Due to the immune system being stimulated by one hyposensitisation vaccine, there is a risk that tolerability may be reduced if a second hyposensitisation therapy is administered concomitantly.	Caution should be exercised with the concomitant use of this drug class. If the patient must be administered a hyposensitisation vaccine, a safety interval of 2 – 3 days should be left between injections.

Modified Ragweed Pollen Allergen Tyrosine Adsorbate	Ref	Effect	Clinical comment
Symptomatic anti-allergic agents (i.e. antihistamines)	T	Concomitant therapy with these agents may mask the patients' current reactivity status.	Caution should be exercised with the concomitant use of this class of therapeutic agent.
Viral or bacterial pathogen vaccines	T	There is a risk of reduced efficacy if a viral or bacterial pathogen vaccine is administered concomitantly with POLLINEX-R.	Concomitant use of POLLINEX-R with viral or bacterial pathogen vaccines has not been established.
ACE inhibitors	T	Systemic reactions may be more severe with concomitant use of ACE inhibitors.	Concomitant use of POLLINEX-R with these drugs is contraindicated.
MAOIs or Tricyclic anti-depressants	T	These drugs may potentiate the effects of epinephrine (if administered during POLLINEX-R administration.	Concomitant use of POLLINEX-R with these drugs is contraindicated.

Legend: T = Theoretical

Drug-Food Interactions

Interactions with food have not been established.
Patients should be advised not to consume a heavy meal immediately prior to receiving the POLLINEX-R injection.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

If dizziness or fatigue is experienced by the patient they should be advised not to drive or operate machinery until these effects have passed.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

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

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.

POLLINEX-R (modified ragweed pollen allergen 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.
Each course of POLLINEX-R consists of four sterile pre-filled syringes or sterile filled vials clearly labelled 1, 2, 3 and 4.

The dosage of allergenic extracts is a highly individualized matter and varies according to the degree of sensitivity of the patient, their clinical response and tolerance to the extract administered during the early phases of an injection regimen. The starting dose should be based on skin tests of the extract to be used for immunotherapy.

- In order to prevent an adverse reaction, the patient's history must be fully considered before administration of POLLINEX-R. The current health condition of the patient should be checked by taking a careful history. Particular attention should be paid to the following points:
    - Recurrent/current fever or inflammatory conditions;
    - Intermittent/current infections;
    - Changes in general health and the use of other medication (particularly symptomatic treatment for allergies);
    - Assessment of lung function in asthmatics e.g. peak-flow measurement.

- If a patient is highly sensitive, the starting dose should be lower. The dosage and the progression from dose to dose should be lower and adapted to the patient's reactivity according to the physician's discretion.

Recommended Dose and Dosage Adjustment

POLLINEX-R should be administered as a course of four 0.5 ml subcutaneous injections. One 300 NU/0.5 ml injection, one 700 NU/0.5 ml injection, one 2000 NU/0.5 ml injection and one 6000 NU/ 0.5 ml injection must be administered prior to the pollen season with a recommended interval of 7 days between injections.

At each strength, the **maximum injection of 0.5 ml must not be exceeded.**

The following is a suggested schedule for average patients; however, the degree of sensitivity varies in many patients. The dosage and progression from dose to dose should be adjusted and should be regulated by the patient's tolerance and reaction.

Table 2-Suggested schedule for average patients

Vial or Syringe No/Label Colour	Recommended Dosage	Interval from Previous Injection (days)	
		Min	Max
1 Grey	0.5 ml 105 PNU	N/A	N/A
2 Green	0.5 ml 250 PNU	7	14
3 Yellow	0.5 ml 700 PNU	7	14
4 Red	0.5 ml 2150 PNU	7	14

An adapted dosing regimen with a lower dose increment applies to highly sensitised patients and may vary according to the degree of sensitivity of the individual. The following may apply to some (but not all) highly sensitised patients.

Table 3-Suggested schedule for highly sensitised patients

Vial or Syringe No/Label Colour	Alternative Dosage (For highly sensitised patients)	Interval from Previous Injection (days)	
		Min	Max
1 Grey	0.2 ml 42 PNU	N/A	N/A
	0.5 ml 105 PNU	7	14
2 Green	0.2 ml 100 PNU	7	14
	0.5 ml 250 PNU	7	14

3 Yellow	0.2 ml 280 PNU	7	14
	0.5 ml 700 PNU	7	14
4 Red	0.2 ml 860 PNU	7	14

Missed Dose
If the recommended interval between injections is exceeded by more than seven days, the treatment should be recommenced from vial or syringe No. 1 for safety reasons.

Administration

Remove the syringe or vial from the refrigerator and allow to warm to room temperature. **Do not heat**. As the product is a suspension, the container must be shaken thoroughly until all of the sediment is evenly resuspended.

POLLINEX-R should be administered at a constant pressure by subcutaneous injection to the lateral/posterior aspect of the middle third of the upper arm. The injection sites should be alternated between arms.

Intravenous and intramuscular injection must be strictly avoided and aspiration should be carried out to ensure that no blood vessels are injured.

It is advisable to administer the injection to anxious or potentially unstable patients while they are lying down.

After the injection the patient must be advised not to rub the injection site and the patient must remain under medical supervision for 30 minutes.

OVERDOSAGE

The likelihood of the patient experiencing systemic adverse reactions is significantly increased in the case of an overdose. To reduce the possibility of these reactions occurring, the dosage interval (7 days between injections) must be respected, the dose must be of the correct strength and volume (maximum volume 0.5 ml) and the vaccine must not be administered via the intramuscular or intravenous route.

In the case of an overdose, adverse reactions as listed in the Adverse Drug Reaction Overview may occur. Following an overdose the risk of severe systemic reactions may be increased. If severe systemic reactions occur refer to the table below for management of the reaction.

Anaphylactic shock

As with any specific immunotherapy there is a risk of anaphylactic shock.

Warning symptoms:
Tingling, itching and burning sensations on and under the tongue, in the throat and particularly on the palms and soles. This may be immediately followed by shock with cyanosis, hypotension, tachycardia, bronchospasm and unconsciousness.

If the patient shows signs of an intense systemic reaction or anaphylactic shock, immediate medical action must be taken in the following order (EAACI, Standards for Practical Allergen Specific Immunotherapy, 2006):

1. Adrenaline/epinephrine (1 mg/ml, 0.5-0.8 mg deeply i.m. or diluted 0.1 mg/ml, 0.3-0.5 mg i.v. (slowly in fractionated doses) may be repeated after 10-20 minutes
2. i.v. saline
3. Place patient in supine position
4. Oxygen 5-10 l/min
5. Check blood pressure, pulse rate and oxygen saturation
6. Antihistamine clemastine (1 mg/ml, 1-2 ml (1-2 mg, iv.))
7. Methylprednisolone 80 mg i.v.
8. Hospitalisation necessary because of the risk of delayed shock

Monitor pulse and blood pressure continuously.

If adrenaline/epinephrine, theophylline, antihistamines or glucocorticoids are administered to children, the doses must be adapted according to the age or weight.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The exact therapeutic mode of action of POLLINEX-R (modified ragweed pollen allergen tyrosine adsorbate) is not known, as is the case with other seasonal immunotherapy (SIT). It has been suggested that elevated levels of IgG blocking antibodies could have an impact on the immediate hypersensitivity reaction of patients exposed to ragweed pollen. In addition, patients who have completed a course of POLLINEX-R show a minor post-seasonal increase in IgE-ragweed-specific antibodies compared with patients treated with a placebo. It is possible that suppression of IgE antibody by POLLINEX-R during the ragweed season will have an effect on the reaction of patients who are allergic to ragweed with regard to their environment.

Pharmacodynamics

ATC Code V01A A20 Various.

POLLINEX-R is intended for treatment of patients with specific IgE-mediated allergy with

symptoms such as rhinitis caused by ragweed pollen. The immune system is the target for the pharmacodynamic effect. The intention is to modulate the immune response of the patient, reducing the IgE mediated hypersensitivity response in favour of more normal tolerance to ragweed pollen.

The precise mechanism of action has not been fully elucidated but there is strong evidence that allergy is a Th2 weighted imbalance in the immune system, manifested in IgE mediated hypersensitivity reactions. Specific immunotherapy or desensitisation is believed to redirect an allergic Th2 biased response in favour of a more normal balanced Th1/Th2 response. The production of allergen specific IgG antibody (especially 'blocking' IgG4 antibody) suppression of specific IgE antibody and decreased mediator (histamine) release from basophils are thought to be important evidence for the redressing of the Th1/Th2 balance.

L-Tyrosine is a naturally occurring, sparingly soluble, amino acid that is utilised for its adsorbent properties. L-tyrosine acts as a short-term depot adjuvant, thereby extending the bioavailability of allergens and enhancing IgG antibody induction.

Pharmacokinetics

Pharmacokinetic studies are not possible for products of specific immunotherapy due to the nature of indicators in product plasma levels being too low to measure.

Hepatic Insufficiency: No data available.

Renal Insufficiency: No data available.

STORAGE AND STABILITY

Store under refrigeration (2 to 8°C). **Do not freeze.**

Keep in a safe place out of the reach of children.

SPECIAL HANDLING INSTRUCTIONS

As the product is a suspension, the product must be allowed to warm to room temperature and then shaken thoroughly until all of the sediment is evenly resuspended.
Any unused product or waste should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Syringes

Each treatment package consists of four pre-filled sterile syringes each containing 0.5 ml suspension for subcutaneous injection.

Syringe	Dosage (Protein	Dosage (NU/0.5 ml)	Final Fill Volume

Number/Colour	Nitrogen Units)		
1 Grey	105	300	0.5 ml
2 Green	250	700	0.5 ml
3 Yellow	700	2000	0.5 ml
4 Red	2150	6000	0.5 ml

Vials

Each treatment package consists of four sterile vials each containing 1.0 ml suspension for subcutaneous injection.

Vial Number/Colour	Dosage (Protein Nitrogen Units)	Dosage (NU/0.5 ml)	Final Fill Volume
1 Grey	210	600	1 ml
2 Green	500	1400	1 ml
3 Yellow	1400	4000	1 ml
4 Red	4300	12000	1 ml

All strengths and presentations of POLLINEX-R contain the following non-medicinal ingredients:

- Disodium Phosphate Dodecahydrate
- Glycerol
- L-tyrosine
- Phenol
- Sodium Chloride
- Sodium Dihydrogen Phosphate Dihydrate
- Water for Injections

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Modified Ragweed Pollen Allergen Tyrosine Adsorbate

Product Characteristics

Ragweed pollen is extracted in Evans solution to produce the ragweed native extract. The native extract is then clarified and dialysed to remove high molecular weight components.

The native extract then undergoes modification by the addition of glutaraldehyde, converting the native extract into an allergoid, reducing allergencity whilst retaining immunogenicity.

The allergoid is dialysed and filtered to remove large particulates and to sterilise the bulk.

The allergoid is then adsorbed onto L-tyrosine and the resulting bulk ragweed modified adsorbate is washed.

The active bulk ragweed modified adsorbate is then serial diluted with L-tyrosine and filled into sterile syringes or vials. The overall tyrosine content of each syringe or vial is 4%.

DETAILED PHARMACOLOGY

Modified ragweed pollen allergen 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 glutaradehyde, 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 rates following subcutaneous and intramuscular administration. LD_{50}'s are show in tables 1 and 2.

Table 1 - Median lethal dose of L-tyrosine

Route of Administration	Mice	LD_{50}(mg/kg)	Rats
s.c.	>5000		>5000
i.m.	>5000		>5000

Table 2 - Median lethal dose of Modified Ragweed Pollen Tyrosine Adsorbate

Route of Administration	Mice	LD_{50}(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.

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

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 pollen allergen 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 pollen allergen tyrosine adsorbate.

Slightly reduced food intake was observed in female rats dosed with modified ragweed pollen allergen tyrosine adsorbate. Food conversion efficiency initially was poorer in rats dosed with modified ragweed pollen allergen 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 pollen allergen 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 pollen allergen tyrosine adsorbate. No changes were seen at sites injected with saline.

<u>20-Day repeat dose toxicity in the dog (Modified ragweed pollen allergen tyrosine adsorbate)</u>

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 pollen allergen tyrosine adsorbate. Brief minimal swelling followed injection of saline. There were no differences in body weight gain between dogs which had received modified ragweed pollen allergen tyrosine adsorbate or saline. Food consumption was not adversely affected by dosing.

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

<u>20-Day local irritancy study in the rat (modified tyrosine adsorbate)</u>

This study was designed to assess the degree of local irritancy of modified ragweed pollen allergen 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 female 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 pollen allergen 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 pollen allergen 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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PART III: CONSUMER INFORMATION

POLLINEX-R
(Modified Ragweed Pollen Allergen Tyrosine Adsorbate)

This leaflet is part III of a three-part "Product Monograph" and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about POLLINEX-R. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
POLLINEX-R is used to treat:

- Seasonal ragweed allergic rhinitis (hayfever) caused by ragweed pollen in patients over the age of 8 years.

What it does:
POLLINEX-R is a seasonal immunotherapy (sometimes known as allergy vaccination or hyposensitisation) that contains extracts of ragweed pollen.

The exact mode of action of POLLINEX-R is not known, as is the case with other seasonal immunotherapies. It has been suggested that the treatment modifies the levels of the patients' antibodies and this changes a patient's reaction when they are exposed to ragweed pollen.

Before you have this treatment you will have tested positive to a skin prick test and/or an IgE antibody blood test completed by your doctor.

Your treatment will begin and will be completed before the start of the ragweed pollen season.

POLLINEX-R is not expected to completely eliminate your various allergic symptoms but should reduce their severity after one course of treatment. POLLINEX-R may also reduce your dependence on other medications that relieve your allergic symptoms such as anti-histamines, nasal and oral steroids.

When it should not be used:

- If you have previously had a severe anaphylactic reaction to a ragweed immunotherapy;
- If you are hypersensitive to any of the excipients;
- If you have not tested positive to a ragweed skin prick test or show no signs of seasonal allergic hayfever to ragweed;
- If you have a condition which causes you to bleed heavily;
- If you have a condition which prevents treatment of possible anaphylactic reactions for example chronic heart and lung disease;
- If you have unstable or severe chronic or seasonal asthma;
- If you have problems with your immune system.

What the medicinal ingredient is:
Modified Ragweed Pollen Allergen Tyrosine Adsorbate

What the important nonmedicinal ingredients are:
Disodium phosphate dodecahydrate;
Glycerol;
L-tyrosine;
Phenol;
Sodium Chloride;
Sodium dihydrogen phosphate dihydrate;
Water for injections.

What dosage forms it comes in:
Suspension for injection 105 PNU/0.5 ml, 250 PNU/0.5 ml, 700 PNU/0.5 ml, 2150 PNU/0.5 ml

WARNINGS AND PRECAUTIONS

Anaphylactic Shock

Severe, immediate reactions including life-threatening anaphylactic shock can occur with the use of POLLINEX-R.

Warning symptoms:
Tingling, itching and burning sensations on and under the tongue, in the throat and particularly on the palms and soles. This may be immediately followed by shock with bluish grey skin colour, decreased blood pressure, increased heart rate, cramp like tightness of the respiratory tract and unconsciousness.

If you show signs of a severe allergic reaction or anaphylactic shock, you must seek medical help immediately.

The product should be administered under the supervision of physicians experienced in specific immunotherapy. An emergency kit will be available. You **must wait** in the surgery or clinic for **at least 30 minutes** after each injection. This may be longer if **you are a high risk patient or experience mild symptoms or signs of an allergic reaction.**

BEFORE you use POLLINEX-R talk to your doctor or pharmacist if:

- You are suffering from an infection or fever;
- You are taking Beta-blockers or Angiotensin – Converting Enzyme (ACE) inhibitors to treat high blood pressure and heart problems;
- You are taking Tricyclic anti-depressants and monoamine oxidase inhibitors (MAOIs);
- You have cardiovascular disease;
- You have unstable or steroid dependent asthma.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with POLLINEX-R include:

- Beta-blockers;
- Immunosuppressant regimes;
- Hyposensitisation therapy;
- Symptomatic anti-allergic agents;
- Viral or bacterial pathogen vaccines;
- ACE inhibitors;
- MAOIs or Tricyclic anti-depressants.

PROPER USE OF THIS MEDICATION

Usual dose:
The following is a suggested schedule for average patients; however, some patients may be more sensitive and would require lower doses. Your doctor should monitor you and adjust your treatment as needed. POLLINEX-R should be administered as a course of four 0.5 ml subcutaneous injections. One 105 PNU/0.5 ml injection, one 250 PNU/0.5 ml injection, one 700 PNU/0.5 ml injection and one 2150 PNU/0.5 ml injection must be administered prior to the pollen season with a recommended interval of 7 days between injections.
At each strength, the **maximum injection of 0.5 ml must not be exceeded.**

Overdose:
The likelihood of severe allergic reactions is increased if an overdose is administered. In the case of an allergic reaction, contact your doctor immediately.

Missed Dose:
If the recommended interval between injections is exceeded by more than seven days, the treatment should be recommenced from vial or syringe No. 1 for safety reasons.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, POLLINEX-R can cause side effects. These include local reactions at the injection site (e.g. swelling, itching, pain, redness, discolouration). Further side effects to occur are respiratory disorders (shortness of breath, throat tightness, throat irritation, blocked sinuses, stuffy/blocked nose, runny nose), gastrointestinal disorders (diarrhoea, sickness/feeling of vomiting, abdominal discomfort), skin disorders (itching, hives/nettle rash), eye disorders (eye swelling) and general disorders (chest discomfort, chills, body temperature increased).

There is the potential risk of severe allergic reactions up to anaphylactic shock.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rare with product class	Severe shortness of breath, hives/nettle rash, drop in blood pressure, cramp-like tightness of respiratory tract, collapse, allergic shock.		✓	✓

You should contact your doctor immediately in the event of any serious side effects which develops while in your doctor's office or at any time following the injection.

This is not a complete list of side effects. For any unexpected effects while taking POLLINEX-R, contact your doctor or pharmacist.

HOW TO STORE IT

POLLINEX-R should be stored in a refrigerator at 2 – 8 °C. **Do not freeze.**

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.takedacanada.com.
or by contacting the distributor, Takeda Canada Incorporated at: 1-888-295-4636

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