

HISTAMINE POSITIVE SKIN TEST CONTROL- histamine phosphate injection, solution
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ALK-Abello, Inc.

Histamine Phosphate

Directions for Use of
Positive Skin Test Control - Histamine
HISTATROL®

Histamine Base 1 mg/mL
(Histamine Phosphate 2.75 mg/mL)
in Glycerin 50% (v/v)

For Percutaneous Testing

Histamine Base 0.1 mg/mL
(Histamine Phosphate 0.275 mg/mL)

For Intracutaneous (Intradermal) Testing

Port Washington, New York 11050

U.S. Government License No. 1256

DESCRIPTION

The chemical formula for Histamine Phosphate is $C_5H_9N_3 \cdot 2H_3PO_4$; its molecular weight is 307.14. For prick, puncture or scratch testing, the product is a sterile solution that contains 1 mg/mL histamine base (2.75 mg/mL Histamine Phosphate) in Water for Injection; it also contains Glycerin 50% (v/v) as viscosity agent and Phenol 0.4% as preservative. For intracutaneous (intradermal) skin testing, the product is a sterile solution that contains 0.1 mg/mL histamine base (0.275 mg/mL Histamine Phosphate) in Water for Injection and Phenol 0.4% as preservative. The product should be stored refrigerated and protected from light.

CLINICAL PHARMACOLOGY

Histamine acts as a potent vasodilator when released from mast cells during an allergic reaction. It is largely responsible for the immediate skin test reaction of a sensitive patient when challenged with an offending allergen.

The effect of added Glycerin (50% v/v) to 1 mg/mL histamine base was studied by puncture testing using a bifurcated needle in twelve volunteer subjects. The mean sum of cross-diameters of the wheals was 13.25 mm (range 10-15 mm) for the non-glycerinated, and 12.54 mm (range 9-15 mm) for the glycerinated formulation. Sum of cross-diameters of erythema was 52.88 mm (range 23-92 mm) for the non-glycerinated, and 54.42 mm (range 19-87 mm) for the glycerinated formulation. These differences are not statistically significant.

INDICATIONS AND USAGE

For use as a positive control in evaluation of allergenic (immediate hypersensitivity or "Type I") skin testing.

CONTRAINDICATIONS

Histamine should not be injected into individuals with hypotension, severe hypertension, severe cardiac,

pulmonary, or renal disease. Not to be used for diagnosis of pheochromocytoma or to test the ability of the gastric mucosa to secrete hydrochloric acid.

WARNINGS

Care must be taken in intracutaneous testing to avoid injection into a venule or capillary. Pull back gently on the syringe plunger and note if blood is drawn. If blood is drawn, withdraw needle and inject into another skin site.

Small doses by any route of administration may precipitate asthma in patients with bronchial hyperactivity. This product is not intended for inhalation, or subcutaneous injection. The utmost caution is advised in using histamine in such patients and in those with a history of bronchial asthma.

PRECAUTIONS

General

A separate sterile needle or other percutaneous testing device should be used for each individual patient to prevent transmission of hepatitis and other infectious agents from one person to another.

Epinephrine Injection (1:1,000) and injectable antihistamines should be available for immediate use in the event the patient exhibits a severe response. A tourniquet can be applied above the test site to slow absorption if a severe response occurs.

Drug Interactions

Drugs can interfere with the performance of skin tests in general, and specifically with histamine¹.

Antihistamines: Response to histamine is suppressed by antihistamines. The length of suppression varies, and is dependent on individual patient, type of antihistamine and length of time the patient has been on antihistamines. The duration of this suppression may be as little as 24 hours (chlorpheniramine), and can be as long as 40 days (astemizole).

Tricyclic Antidepressants: These exert a potent and sustained decrease of skin reactivity to histamine, which may last for a few weeks.

Beta₂ Agonists: Oral terbutaline and parenteral ephedrine, in general, have been shown to decrease allergen induced wheal. Theoretically, this may also reduce whealing capacity to histamine.

Dopamine: Intravenous infusion of dopamine has been shown to inhibit skin test responses to histamine.

Beta Blocking Agents: Propranolol can significantly increase skin test reactivity, including histamine.

Other Drugs: Short acting steroids, inhaled beta agonists, theophylline and cromolyn do not seem to affect skin test response.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted with Histamine.

Nursing Mothers

It is not known if Histamine administered percutaneously or intracutaneously appears in human milk. Because many drugs are excreted in human milk, caution should be exercised when histamine is administered to a nursing woman.

Pregnancy Category C

It is not known whether Histamine can cause fetal harm when administered during pregnancy or whether it can affect reproduction capacity. Histamine should be given during pregnancy only if clearly needed.

There are no adequate and well-controlled studies during pregnancy. However, based on histamine's known ability to contract uterine muscle, exposure or repeated doses should be avoided.

HISTATROL[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus or mother.

Pediatric Use

Histamine solutions for percutaneous testing have been given safely in infants and young children.^{2,3,4,5} Neonates and infants have lower skin test reactivity to histamines as well as common allergens.^{3,4,5,6} About 20% of infants less than six months of age have been observed to have a negative reaction to histamine hydrochloride (1 mg/mL of salt).⁴ Skin test reactivity gradually increases to age six and plateaus to age sixty.^{2,3} Therefore, small skin test reactions should be anticipated in children under age six.

ADVERSE REACTIONS

Local:

Reactions such as wheal, erythema and localized pruritus are to be expected, but if very large (i.e. greater than 4+ as described dosage and administration) may be the first manifestation of a systemic reaction.

Systemic:

Following the injection of large doses of histamine, systemic reactions may include flushing, dizziness, headache, bronchial constriction, urticaria, asthma, marked hypertension or hypotension, abdominal cramps, vomiting, metallic taste, and local or generalized allergic manifestations (see also **OVERDOSAGE**).

OVERDOSAGE

A large subcutaneous dose of Histamine Phosphate may cause severe occipital headache, blurred vision, anginal pain, a rapid drop in blood pressure, and cyanosis of the face. Overdosage may cause severe symptoms including vasomotor collapse, shock, and even death.

Epinephrine Injection 0.01 mg/kg to a maximum of 1.0 mg given subcutaneously or intramuscularly should be used in case of emergency due to severe reactions (see Precautions). An antihistamine preparation may be given intramuscularly to ameliorate systemic reaction to overdose.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For Prick, Puncture and Scratch Testing

Histamine base 1 mg/mL (Histamine Phosphate 2.75 mg/mL) should be used to give a reaction. (Refer to Interpretation Section.)

Prick, Puncture or Scratch Test Techniques

1. The skin in the test area should be cleansed with alcohol and air dried.
2. The histamine control skin test solution should be placed at the same site with the other skin test antigens, either on the patient's back or on the volar surface of the forearm. The patient should be placed in a comfortable position before the testing is begun.
3. For the prick test, a sharp needle is used to puncture the skin, but not to draw blood. If the scratch

test is used, carefully break or scratch the skin with a sterile scarifier. Do not draw blood. Each scratch should be about 2 mm - 4 mm in length.

4. A small drop of the histamine base 1 mg/mL (Histamine Phosphate 2.75 mg/mL) is placed on the abraded skin site no closer than 4 or 5 cm from an adjacent test site. Some physicians prefer to place the solution on the test area and then prick through the drop with a sharp needle.
5. Use a separate sterile scarifier or needle for each patient.
6. The test should be read at 15 minutes; if a large wheal reaction occurs before that time the test site should be wiped free of histamine.

Interpretation

The patient's response is based on the size of: erythema (degree of redness) and/or size of wheal (smooth, slightly elevated area) which appear after 10 minutes.

For percutaneous testing, different devices and/or techniques influence the size of the reaction. Therefore, it is important to refer to the device manufacturer's or distributor's instructions when grading reactions.

For prick, puncture and scratch testing, histamine base 1 mg/mL (Histamine Phosphate 2.75 mg/mL) should be used to give a positive reaction. In a large population, the NHANES II survey reports a mean diameter (average of length and width) wheal of $4.4 \text{ mm} \pm 1.65 \text{ mm}$ (\pm standard deviation) and a mean erythema of $18.4 \text{ mm} \pm 8.55 \text{ mm}$ (\pm standard deviation) when using 25 gauge B-D needle by prick puncture (Pepys) technique.⁷ All positive reactions should be interpreted against an appropriate negative control.

For Intradermal Skin Testing

Histamine base 0.1 mg/mL (Histamine Phosphate 0.275 mg/mL) or 0.01 mg/mL should be used to give a reaction. (Refer to Interpretation Section.)

Intracutaneously (Intradermal) Test Techniques

1. The skin should be cleansed with alcohol and air dried.
2. A sterile one milliliter tuberculin syringe with 26 or 27 gauge needle should be used. A single sterile syringe should be used for each solution to assure sterility. Only the histamine base 0.1 mg/mL (Histamine Phosphate, 0.275 mg/mL) or greater dilution solution should be used.
3. The histamine base skin test solution should be injected at the same site with the other skin test allergens, either on the patient's back or on the arm. The patient should be placed in a comfortable position before the testing is begun.
4. The skin is held tense and the needle is inserted almost parallel to the skin, bevel side up, far enough to cover the beveled portion. Slowly inject 0.01 mL or 0.02 mL, making a small bleb approximately 3 mm - 5 mm in diameter.
5. The test should be read in 15 minutes.

Interpretation

The patient's response is based on the size of: erythema (degree of redness) and/or size of wheal (smooth, slightly elevated area) which appear after 10 minutes.

For intradermal skin testing, histamine base 0.1 mg/mL (Histamine Phosphate 0.275 mg/mL) or 0.01 mg/mL should be used to give a positive reaction. The available 0.1 mg/mL concentration must be diluted ten-fold to achieve this dose. All positive reactions should be interpreted against an appropriate negative control. In two successive years of testing, the Committee on Standardization of the American College of Allergy reported positive reactions at histamine base doses of 0.01 mg/mL and higher. Mean sum of wheal diameters was approximately $14 \text{ mm} \pm 4.8 \text{ mm}$ and sum of erythema diameter was approximately $52 \text{ mm} \pm 21.6 \text{ mm}$ following 0.01 mL intradermal doses of 0.01 mg/mL histamine base. When 0.01 mL of 0.1 mg/mL histamine base was injected, the sum of cross-diameters of wheal ranged

from 15-20 mm and the sum of cross-diameters of erythema ranged from 60-80 mm.⁸

HOW SUPPLIED

Multidose vials containing 5 mL histamine base, 1 mg/mL (Histamine Phosphate 2.75 mg/mL) in Glycerin 50% (v/v) for prick, puncture, or scratch testing. Multidose vials containing 5 mL histamine base, 0.1 mg/mL (Histamine Phosphate 0.275 mg/mL) in aqueous solution for intradermal testing. Store at 2° - 8°C.

REFERENCES

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8. Committee on Standardization. Report of the Committee on Standardization: 1. A method of evaluating skin test response. *Ann. Allergy* 29:30-34, 1971.

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Distributed in Canada by:

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Mississauga, Ontario

Canada L4Z 2H6

PRINCIPAL DISPLAY PANEL

POSITIVE SKIN TEST CONTROL-HISTAMINE

5mL sterile multiple dose vial

FOR INTRADERMAL TESTING ONLY

HISTATROL®

HISTAMINE BASE 0.1 mg/mL

CAUTION: Rx Only.
Dose: See accompanying circular.
NDC: 0268-0248-05



POSITIVE SKIN TEST CONTROL-HISTAMINE

DIN 00609706 GTIN:00302680248056
5mL sterile multiple dose vial
FOR INTRADERMAL TESTING ONLY
HISTATROL®
HISTAMINE BASE 0.1 mg/mL
(Histamine Phosphate 0.275 mg/mL), Preservative: 0.4% Phenol.



SN:
Port Washington, NY 11050 - U.S. License 1256 - HIST15999V
Dist. in Canada by: ALK-Abello Pharm., Inc., Mississauga, On, L4Z 2H6

Lot:
Exp:
Store between 2°C and 8°C.
Protect from light.

PRINCIPAL DISPLAY PANEL

POSITIVE SKIN TEST CONTROL-HISTAMINE
5mL sterile multiple dose vial
FOR PERCUTANEOUS TESTING ONLY
HISTATROL®
HISTAMINE BASE 1 mg/mL

CAUTION: Rx Only.
Dose: See accompanying circular.
NDC: 0268-0247-05



POSITIVE SKIN TEST CONTROL-HISTAMINE

DIN 00609692 GTIN:00302680247059
5mL sterile multiple dose vial
FOR PERCUTANEOUS TESTING ONLY
HISTATROL®
HISTAMINE BASE 1 mg/mL
(Histamine Phosphate 2.75 mg/mL), Contains Glycerin 50% (v/v),
Preservative: 0.4% Phenol



SN:
Port Washington, NY 11050 - U.S. License 1256 - HIST14999V
Dist. in Canada by: ALK-Abello Pharm., Inc., Mississauga, On, L4Z 2H6

Lot:
Exp:
Store between 2°C and 8°C.
Protect from light.

HISTAMINE POSITIVE SKIN TEST CONTROL

histamine phosphate injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0268-0248
Route of Administration	INTRADERMAL		
Active Ingredient/Active Moiety			
Ingredient Name	Basis of Strength	Strength	
HISTAMINE PHOSPHATE (UNII: QWB37T4WZZ) (HISTAMINE - UNII:820484N8I3)	HISTAMINE	0.275 mg in 1 mL	

Inactive Ingredients

Ingredient Name	Strength
PHENOL (UNII: 339NCG44TV)	0.004 mL in 1 mL
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0268-0248-05	5 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product	10/23/1989	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103754	10/23/1989	

HISTAMINE POSITIVE SKIN TEST CONTROL

histamine phosphate solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0268-0247
Route of Administration	PERCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HISTAMINE PHOSPHATE (UNII: QWB37T4WZZ) (HISTAMINE - UNII:820484N8I3)	HISTAMINE	2.75 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
PHENOL (UNII: 339NCG44TV)	0.004 mL in 1 mL
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
GLYCERIN (UNII: PDC6A3C0OX)	0.5 mL in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0268-0247-05	5 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product	10/23/1989	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103754	10/23/1989	

Labeler - ALK-Abello, Inc. (809998847)

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