PrPRE-PEN®

Benzylpenicilloyl Polylysine Injection, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intradermal Scratch/puncture	Solution / 6 x 10^{-5} M of benzylpenicilloyl	Sodium Chloride, Sodium Hydroxide, Sodium Phosphate Monobasic, Water for Injection

INDICATIONS AND CLINICAL USE

PRE-PEN® (benzylpenicilloyl polylysine injection USP) is indicated for the assessment of sensitization to penicillin (benzylpenicillin or penicillin G) in patients suspected to have clinical penicillin hypersensitivity. A negative skin test to PRE-PEN® is associated with an incidence of immediate allergic reactions of less than 5 % after the administration of therapeutic penicillin, whereas the incidence may be more than 50 % in a history-positive patient with a positive skin test to PRE-PEN®. These allergic reactions are predominantly dermatologic. Whether a negative skin test to PRE-PEN® predicts a lower risk of anaphylaxis is not established. Similarly, when deciding the risk of proposed penicillin treatment, there are not enough data at present to permit relative weighing in individual cases of a history of clinical penicillin hypersensitivity as compared to positive skin tests to PRE-PEN® and/or minor penicillin determinants.

Geriatrics (> 65 years of age):

The safety and efficacy of PRE-PEN® has not been established in elderly patients.

Pediatrics (< 12 years of age):

The safety and efficacy of PRE-PEN® has not been established in children.

CONTRAINDICATIONS

PRE-PEN® (benzylpenicilloyl polylysine injection USP) is contraindicated in those patients who have exhibited either a systemic or marked local reaction to its previous administration. Patients known to be extremely hypersensitive to penicillin should not be skin tested.

WARNINGS AND PRECAUTIONS

The risk of sensitization to repeated skin testing with PRE-PEN® (benzylpenicilloyl polylysine injection USP) is not established. Rarely, a systemic allergic reaction including anaphylaxis may follow a skin test with PRE-PEN®. To decrease the risk of a systemic allergic reaction, puncture skin testing should be performed first. Intradermal skin testing should be performed only if the puncture test is entirely negative.

Whenever possible, skin testing with PRE-PEN® should be preceded by a carefully obtained history. Not only should history of penicillin intolerance be noted, but also history of penicillin therapy as well as personal and familial histories of atopy and allergic diatheses. Patients with personal or familial histories of allergic diatheses or atopy should only be skin tested when penicillin therapy is contemplated or if there exists a history of penicillin intolerance.

The application of a specific allergen to an unsuspected, exquisitely sensitive patient is never without hazard and all precautions should be taken for handling immediate anaphylactoid type reactions by having epinephrine and anti-histamines available.

No reagent, test, or combination of tests will completely assure that a reaction to penicillin therapy will not occur.

The value of the PRE-PEN® skin test alone as a means of assessing the risk of administering therapeutic penicillin (when penicillin is the preferred drug of choice) in the following situations is not established:

1. Adult patients who give no history of clinical penicillin hypersensitivity.
2. Pediatric patients.

In addition, the clinical value of PRE-PEN® where exposure to penicillin is suspected as a cause of a current drug reaction or in patients who are undergoing routine allergy evaluation is not known. Likewise, the clinical value of PRE-PEN® skin tests alone in determining the risk of administering semisynthetic penicillins (e.g. ampicillin, oxacillin, amoxicillin), cephalosporin-derived antibiotics, and penem antibiotics is not known.

In addition to the results of the PRE-PEN® skin test, the decision to administer or not administer penicillin should take into account individual patient factors.

Healthcare professionals should keep in mind the following:

1. A serious allergic reaction to therapeutic penicillin may occur in a patient with a negative skin test to PRE-PEN®.
2. It is possible for a patient to have an anaphylactic reaction to therapeutic penicillin in the presence of a negative PRE-PEN® skin test and a negative history of clinical penicillin hypersensitivity.
3. If penicillin is the drug of choice for a life-threatening infection, successful desensitization with therapeutic penicillin may be possible irrespective of a positive skin test and/or a positive history of clinical penicillin hypersensitivity.

Special Populations

Pregnant Women: Animal reproduction studies have not been conducted with PRE-PEN®. It is not known whether PRE-PEN® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The hazards of skin testing in such patients should be weighed against the hazard of penicillin therapy without skin testing.

Nursing Women: The safety of PRE-PEN® skin testing in nursing women is not established.

ADVERSE REACTIONS

Occasionally, patients may develop an intense local inflammatory response at the skin test site. Rarely, patients will develop a systemic allergic reaction, manifested by generalized erythema, pruritus, angioedema, urticaria, dyspnea, hypotension, and anaphylaxis. The usual methods of treating a skin test antigen-induced reaction—the applications of a venous occlusion tourniquet proximal to the skin test site and administration of epinephrine are recommended. The patient should be kept under observation for several hours.

DRUG INTERACTIONS

Skin testing responses can be attenuated by interfering drugs (e.g. H1- anti-histamines and vasopressors). Skin testing should be delayed until the effects of such drugs have dissipated, or a separate skin test with histamine can be used to evaluate persistent antihistaminic effects in vivo.

DOSAGE AND ADMINISTRATION

Due to the risk of potential systemic allergic reactions, skin testing should be performed in an appropriate healthcare setting under direct medical supervision.

Puncture Testing:

Skin testing is usually performed on the inner volar aspect of the forearm. The skin test antigen should always be applied first by the puncture technique.

After preparing the skin surface, apply a small drop of PRE-PEN® solution using a sterile 22-28 gauge needle. The same needle can then be used to make a single shallow puncture of the epidermis through the drop of PRE-PEN®. Very little pressure is required to break the epidermal continuity. Observe for the appearance of a wheal, erythema, and the occurrence of itching at the test site during the succeeding 15 minutes at which time the solution over the puncture site is wiped off. A positive reaction consists of the development within 10 minutes of a pale wheal, sometimes with pseudopods, surrounding the puncture site and varying in diameter from 5 to 15 mm (or more). This wheal may be surrounded by a variable diameter of erythema, and accompanied by a variable degree of itching. The most sensitive individuals develop itching quickly, and the wheal and erythema are prompt in their appearance. As soon as a positive response as defined above is clearly evident, the solution over the scratch should be immediately wiped off. If the puncture test is either negative or equivocally positive (less than 5 mm wheal with little or no erythema and no itching), an intradermal test may be performed.

The Intradermal Test:

Using a 0.5 to 1.0 cc syringe with a 3/8" to 5/8"long, 26 to 30 gauge, short bevel needle, withdraw the contents of the ampule. Prepare with an alcohol swab a skin test area on the upper, outer arm, sufficiently below the deltoid muscle to permit proximal application of a tourniquet later, if necessary. Be sure to eject all air from the syringe through the needle, then insert the needle, bevel up immediately below the skin surface. Inject an amount of PRE-PEN® (not more than 0.03 mL intradermally) sufficient to raise a small intradermal bleb of about 3 mm in diameter, in duplicate at least 2 cm apart. Using a separate syringe and needle, inject a like amount of saline or allergen diluting solution as a control at least 5 cm removed from the antigen test sites. Most skin reactions will develop within 5-15 minutes and response to the skin test is read at 20 minutes as follows:

Negative response — no increase in size of original bleb and no greater reaction than the control site.

Ambiguous response—wheal only slightly larger than initial injection bleb, with or without accompanying erythematous flare and slightly larger than the control site; OR discordance between duplicates.

Positive response—itching and significant increase in size of original blebs to at least 5 mm. Wheal may exceed 20 mm in diameter and exhibit pseudopods.

If the control site exhibits a wheal greater than 2-3 mm, repeat the test, and if the same reaction is observed, a physician experienced with allergy skin testing should be consulted.

Administration

PRE-PEN® is stable only when kept under refrigeration. (2-8° C). It is therefore recommended that test materials subjected to ambient temperatures for over a day be discarded. As with all parenteral drug products, PRE-PEN® should be inspected visually for particulate matter and discoloration prior to administration.

OVERDOSAGE

Symptoms of overdosage are due to hypersensitivity and are those stated in "Adverse Reactions". Severe reactions may be avoided by first applying PRE-PEN® (benzylpenicilloyl polylysine injection USP) as a scratch test. Systemic reactions are treated by the classic methods for managing immediate anaphylactoid reactions: epinephrine intramuscularly plus antihistamines and corticosteroids.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PRE-PEN® (benzylpenicilloyl polylysine injection USP) is a skin test antigen reagent that reacts specifically with benzylpenicilloyl IgE antibodies initiating the release of chemical mediators which produce an immediate wheal and flare reaction at a skin test site. All individuals exhibiting a positive skin test to PRE-PEN® possess IgE against the benzylpenicilloyl structural group which is a hapten. A hapten is a low molecular weight chemical that conjugates with a carrier (e.g. poly-l-lysine) resulting in the formation of an antigen with the hapten's specificity. The benzylpenicilloyl hapten is the major antigenic determinant in penicillin allergic individuals. However, many individuals reacting positively to PRE-PEN® will not develop a systemic allergic reaction on subsequent exposure to therapeutic penicillin, especially among those who have not reacted to penicillins in the past. Thus, the PRE-PEN® skin test determines the presence of penicilloyl IgE antibodies which are necessary but not sufficient for acute allergic reactions due to the major penicilloyl determinant.

Non-benzylpenicilloyl haptens are designated as minor determinants, since they less frequently elicit an immune response in penicillin treated individuals. The minor determinants may nevertheless be associated with significant clinical hypersensitivity. PRE-PEN® does not react with IgE antibodies directed against non-benzylpenicilloyl haptens.

STORAGE AND STABILITY

To maintain stability of PRE-PEN® (benzylpenicilloyl polylysine injection USP) proper storage conditions are essential. PRE-PEN® is optimally stored under refrigeration (2-8° C). PRE-PEN® subjected to ambient temperatures for more than 24 hours should be discarded. Do not use after the expiration date shown on the ampule label.

SPECIAL HANDLING INSTRUCTIONS

PRE-PEN® (benzylpenicilloyl polylysine injection USP) is supplied in ampules containing 0.25 mL. Ampules are opened by snapping the neck of the ampule using two forefingers of each hand. Visually inspect for glass chards before use. PRE-PEN® should be discarded if particulate matter, precipitate, haziness, leakage or discoloration is present. Each ampule is for single patient use only. Discard any unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PRE-PEN® (benzylpenicilloyl polylysine injection USP) is a clear, colorless, sterile solution of benzylpenicilloyl polylysine at a concentration of 6×10^{-5} M (benzylpenicilloyl) in 0.01 M phosphate buffer with 0.15 M sodium chloride, supplied in ampules containing 0.25 mL. Nonmedicinal ingredients include: Sodium Chloride, Sodium Hydroxide, Sodium Phosphate Monobasic, Water for Injection. Each single dose ampule contains 0.25 mL of PRE-PEN® and is sufficient material to perform both scratch and intradermal tests. PRE-PEN® is supplied in a box of 5 single dose ampules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

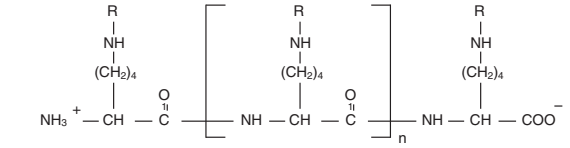
Drug Substance

Proper name: Benzylpenicilloyl polylysine

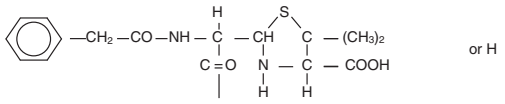
Chemical name: 2-[2-[(6-hydroxy-6-oxohexyl)amino]-2-oxo-1-[(2-phenylacetyl)amino]ethyl]-5,5-dimethyl-1, 3-thiazolidine-4-carboxylic acid

Molecular formula and molecular mass: $C_{22}H_{31}N_3O_6S$, 14,000

Structural formula:



Where "n" is an integer greater than 40 and "R" is:



Benzylpenicilloyl

IMMUNOLOGY

Millions of people have received penicillin since it became available and various estimates of the incidence of hypersensitivity to it range from no greater than 1 % to more than 10 %. There is extensive human exposure to penicillin, not only from its therapeutic use but in the past from contamination of foods and the environment. Penicillin itself appears to have a low potential for sensitization, but at least seven different degradation products of penicillin have been implicated in penicillin allergy with the penicilloyl group being involved 80-90 % of the time.

The relationship of immediate penicilloyl skin reactions to penicillin hypersensitivity is established by the following observations:

1. Patients with a history of penicillin allergy react much more frequently to benzylpenicilloyl polylysine, penicillin and conjugated and unconjugated penicillin derivatives, than patients with no such history.
2. Patients with no history of penicillin hypersensitivity but with a positive skin reaction to benzylpenicilloyl polylysine (and other penicillin derivatives) are much more likely to react to subsequent penicillin therapy than patients with a negative skin reaction.
3. Patients with a history of penicillin allergy but with a negative reaction to benzylpenicilloyl polylysine (and other penicillin derivatives) appear less likely to develop immediate or accelerated hypersensitivity reactions to subsequent penicillin therapy than patients with a positive skin reaction.

Hypersensitivity to penicillin tends to be evanescent. The incidence of penicilloyl positive skin test will generally be higher in patients who have recently shown acute penicillin allergy (80 % - 90 %) than in patients whose allergic reaction was ten or more years past (20 % to 30 %). Many international studies suggest that patients with histories of penicillin allergy who have negative skin reactions to benzylpenicilloyl polylysine, penicillin and other unconjugated derivatives of penicillin can frequently tolerate therapeutic administration of the antibiotic. It is important to remember, however, that administration of penicillin to such patients should only be done when there are strong medical indications for its use.

REFERENCES

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PART III: CONSUMER INFORMATION

PRE-PEN®

Benzylpenicilloyl Polylysine Injection

This leaflet is part III of a three-part "Prescribing Information" published when PRE-PEN® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PRE-PEN®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
PRE-PEN® is a skin test for the diagnosis of penicillin allergy.

What it does:
In penicillin allergy, people can react to different parts of the penicillin molecule. These parts are named major determinants and minor determinants based on the frequency of reactions to the different parts. Testing to the major determinant is done using PRE-PEN®. PRE-PEN® reacts specifically with skin sensitizing antibodies to produce redness and swelling. This may indicate an increased risk of allergic reactions to penicillin therapy.

When it should not be used:
If you have previously experienced a general or marked skin reaction to PRE-PEN® or if you are extremely hypersensitive to penicillin you should not be skin tested with PRE-PEN®.

What the medicinal ingredient is:
Benzylpenicilloyl-polylysine

What the nonmedicinal ingredients are:
Sodium Chloride, Sodium Hydroxide, Sodium Phosphate Monobasic, Water for Injection

What dosage forms it comes in:
0.25 mL ampule containing: 6 x 10^{-5} M of benzylpenicilloyl sterile solution.

WARNINGS AND PRECAUTIONS

BEFORE you use PRE-PEN® talk to your doctor or pharmacist if:

- You or someone in your family has intolerance to penicillin or other antibiotics in the past. In this case you should only be given PRE-PEN® before using penicillin treatment or if you have a known intolerance to penicillin.
- You are extremely hypersensitive to penicillin
- You are taking any medications that will interact with this product.
- You are pregnant or trying to get pregnant
- You are nursing (breastfeeding)
- You are younger than 12 or older than 65 years old

Rarely, a systemic allergic reaction (rash, hives, swelling of the face, throat, lips, difficulty swallowing or breathing, drop of blood pressure) may follow a skin test with PRE-PEN®. To decrease this risk a scratch/puncture skin test should be performed first by your health care provider. The full intradermal skin testing should be performed only if the scratch/puncture test is entirely negative (does not react).

A negative test result with PRE-PEN does not guarantee that you will not have an allergic reaction to penicillin.

A positive test result with PRE-PEN means that you have a greater risk of allergic reaction to penicillin. Your doctor will decide if penicillin is the appropriate treatment for you.

INTERACTIONS WITH THIS MEDICATION

BEFORE you use PRE-PEN® talk to your doctor or pharmacist if are taking any other drug especially:

- antihistamines (allergy medication)
- vasopressors (medications that constrict the blood vessels)

PROPER USE OF THIS MEDICATION

Due to the risk of potential systemic allergic reactions, skin testing should be performed in an appropriate healthcare setting under direct medical supervision.

PRE-PEN® is supplied in ampules for single-use administration.

Usual dose:

Scratch test – a drop of PRE-PEN®.

Intradermal test – not more than 0.03 mL of PRE-PEN® intradermally.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Occasionally, PRE-PEN® may cause a red, itchy, local inflammatory response at the skin test site or hives.

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 seek Immediate Emergency Medical Attention
		Only if severe	In all cases	
Uncommon	Allergic Reaction: facial swelling, itchiness, and difficulty swallowing or breathing			✓
	Low blood pressure; light headedness, dizziness			✓

This is not a complete list of side effects. For any unexpected effects while taking PRE-PEN®*, contact your doctor or pharmacist.*

HOW TO STORE IT

PRE-PEN® must be stored at 2° to 8° C. If left at room temperature for more than 24 hours PRE-PEN® should be discarded. Do not use PRE-PEN® after the expiration date shown on the ampule label. PRE-PEN® should be discarded if particulate matter, precipitate, haziness, leakage or discoloration is present.

MORE INFORMATION

This document plus the full prescribing information, prepared for health professionals can be found at:
http://www.alk-abello.com/ca/products/pre-pen
or by contacting the sponsor, ALK-Abelló Inc
at: 1-800-325-7354

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REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

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