HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

29 February 2012

SOLUPRICK NEGATIVE CONTROL, solution for skin-prick test
1 vial of 2 ml (CIP code: 388 794-3)

SOLUPRICK POSITIVE CONTROL 10 mg/ml, solution for skin-prick test
1 vial of 2 ml (CIP code: 388 793-7)

Applicant: ALK ABELLO

Negative control: No active ingredient
Positive control: Histamine dihydrochloride, 10 mg/ml
ATC code: V04CL (allergy tests)

List I
Reserved for professional use

Date of Marketing Authorisation: 7 January 2009
(Mutual recognition procedure, reporter country: Denmark)

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

SOLUPRICK POSITIVE CONTROL: Histamine dihydrochloride

SOLUPRICK NEGATIVE CONTROL: No active ingredient

1.2. Indications

SOLUPRICK POSITIVE CONTROL
"Positive control for skin tests for the diagnosis of IgE-dependent allergy."

SOLUPRICK NEGATIVE CONTROL
"Negative control for skin tests for the diagnosis of IgE-dependent allergy."

1.3. Dosage

"Reserved for diagnostic use only.

The skin-prick test technique consists of the introduction of test substance into the superficial layer of the skin by administering a microinjection, with the aid of a lancet, through a droplet of solution first placed on the surface of the skin on the volar side of the forearm or on the back.

SOLUPRICK POSITIVE CONTROL and NEGATIVE CONTROL (histamine dihydrochloride 10 mg/ml) are used as positive or negative controls to evaluate the skin reactivity when carrying out the prick test with specific allergenic extracts (with the positive control) and to evaluate the nonspecific skin reactivity (with the negative control).

Skin-prick testing should be performed by experienced personnel only.

Instructions for use
The skin-prick test is normally performed on the volar side of the forearm. Alternatively, the test may be performed on the patient's back.
The skin must be clean and dry. The skin surface used for the test must be cleaned with the aid of cotton wool moistened with alcohol.
Each test solution is applied to the skin in the form of droplets placed at least 1.5 cm apart. The forearm should be at rest. Apply positive control and the negative control solutions last, after the allergic solutions.
Pierce the skin perpendicularly through the drop using a standard lancet with a 1 mm tip. A new lancet must be used for each allergen tested.
Apply a slight, constant pressure for approximately 1 second then draw the lancet straight back.
Without contaminating the site next to the test, remove the surplus solution with a paper tissue.
The reactions are read about 15 minutes after piercing the skin. A positive reaction is a wheal with or without erythema.
The result may be transferred to a test form as follows: mark the contour of the relevant wheal and transfer the result to the test form with the adhesive side of transparent tape, where after the reaction can be read on graph paper.
A wheal with a diameter of ≥ 3 mm is considered to be a positive reaction.
For the negative control, no reaction is expected. In the case of a positive reaction with the negative control, the results of skin-prick tests carried out with the allergenic extracts must be regarded as uninterpretable."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

V : various
V04 : diagnostic agents
V04C : other diagnostic agents
V04CL : allergy tests

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

Positive of negative control solution for the prick test diagnostic method

- None is included in the list of reimbursable medicines.
- Both ALYOSTAL PRICK POSITIVE CONTROL and ALYOSTAL PRICK NEGATIVE CONTROL (STALLERGENES SA) were granted a Marketing Authorisation for this indication in 2010, but are not included in the list of medicines approved for use by hospitals (no demand)

In practice, a 10 mg/ml solution of histamine dihydrochloride and the prick test diluent supplied by the pharmaceutical companies that sell the allergens are used.

3 ANALYSIS OF AVAILABLE DATA

The principle of the prick test is to look for a skin reaction after administration of a dose of allergen in the superficial layers of the skin. In allergic patients whose serum contains specific IgEs, the presence of the allergen will lead to the release of inflammation mediators, principally histamine, by mast cells. These mediators are responsible for the appearance, within about twenty minutes, of a wheal and local erythema.

In addition to the allergens selected for the test, a positive control and a negative control are always included.[1,2] Histamine, the major mediator of the type I immediate allergic reaction, is generally used as the positive control, and should provoke a skin reaction resembling an allergic reaction in a reproducible manner.

The prick-test technique has been in routine use in France for several decades. An extemporaneous preparation based on histamine or a solution supplied by the pharmaceutical company is used as the positive control. The test diluent is used as the negative control. The first Marketing Authorisation for a histamine positive control in France was obtained in 2009 for SOLUPRICK.

3.1. Diagnostic value

SOLUPRICK POSITIVE CONTROL

The reproducibility of the reaction to histamine administered in the prick test was examined by Taudorf[3] in 1985 in healthy volunteers, using three doses (1 mg, 5 mg et 10 mg). The least variable area of skin reaction (erythema and wheal) was obtained with the 10 mg dose (wheals > 4 mm, standard deviation < 20%).

The variability of the reaction to 10 mg/ml of histamine[4] was assessed in 1998 in a second study in the course of 528 prick tests carried out with two different devices: mean size of the wheal 6.21 or 5.64 mm, depending on the device used, with standard deviations of 1.35 and 0.97 respectively.

These two studies justify the concentration of 10 mg of histamine currently used for the positive control.

No clinical studies were submitted by the company.

SOLUPRICK NEGATIVE CONTROL

The objective of this test is to check for false positives caused by the pressure of the lancet on the skin.

3.2. Adverse effects

The SCP indicates that, in addition to the expected effect of the histamine (wheal or erythema), there may be mild pain at the injection point.

According to the last periodic safety update report (PSUR) submitted by the company (August 2009 to July 2010), no adverse effects have been reported in relation to the 20,000 boxes of SOLUPRICK positive control and negative control sold world-wide.

[1] Skin tests in allergology: really so simple? Rev med Suisse 2005 13; 1: 997-1002.
[2] Bousquet J *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA) Update; Allergy 2008: vol 63 (Suppl. 86): 8–160.
[3] Taudorf, E et al. Reproducibility of histamine skin prick test. Inter and Intravariation using Histamine dihydrochloride 1, 5 and 10 mg/ml. Allergy 1985; 40: 344-49.
[4] Illi S, Garcia-Marcos L, Hernando V, Guillen JJ, Liese A, von Mutius E. Reproducibility of skin prick test results in epidemiologic studies: a comparison of two devices. Allergy 1998; 53: 353-58.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

In some cases, allergy can manifest itself in the form of a serious allergic reaction which, in the most severe cases, can be life threatening.

These proprietary medicinal products are used within the framework of the aetiological diagnosis of allergies by means of the skin allergy test.

The value of a positive control and of a negative control in the implementation of the prick test is established by use.

There are no alternative products included in the list of medicines approved for use in hospitals.

It is not expected that the proprietary medicinal product SOLUPRICK will benefit public health.

The actual benefit of SOLUPRICK positive 10 mg/ml is substantial.

The actual benefit of SOLUPRICK negative control is substantial.

4.2. Improvement in actual benefit (IAB)

SOLUPRICK POSITIVE CONTROL 10 mg/ml and SOLUPRICK NEGATIVE CONTROL offer no improvement in actual benefit (IAB V) within the current diagnostic strategy.

4.3. Diagnostic use

In a patient with signs of allergy, the allergological investigation always starts by questioning the patient and may be extended to include allergy tests in order to identify the allergen responsible.
Skintests are used to investigate immediate hypersensitivity reactions in order to identify an allergen, which may be a medicine, a respiratory allergen or a foodstuff.

In asthma, an allergological investigation is recommended by the *société de pneumologie de langue française*[5] (SPLF; French-language Society of Pneumology) in asthmatics who are more than 3 years old (grade A) and in children more than 3 years old who have recurrent or severe respiratory symptoms, who require continuous treatment, or who have extra-respiratory symptoms that suggest an allergic origin (grade B). In these cases, prick tests are recommended (grade B) as the first-line investigation.

In allergic rhinitis, the American recommendations (ARIA[2]) indicate that an allergological examination from a diagnostic viewpoint should be carried out in patients with persistent allergic rhinitis who present moderate or severe symptoms.

There are two types of skin test that investigate immediate hypersensitivity reactions: prick tests and the intradermal reaction test. The prick-test technique allows testing for a wide variety of allergens. The test medicine, foodstuff, or a drop of the solution containing the allergen is placed on the skin. A lancet is used to prick the skin through the solution or foodstuff.

[5] Recommendations de la SPLF sue Asthme et Allergie. Expert conference – Short text. Rev Mal Respir 2007; 24: 221-32.

In addition to the allergens selected for the test, a positive control and a negative control are always included.[6,7] The procedure of performing a prick test with a positive and a negative control is recommended by the SPLF[4] (grade A) and by the ASCIA[8] (Australian Society of Clinical Immunology and Allergy). The positive control provides a basis for the evaluation of the histamine reaction and helps rule out certain technical causes of false negatives (for example, due to the use of antihistamines). The negative control with the diluent used for the test solution permits the identification of dermographism, which leads to false positives. If the positive control is not positive or if the negative control is not negative, the test cannot be interpreted.

Positive skin tests do not necessarily suggest a clinical allergy, but they are evidence of sensitisation.

4.4. Target population

A positive control and a negative control are always included in a series of prick tests, and the target population of SOLUPRICK corresponds to the number of test series carried out per year in the hospital. The available data do not permit an estimate of this population.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indications shown in the Marketing Authorisation.

[6] Skin tests in allergology: really so simple? Rev med Suisse 2005 13; 1: 997-1002.
[7] Bousquet J *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA) Update; Allergy 2008: vol 63 (Suppl. 86): 8–160.
[8] Skin-prick testing for the diagnosis of allergic disease – A manual for practitioners – ASCIA skin prick testing working party ASCIA 2006 Revised March 2009 – http://www.allergy.org.au-