CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

HAL Allergy Prick Test Controlevloeistoffen, solution for skin-prick test HAL Allergy Benelux B.V., the Netherlands

histamine (as dihydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2307/001/MR
Registration number in the Netherlands: RVG 16820

9 September 2013

Pharmacotherapeutic group:	diagnostic agents, tests for allergic diseases
ATC code:	V04CL
Route of administration:	intradermal
Therapeutic indication:	positive control in the diagnosis of IgE-mediated allergic conditions
Prescription status:	prescription only
Date of first authorisation in NL:	6 March 2000
Concerned Member States:	Mutual recognition procedure with AT, BE, DE, EL, ES, IT, PT, RO, SI
Application type/legal basis:	Directive 2001/83/EC, Article 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for HAL Allergy Prick Test Controlevloeistoffen, solution for skin-prick test from HAL Allergy Benelux B.V. The date of authorisation was on 6 March 2000 in the Netherlands.

The product is for diagnostic use only. It is to be used as a positive control in the diagnosis of IgE-mediated allergic conditions via a prick test on the skin.

A comprehensive description of the indications and posology is given in the SPC.

Skin testing is a bioassay that detects the presence of allergen-specific IgE on a patient's mast cells. A positive skin test reaction (typically, a wheal 3 mm in diameter, accompanied by surrounding erythema) reflects the presence of mast cellbound immunoglobuline E (IgE) specific to the tested allergen.
About 15-20 minutes after the application of allergen to skin, the test site is examined for a wheal and flare reaction. Because of intra and interpatient variability in cutaneous reactivity, it is essential to include a positive and a negative control when one or more allergens are tested.
Positive control solutions are needed to detect suppression of allergic reactions by medications or disease, detect the exceptional patient who is poorly reactive to histamine, and determine variations in technician performance. Skin reactivity to histamine has long been used in skin prick tests as a standard and/or as positive control.
Negative control solutions contain the excipients present in the test allergen solutions. Rarely, a patient has a wheal-and-erythema reaction to the negative control (e.g. extremely sensitized patients). The negative control also detects traumatic reactivity induced by the skin test device and the technique of the tester.

Histamine is an agonist of various histamine receptor subtypes present in various cutaneous tissues. When used as stated, histamine initiates a local limited reaction, which results in the formation of swelling and erythema around the site of application. In general, the skin reaction and localised pruritus resolve within a period of 30 minutes to 1 hour.

This mutual recognition procedure concerns a well-established use application. The application is supported with literature, *i.e.* 12 published articles from 1985 to 2006.

The marketing authorisation is granted based on article 10a of Directive 2001/83/EC.

HAL Allergy Prick Test has been registered in the Netherlands since March 2000. Originally the formulation contained histamine diphoshate 10 mg/ml. The currently registered formulation in the Netherlands contains histamine HCl 10 mg/ml. An exploratory test has been performed comparing the wheal size of both solutions in 9 patients.

In 1993, the EAACI (European Academy of Allergology and Clinical Immunology) subcommittee on Allergen Standardization and Skin Tests recommended to use a cut-off limit of the wheal size of > 3 mm diameter (≈ 7 mm2 area) in skin prick tests. A histamine HCl concentration of 10 mg/ml fulfils this condition and a histamine concentration of 10 mg/ml is superior in reproducibility of the response than a lower concentration of 1 mg/ml.

This application concerns a bibliographical application based on well-established medicinal use of the product. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ‘’Medicinal use’’ does not exclusively mean ‘’use as an authorised medicinal product’’, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation

submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a well-established use application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is histamine dihydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white, crystalline powder, which is very soluble in water. The molecule has no chiral centre. Physical parameters such as polymorphism and particle size are not relevant, considering that the drug substance is dissolved in the product.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process has been sufficiently described. The active substance was adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur. and two additional limits. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production batches.

Stability of drug substance
Stability testing on the active substance has been initiated for three production batches. Meanwhile the drug substance will be tested according to the approved specification before use in the manufacturing process of the drug product. This is considered acceptable.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
HAL Allergy Prick Test Controlevloeistoffen is a clear, viscous and slightly acidic solution for skin-prick

test, with pH 5.0 – 6.5. One ml solution for skin- prick test contains 10 mg histamine dihydrochloride equivalent to 6 mg histamine. A glass bottle of 3 ml contains 18 mg histamine.

The solution is packed in brown glass bottles of 3 ml, closed with a dropper integrated into the screw top or a clear glass 6 ml bottle (Ph.Eur. type I) containing 3 ml solution, closed with a bromobutyl rubber stop and a removable aluminium ring with plastic cap. In the latter case, a plastic dropper that may be used only in combination with the HAL Allergy Prick Test is provided separately in a sterile laminated pouch.

The excipients are: sodium chloride, sodium hydrogen carbonate, phenol, glycerol, water for injection.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. It has sufficiently been demonstrated that the composition is usual for this type of product and that the manufacturing process is straightforward and under control. The concentration and composition of the HAL Allergy Prick Test are in compliance with the recommendations in the Nordic guidelines for standardisation of allergen products. The product complies with the Ph. Eur. preservative efficacy test and stability is acceptable.

Microbiological attributes
The product is a liquid used for skin prick tests. When it is considered as a parenteral product, it has to be sterile in accordance with Ph.Eur. monograph 520 on Parenteral preparations. A combination of aseptic filtration and aseptic processing is used for the manufacture. The HAL Allergy Prick Test is for multidose use. Therefore 5 mg/ml (0.5%) phenol is added as preservative. A concentration of 0.5% phenol is recommended in the literature and is found acceptable for the preservation of Cholera vaccine (Ph. Eur. Monograph 154) and Typhoid vaccine (Ph.Eur. monograph 156). Toxic effects are not expected for this low dose of phenol. No adverse events have been reported over years of widespread use.

Manufacturing process
The manufacturing process consists of dissolving the drug substance and excipients in the water for injection, sterile filtration and filling of the solution into heat sterilised packaging and closing the packaging. All steps are performed at aseptic conditions. The manufacturing process has been adequately validated, according to relevant European guidelines.

Control of excipients
The excipients comply with the Ph. Eur. Phenol complies with the USP. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance (clarity, colour), identity, assay, impurities, content of phenol, sterility, pH, fill weight. The release and shelf-life specifications are identical. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three production batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided two pilot batches stored during 36 months at 2-8°C and 6 months at 45°C/75%RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. The shelf-life of three years at 2-8°C is justified, based on the results.

In-use stability
No in-use stability test has been performed with HAL Allergy Prick Test, however the MAH did perform in-use stability testing with a comparable product: HAL Allergy Prick Test Grasses 10,000 AU/ml. The in-use test was specifically targeting sterility and was done for 52 weeks in which every week the product was opened and kept outside the refrigerator for 2 hours. The sterility maintenance was confirmed. Knowing that the study is not completely reflecting current standards, the MAH proposed a limited in-use claim of 2

months and will initiate on short notice a new in-use stability study as post-approval commitment. This is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

HAL Allergy Prick Test 10 mg/ml is a well-established medicinal product that has been registered in the Netherlands for over 10 years. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Pharmacology
Experimental pharmacology data are not available. This is not a concern. Histamine is a well-known compound. It binds to four major histamine-specific receptors (H1, H2, H3, and H4), present in different tissues of the skin. Histamine dilates post capillary venules, activates the endothelium, and increases blood vessel permeability. This leads to local oedema (swelling), warmth, redness, and the attraction of inflammatory cells. It also irritates nerve endings (leading to itching or pain). Cutaneous signs of histamine release are the "flare and wheal"-reaction, similar to that elicited by an allergen to which an individual has mast cell-bound IgE specific to the tested allergen. In animals, systemic adverse effects from the use of histamine in skin prick tests are rare and not serious in nature.

Pharmacokinetics
Experimental pharmacokinetic data are not available. In addition, no data have been reported in the literature regarding the pharmacokinetics of histamine when used as positive control in skin prick tests. This is acceptable, because the administered amount is approximately 10^{-2} ng histamine, and application is locally near the junction between the dermis and epidermis in the skin. This route of administration is different from subcutaneous or dermal injection. Histamine and its metabolites have been identified in the urine of various mammals. It is rapidly cleared, primarily via the kidneys at higher doses, and only a small fraction of histamine is excreted unchanged.

Toxicology
Toxicity studies are not required. As the amount of HAL Allergy Prick Test administered is extremely small, and application is locally near the junction between the dermis and epidermis in the skin, no toxic reactions are expected from preclinical point of view.

Environmental risk assessment
According to Directive 2001/83/EC, an environmental risk assessment is required for bibliographic application based on well-established use (article 10a). However, an ERA is not required in view of the provided rationale that marketing authorization of HAL Allergy Prick Test is not expected to increase the exposure of the environment to histamine since that it will replace similar, generic histamine products already on the market.

II.3 Clinical aspects

The use of HAL Allergy Prick Test is well-established. A clinical overview has been provided, which is based on scientific literature, as required for a bibliographical application. Reference is made to 12 published articles from 1985 to 2006. The only study performed was an exploratory clinical test by HAL comparing the wheal size of the previously registered solution containing histamine diphosphate with the new solution containing histamine diHCl.

Pharmacokinetics
No specific pharmacokinetic studies have been performed to investigate the systemic absorption of locally applied histamine to the skin. Histamine applied to a patient in a skin prick test is presumed to be broken down in a similar way as endogenous histamine, i.e. rapid metabolism by two main pathways: methylation by histamine-N-methyltransferase and oxidative deamination by diamineoxidase.

Pharmacodynamics
Histamine is an endogenous compound involved in the regulation and modulation of local immune responses. In addition, histamine regulates physiological functions in the gut and stomach and acts as a neurotransmitter in the nervous system. In the body, histamine is derived from the decarboxylation of the amino acid histidine, a reaction catalysed by the enzyme L-histidinedecarboxylase. Histamine acts on the specific histamine membrane receptors H1, H2, H3 and H4, present on the target cells. Activation of these receptors causes amongst others vasodilation, bronchoconstriction, smooth muscle activation, and separation of endothelial cells (responsible for an allergic reaction).

Pharmacodynamics of skin prick test
Skin tests involve the introduction of allergen through a break in the skin to provoke an allergic response of the skin. The allergens applied in a skin test provoke an IgE-mediated allergic reaction.
This IgE-mediated reaction (immediate reaction) results in a dermal response which is marked by a wheal and flare reaction and which is dependent on both chemical and neurogenic mediators. The wheal-and-flare reaction is mainly due to the activation of mast cells releasing vasoactive agents, which cause both plasma extravasation and vasodilation. Histamine is the major, but not exclusive, mediator of the wheal-and-flare reaction. The immediate reaction is often, but not always, followed by a late-phase reaction developing over the next 3 to 5 hour, peaking at 6 to 12 hour, and resolving in approximately 24 hour. The late-phase reaction appears as an ill-defined edematous reaction, which is related temporally to an influx of inflammatory cells.
Histamine mimics the allergen-induced wheal-and-flare reaction of intradermal reactions when injected into the skin by prick tests as positive control. Immediate skin reactions to histamine typically peak at 8 minutes, whereas those to allergen peak at 15 minutes. However, injection of histamine never produces a late-phase reaction.

Pharmacodynamic interactions
Antihistamines, used by a patient, interfere with the development of the wheal-and-flare reaction and should be stopped before skin prick testing. First-generation antihistamines may be stopped 2 to 3 days before testing, but the newer, second-generation antihistamines can affect skin testing results for 3 to 10 days or longer. Medications with antihistamine properties, such as anticholinergic agents, phenothiazine, and tricyclic antidepressants, should also be discontinued before skin testing. Histamine H2-receptor antagonists (e.g., cimetidine, ranitidine) have a limited inhibitory effect; these medications may be stopped on the day of skin testing. Inhaled and short-term systemic corticosteroids generally do not significantly suppress the wheal-and-flare reaction of skin tests.

II.3.1 Clinical efficacy

Dose-response and dose-justification
Histamine diHCl in a concentration of 10 mg/ml is usually used as positive control in skin prick tests.
Several studies have been published investigating the wheal response at different or a range of histamine concentrations.

In a large study in the United Kingdom in 1985 with a total of 893 subjects (47% male, 53% female, age range 18 to 86 years, > 95% Caucasian), over 90% of the patients responded positively to 1 mg/ml histamine phosphate. Still, about 7% of the subjects did not respond with a wheal area of at least 2 mm in diameter, indicating a histamine phosphate concentration of 1 mg /ml may be too low to be used as positive control in skin prick tests.

In 7 otherwise healthy Swedish volunteers (age range 20-38 years) with grass pollinosis, a concentration histamine diHCl of 0.8 mg/ml or higher was needed for a positive mean wheal response, i.e. a wheal of at

least 2 mm in diameter. Mean wheal increased with increasing histamine concentrations. Histamine diHCl 10 mg/ml induced a wheal of about 5.5 mm in diameter.

The dose-response relationship was confirmed by another study in which the median wheal area for 1, 10 and 100 mg/ml histamine diHCl was 3, 10 and 44 mm2 in 7 Danish persons (age range 31-37 years) without allergic symptoms.

In 1993, the EAACI (European Academy of Allergology and Clinical Immunology) subcommittee on Allergen Standardization and Skin Tests recommended to use a cut-off limit of the wheal size of > 3 mm diameter (≈ 7 mm2 area) in skin prick tests. A histamine diHCl concentration of 10 mg/ml fulfils this condition and is superior in reproducibility of the response compared to a lower concentration of 1 mg/ml.

Variability in histamine response

Although there are intra (circadian rhythm) and interindividual (age, gender, ethnic) differences observed in skin reactivity to histamine these differences are on average quite small and can be considered clinically non-relevant for interpreting skin prick tests in most cases.

The demographic factors determining the response to histamine diHCl 10 mg/ml were investigated in 620 Caucasian individuals (49.5% male, 50.5% female, age range 10 to 80 years, 502 allergic and 118 non-allergic subjects) living in a semi-rural area of Northern Italy. Histamine reactivity was found to be higher in allergic than non-allergic individuals. Age and histamine reactivity were significantly correlated in the study subjects, with a greater wheal at higher age. In male subjects, a higher skin prick test response to histamine was seen versus female subjects in the allergic population, but this did not apply to non-allergic subjects. A positive correlation was observed between the number of positive allergens at skin prick test and the wheal reaction to histamine, i.e. the more allergic a subject, the more reactive to histamine this subject was.
Other studies showed similar results.
In a study in the UK with 893 subjects (47% male, 53% female, age range 18 to 86 years, > 95% Caucasian) the response to histamine diHCl 1.0 mg/ml did not differ significantly between sexes, but older subjects tended to have a larger wheal response.
In 7 normal persons without allergic symptoms and a negative reaction to standard allergens, the median wheal area for 10 mg/ml histamine diHCl was 10 mm2, while in 7 latent allergic subjects (positive reaction to one or more allergens but without clinical allergic symptoms) and 20 manifest allergic subjects (positive reaction and a case history of allergic diseases), the median wheal area was 14 and 25 mm2, respectively.
Within Europe there is difference in response to histamine. The mean wheal produced by histamine 10 mg/ml was 4.8 mm in Estonian children, 5.5 mm in Polish children and 6.2 mm in Swedish children.

Not only the patient's characteristics determine the histamine response, but also studies indicate that the histamine skin reactivity increased during the past two decades. In non-selected 9-year-old school children, the mean wheal diameter induced by histamine diHCl at a concentration of 10 mg/ml was significantly higher in 1999 than in 1983 (5.28 ± 0.82 versus 3.25 ± 0.97 mm). In both years, the studied population, consisting of about 170 boys and girls was drawn from small towns without undue pollution, without influxes of new families to the area. Histamine response was determined using the same methodology and there were no relevant differences in gender, height and weight distribution between the groups. Likewise, in a longitudinal study conducted only 4-5 years apart in Estonian children, wheals in histamine 10 mg/ml increased from 4.5 ± 0.4 to 5.9 ± 0.2 mm.

Efficacy of the HAL Allergy Prick Test

One exploratory clinical test has been performed by HAL comparing the wheal size of the previously registered solution containing histamine diphosphate with the new solution containing histamine diHCl. Nine non-selected patients were tested trice per solution and the mean of the 3 tests was calculated for each patient. The overall mean wheal diameter as results of the histamine diHCl was 6.0 mm (range 4.0 to 7.7 mm). The mean wheal diameter for the histamine diphosphate formulation was 6.1 mm (range 4.3 to 8.0 mm), indicating that the two preparations were clinically comparable. The cut-off criterion for the wheal diameter of 3 mm was achieved for all 3 tests in all subjects for both formulations and the mean

value of 6 mm corresponds well with the results of histamine tests presented in literature as described in the previous paragraph.

Efficacy and use of skin prick tests

Skin testing remains the central test to confirm an allergic response to aeroallergens, foods, hymenoptera venoms and drugs. Skin tests can be achieved via skin prick or puncture testing or intradermal testing. Nonetheless, the diagnosis of allergic disease should be made together with the history of the patient's complains and physical examination.

Different methods and test devices are available to perform an allergy skin test. These include skin prick test, skin puncture test and intradermal testing. Factors that can affect the results of the skin tests include type of skin testing, device used, placement of tests, the particular extracts being used, and the potential confounder of medications that may suppress skin test response. Direct comparisons indicate that intradermal testing is more reproducible, correlates better with clinical allergy and is more sensitive than percutaneous testing, but is also more likely to induce systemic anaphylactic reactions.

Factors as economy of time, patient comfort and safety favor the percutaneous tests as the routine for allergy testing. Skin prick testing is minimally invasive and when performed correctly has good reproducibility. It is easily quantifiable and allows the evaluation of multiple allergens at one session. Skin prick testing has demonstrated good correlation with results of nasal challenge and bronchial challenges. There is no evidence of false-positive skin prick test results attributable to the large adjacent reactions even when the test sites were only separated by 2 cm. Skin prick tests are generally recommended as the first choice diagnostic tests. Intradermal testing is usually reserved for special situations.

II.3.2 Clinical safety

Safety of histamine as positive control in skin prick tests

Every person is expected to react to the histamine. Failure of the reaction to the positive response is an indication for failure of the skin prick test and the rest of the allergens tested cannot be interpreted because of this overall suppression of the allergic reaction.

Safety of histamine as positive control in skin prick test is rarely discussed. Studies investigating the reaction of histamine test up to a dose of 100 mg/ml in 34 healthy volunteers do not mention any adverse event occurring. A study in 620 subjects dosed with a positive control of 10 mg/ml histamine diHCl does also not mention any reaction of histamine of the prick test itself other than the intended reaction. No publications were found specifically discussing the safety of a positive control containing histamine for use in skin tests and reviews on skin prick test do not mention any severe or mild systemic response due to histamine in the positive control.

General safety of skin prick tests

Allergic skin testing, which includes the use of a positive histaminic control, is a safe diagnostic procedure. The risk of fatality due to skin prick testing is extremely remote, and severe or anaphylactic reactions are very rare. A few fatalities have been reported in the past, which were associated with biologic products that are no longer used such as tetanus or diphtheria toxins or pneumococcal antiserum. In the largest available surveys conducted, only 7 deaths following skin testing procedures were reported, but 5 of them were due to intradermal tests.

Recent surveys indicate that the overall risk of inducing anaphylactic reactions by skin prick testing is less than 0.02%. Mild systemic reactions with itching and generalized rash have been recorded but are unusual. Five mild reactions were recorded in a study with over 18,000 patients receiving a skin prick test which always includes a negative and a positive control (ratio 1: 3000). These calculations consider the method of skin prick testing as a whole including the reactions to the allergens.

Due to the rarity of severe reactions with skin prick testing, identification of possible risk factors or populations at risks is not feasible. In general, patients with history of previous anaphylactic reactions, young children, pregnant women, patients with uncontrolled asthma, or otherwise high degree of allergic reactivity should be considered at higher risk of systemic/anaphylactic reactions.

Skin prick testing is not to be used when there is a history of anaphylaxis to the test allergy and patients with ongoing allergic symptoms should not be tested until their symptoms are stable.

In pregnant women, it is recommended to postpone skin prick tests or use other (serological) tests. The theoretical risk of a reaction necessitates that antihistamines and adrenaline should be readily available when performing allergen skin prick testing.

Contraindication and warnings
The following contra-indications are included in the product information:
- Any disease seriously harming the patient's general condition;
- Any skin lesion in the area where the test is performed;
- Prick tests should preferably not be performed during treatment with beta-blockers;
- Age under 1 year
- Hypersensitivity to histamine or any of the excipients of the product.

The following special warnings are included in the product information:
- The test solutions are intended solely for prick tests and may not be used for intracutaneous skin tests using injection needles.
- During and after completion of the prick test, patients should be instructed not to rub the skin in the test area or to scratch at this site.

The contraindication on the use of beta-blockers is related to case reports that suggest that when systemic allergic reactions occur secondary to immunotherapy, drugs, foods, and insects stings, they may be of greater severity in patients taking beta-blockers. In case reports of patients with severe anaphylactic reactions, several patients were coincidently on beta-blocker medications.
Beta-blockers are relatively contraindicated in both skin testing and immunotherapy as beta-blockade may place atopic subjects at an increased risk of an anaphylactic reaction. Beta-blockers may worsen anaphylaxis severity, make treatment of anaphylaxis more difficult and increase the incidence of anaphylaxis itself. In a recent retrospective analysis in 191 patients, who were taking beta-blockers when skin testing occurred no adverse event occurred. However, the number of patients is not large enough to conclude on the potential of beta-blockers to amplify the effects of anaphylaxis. Therefore these drugs are relatively contraindicated during allergy skin testing.

Safety in special patient groups, pediatrics
Skin prick tests are commonly and routinely used in children. Several studies have been published investigating or mentioning the use of skin prick test in children without further safety concerns.
Very young children, i.e. infants, require particular caution, since the risk factors in this group are different and more relevant than in adults. Infants tend to have a less reactive skin with fewer mast cells than older children and adults. Therefore for children younger than 1 year it can be considered unethical to perform skin prick tests in this group of patients if the physician cannot correctly interpret the results. To avoid misinterpretation of test results, the proposed product information recommends to conduct the tests in children of 1 year and older.

II.3.3 Benefit-risk assessment

Skin prick tests, including the use of a positive control like histamine, are usually used to diagnose a patient's allergy to a specific allergen.
The usage of HAL positive skin prick test has been registered since March 2000 in the Netherlands. No reasons to discuss the benefit risk have emerged since the registration in the Netherlands.
Every person is expected to react to the histamine. Failure of the reaction to the positive control is an indication for failure of the skin prick test and the rest of the allergens tested cannot be interpreted because of this overall suppression of the allergic reaction. Therefore the use of a positive control like histamine is necessary.

When properly applied, the tests are safe and only mild reactions as itching and generalised rash have been reported. No adverse reports were received for HAL Allergy Prick Test during the period 2005 to 2009.
Children younger than 1 year have a less sensitive skin and results may be misinterpreted. Therefore the use of this product in this group of patients is contra-indicated.

In pregnant women, it is recommended to postpone skin prick tests or use other (serological) tests.
Beta-blockers are contraindicated as they may place atopic subjects at an increased risk of an anaphylactic reaction. Beta-blockers may worsen anaphylaxis severity, make treatment of anaphylaxis more difficult and increase the incidence of anaphylaxis itself.

The theoretical risk of a severe reaction necessitated that antihistamines and adrenaline should be readily available when performing allergen skin prick testing.

Conclusion
The benefit-risk for this positive skin prick test is positive provided that the product is used in accordance with the limitations set in the product information.

Pharmacovigilance system
The member states consider that the current Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
No Risk Management Plan (RMP) has been submitted and the absence of a RMP is acceptable, as the product is considered well-established.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is considered appropriate.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test was performed in 2007 on the Dutch PIL which also contains information on the allergenes, next to the positive and negative prick test. The test passed the criteria for readability. A bridging report stating that the obtained results are still applicable for the PL no longer containing the information on allergens.
As member states agree that the user testing performed in 2007 also applies to the PL only containing the information on the positive prick test. Additional user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

HAL Allergy Prick Test Controlevloeistoffen, solution for skin-prick test can be considered effective in the approved indication as a positive control in the diagnosis of IgE-mediated allergic conditions via a prick test on the skin. It is for diagnostic use only.

Histamine is a well-known active substance with established efficacy and tolerability. For this application, no original clinical study data nor clinical trials were conducted or presented.
The medicinal product is manufactured in an established process and its quality is sufficiently guaranteed.

Skin testing remains the central test to confirm an allergic response to aeroallergens, foods, hymenoptera venoms and drugs. The efficacy is well-established.
Allergic skin testing, which includes the use of a positive histaminic control, is a safe diagnostic procedure. The risk of fatality due to skin prick testing is extremely remote, and severe or anaphylactic reactions are very rare. The benefit/risk ratio can be regarded as positive if the product is used correctly and under the conditions stipulated in the SPC.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and contain appropriate information.

The Board followed the advice of the assessors. HAL Allergy Prick Test Controlevloeistoffen, solution for skin-prick test is authorised in the Netherlands on 6 March 2000.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The other member states mutually recognised the Dutch evaluation for the marketing authorisation. The mutual recognition procedure was finished on 12 March 2013.

The date for the first renewal will be: 12 March 2018.

The following post-approval commitment has been made during the procedure:

<u>Quality - medicinal product</u>
- The MAH committed to conduct a new in-use stability study.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached