

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as amended**

**Vespula venom
Honey bee venom
ALK-depot SQ
Alutard SQ/ALK 802
Pharmalgen
Reless
VENOMENHAL**

**DE/W/0010/pdWS/001
and
DE/W/0012/pdWS/001**

**Marketing Authorisation Holders:
ALK Abelló/ ALK-SCHERAX
HAL Allergy/HAL Allergie GmbH/
Diagnostic Therapie Halcis Alergie SRL**

| | |
|--|------------|
| Rapporteur: | Germany |
| Finalisation procedure (day 120): | 12.03.2010 |
| Date of finalisation of PAR | 07.12.2010 |

ADMINISTRATIVE INFORMATION

| | |
|--|---|
| Invented name of the medicinal product(s): | See section VI |
| INN (or common name) of the active substance(s): | Honey bee venom Vespula venom |
| MAH (s): | See section VI |
| Pharmaco-therapeutic group (ATC Code): | V01AA07 Insects |
| Pharmaceutical form(s) and strength(s): | Suspension for injection (100/1000/10000/100000 SQ-U/ml) Powder and solvent for solution for injection (100µg/ml) Lyophilisate and solvent for injection (120 µg/vial) |

General notice on the preparation of the Public Assessment Report:

As the majority of studies were performed in parallel with both, *Apis mellifera*- and *Vespula*- venom and a simultaneous response to the list of questions was agreed upon, the Public Assessment Report is prepared as a combined Assessment Report for *Apis mellifera* and *Vespula* spp. venom.

The MAH followed the Rapporteur's advice to simultaneously provide supplementary information requested from the *Apis mellifera* venom and the *Vespula* spp venom procedure. Thus responses to the list of questions regarding *Apis mellifera* venom were mainly identical with the request that arose from the *Vespula* spp venom procedure because the majority of the published studies was conducted using both, *Apis mellifera* and *Vespula* spp venom.

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I. EXECUTIVE SUMMARY

This Article 45 Worksharing Procedure concerns the hymenoptera venoms (*Vespula* venom (wasp venom) and *Apis mellifera* (honey bee) venom) for allergen-specific immunotherapy.

Allergen-specific immunotherapy consists in the administration of increasing amounts of the allergens to which a patient has developed a clinically relevant allergy up to a maintenance dose which is applied regularly for 3 to 5 years. It was first used nearly one hundred years ago and remains in use worldwide for treatment of allergic rhinitis, asthma and the life-threatening hymenoptera venom allergy. It has been recognised as the only effective treatment for type I allergic diseases when the appropriate quantities of allergens are used. The immunological mechanisms by which specific immunotherapy is effective include the modulation of T cells and the response of B-cells and is accompanied by a constant or decreased titre of the allergy-mediating allergen-specific IgE-antibodies and increases in allergen specific IgG antibodies, predominantly IgG4 (Carnes & Robinson, 2008, EMEA/CHMP/EWP/18504/2006). However, the mechanism of action is still not fully understood. Many investigations on the mechanism as well as on the clinical relevance of the alteration of immunologic parameters are ongoing.

In 2004, an editorial published in the New England Journal of Medicine comments on the indication of allergen-specific immunotherapy in insect sting-allergic children (Gruchalla R, 2004).

As previously demonstrated for adults (Reisman et al., 1992), a more recent study showed that a large percentage of children who have moderate-to-severe systemic allergic reactions to insect stings are likely to have similar systemic reactions if they receive subsequent stings (Golden et al., 2004). A most relevant study result is that even many years after hymenoptera venom immunotherapy had been discontinued it still appeared to exert an effect, as shown by a marked reduction in the rate of systemic reactions among children who had previously had moderate-to-severe systemic allergic reactions. In addition, like adults, the few children who had been treated and who nevertheless had subsequent systemic reactions had more severe original reactions. These findings support the use of hymenoptera venom immunotherapy in children who have a moderate-to-severe systemic allergic reaction to insect stings. The study results also support the consideration of prolonged therapy for children with especially severe systemic allergic reactions to insect stings, which is similar to the recommendations for adults. There is evidence that children do not outgrow insect-sting allergy. According to Golden and co-workers (2004) for most children who have systemic allergic reactions to insect stings with dermatologic manifestations only hymenoptera venom immunotherapy may not be warranted. For the small percentage of children who have more severe sting-induced systemic allergic reactions it is very likely that they will have similar severe reactions if they receive subsequent stings and, consequently, these children should receive immunotherapy.

There is broad post-marketing experience with hymenoptera venom preparations used for specific immunotherapy.

In accordance with Article 45 of the Regulation (EC) No. 1901/2006, studies assessed in this procedure are paediatric studies completed before 26 January 2007, which have not previously been submitted.

There are differences within the EU member states regarding the exact wording of the SmPC.

Harmonization of the paediatric related information in the SmPCs throughout Europe was intended in the worksharing procedure. The recommendations (see section II) were accepted by all member states except the Netherlands.

II. RECOMMENDATION (DAY 120)

Based on the review of the presented paediatric data the Rapporteur considers that:

The presentation of the data was partly insufficient but it does not seem that the submitted publications and non-published studies reveal so far unknown aspects. Details on pre-clinical studies were provided by the MAHs as requested.

It is acknowledged that the MAH have provided information on specific immunotherapy as far as possible and that study data on children are sparse.

Therefore, from the available data and supplementary information as provided by the MAHs it is not possible to prove efficacy of insect venom immunotherapy in children. Therefore no specific indication for the use in children can be given and an extension to use honey bee or wasp venom in the paediatric population younger than 5 years is not possible.

However according to the published relevant position papers and the revised Standard PIP for allergen products for specific immunotherapy an absolute contra-indication for children younger than 5 years is not justified but venom immunotherapy should only be performed in selected and justified cases in this age group. Therefore the warning “Special care should be given to the risk-benefit assessment with regard to treatment of children younger than 5 years of age.” should be given.

For consistency between the products across the EU, it is recommended that all SmPCs contain the following statements **except for the medicinal products authorised in NL** as the Dutch MEB is not prepared to endorse the Rapporteur’s conclusion (see also under section V at the end of this report):

Proposed paediatric related wording in the SmPC

4.1 Therapeutic Indication

No change

4.2 Posology and method of administration

A harmonization of measures to be taken in case of swelling should be obtained.

The Rapporteurs suggestion is to harmonize this part of the SmPC by using the table below as originally provided by one MAH for aqueous as well as depot preparations.

| Maximum diameter of swelling | | Recommended dose reduction |
|------------------------------|----------|---|
| Children | Adults | |
| < 5 cm | < 8 cm | Continue upward titration according to up-dosing schedule |
| 5-7 cm | 8-12 cm | Repeat dose last given |
| 7-12 cm | 12-20 cm | Reduce dose to dose given the time before last |
| 12-17 cm | > 20 cm | Reduce dose to dose given 2 times before last |
| >17 cm | | Reduce dose to dose given 3 times before last |

4.3 Contraindication

Treatment of children younger than 5 years of age is not a contraindication as defined by the position papers of Research Groups, therefore it should not be stated as contraindication, but in Section 4.4

4.4 Special warning and precaution for use

Special care should be given to the risk-benefit assessment with regard to treatment of children younger than 5 years of age. For children ≥ 5 years of age clinical data of efficacy are sparse, however data on safety do not reveal a higher risk as for adults.

Proposed paediatric related wording in the PIL:

None of the MAH provided data on the current PILs nor on a harmonised PIL.

In the case that a PIL is provided, the rapporteur proposes the following wording:

WHAT XXX IS AND WHAT IT IS USED FOR

No specific indication for children can be made.

BEFORE YOU TAKE XXX

Take special care with XXX

Special care should be given to children younger than 5 years of age are treated with XXX. The physician must carefully weight the risk-benefit for the individual child.

For children ≥ 5 years of age clinical data of efficacy are sparse, however data on safety do not reveal a higher risk as for adults

HOW TO TAKE XXX

The Dosage Reduction Scheme in case of swelling after the administration should be as proposed for the SmPC.

No differentiation on the recommended up-dosing or maintenance dose between adults and children should be made.

For the products authorised in NL:

The wording of the SmPC and the PIL remains as currently authorised (see Section V))

III. INTRODUCTION

Two MAHs (ALK Abello and HAL Allergy) originally submitted 4 original publications and one MAH (ALK Abello) additionally a list of study results, extracted from publications for hymenoptera venoms (active substances: *Apis mellifera*- and *Vespula* venom), in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided by the MAHs.

The MAH ALK Abello and HAL Allergy stated that the submitted paediatric study(ies) do not influence the benefit-risk assessment for *hymenoptera* -venom immunotherapy and that there is no consequential regulatory action necessary.

In addition, the following documentation has been included as per the procedural guidance and as response to the list of question:

- line listings
- annexes including SmPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product
- lists of the current wording (in English) relevant for paediatric patients in the SmPCs from all MS in which wasp or bee venom is an approved medical compound (including section 4.1).

IV. SCIENTIFIC DISCUSSION

Indication

Honey bee venom and wasp venom are for diagnostic use (prick-testing and intracutaneous testing) and for causal treatment of patients with an IgE-mediated insect venom allergy who have suffered a systemic reaction after an insect sting.

Scientific Background

The effects produced in the human organism by subcutaneous injection of insect venoms are well-known from stings, which human beings had to sustain ever since. Bee and wasp stings are known to provoke local toxic and systemic immunologic reactions, the former are relatively harmless, the latter result in severe allergic reactions. Concerned persons suffer from allergy that can be life-threatening upon a second exposition. The helpless situation of those patients encouraged physicians since more than 80 years successfully to use preparations of bee and wasp venom therapeutically in a specific immunotherapy (SIT) with hymenoptera venoms. In the course of this therapy, the allergic organism will be challenged with increasing doses of these allergenic agents up to a maintenance dose, aiming at the desensitization of the patients and protection against the dangerous hyperreactivity when getting stung again. A number of honeybee and wasp venom preparations are presently available for diagnostic and therapeutic use in honeybee and wasp venom allergy.

Severe allergic reactions to hymenoptera venoms in children are rare but do occur during early childhood. Immunotherapy may be initiated by a doctor trained in paediatric allergology (Bousquet et al., 1998).

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

From the brief documentation provided by the MAHs, the pharmaceutical formulations used in the clinical studies are the following:

1. Aluminium hydroxide-absorbed wasp venom / bee venom as suspension for injection (Alutard SQ, ALK-Depot SQ)
2. Aqueous extracts as lyophilisate for injection (Pharmalgen, Reless)
3. VENOMENHAL Wasp/ Bee contains either 1 mg lyophilised wasp venom / bee venom to be reconstituted with 10 ml solution containing sodium chloride, phenol, human serum albumin and water *ad injectionem*; or VENOMENHAL Wasp / Bee contains 6 vials with each 120 micrograms pure, freeze-dried insect venom of *Vespula* species/ bee venom, powder and solvent for solution for injection.

IV.2 Non-clinical aspects

1. Introduction

No list of the non-clinical studies with a brief description for each study was submitted (see also line-listing provided by the MAHs).

The MAHs originally submitted no report(s) considering non-clinical aspects.

The MAHs originally submitted no extended synopsis for non-clinical aspects.

2. Non clinical study(ies)

None provided by the MAHs.

3. Discussion on non clinical aspects

None provided by the MAHs.

Rapporteur's comment:

Although long term experience for specific immunotherapy with hymenoptera venoms exists and their primary pharmacodynamic action is an immunomodulatory or antiallergic one, at least a detailed summary of pre-clinical data (study data and data from the literature), even if these have been obtained without the explicit consideration of paediatric aspects, should have been provided.

Request for supplementary information:

No pre-clinical data or the respective summary of own studies and/or data from the literature were submitted. This should be provided by the MAH and discussed with regard to the paediatric population.

HAL provided a summary of nonclinical study data consisting of 4 single-dose toxicity studies in mice and rabbits with both venoms without the explicit consideration of paediatric aspects.

ALK provided data of one sub acute toxicity study in mice which has been carried out on Pharmedgen Apis mellifera venom and Pharmedgen Vespula spp. allergen extracts. Since Pharmedgen products are not purified and therefore contain more potentially toxic substances than the remaining ALK-Abelló A/S Vespula spp. extracts this study is valid for all other ALK Vespula spp. products. The sub-acute study showed that a dose of >103 times the maximum dose recommended for treatment did not cause systemic toxic effect in mice when administered 5 times a month during a 6 months exposure. Moreover, the extracts have been used in clinical practise for several years in a significant numbers of adult and paediatric patients.

Rapporteur's comment:

Details on pre-clinical studies were provided by the MAHs.

The issue has been solved.

IV.3 Clinical aspects

1. Introduction

The MAHs submitted publications on immunotherapy studies with wasp venom and or bee venom. Mostly the immunotherapy studies were combined studies with both venoms, not all studies were published internationally:

1, 2, 6, and 8 have been provided by ALK Abello; 3, 4, 5 and 7 by HAL Allergy

1. *Higher frequency of early local side effects with aqueous versus depot immunotherapy for Hymenoptera venom allergy*
2. *Insect sting allergy. A study from 1980 to 2003 of patients who started treatment with venom immunotherapy between 1980 and 1998*
3. *Anwendungsbeobachtung mit VENOMENHAL bei Patienten mit einer Allergie gegen Bienen- oder Wespengift.*
4. *A comparison of the diagnostic properties of VENOMENHAL® and Reless® AMKlh95432*
5. *A clinical study on the safety and efficacy of VENOMENHAL® AMKlh95435[klinstud]*
6. *Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial*
7. *Another study on honey bee- and Vespula-venom therapy as provided by HAL Allergy upon request*
8. *A table representing a synopsis of published studies on honey bee- and Vespula-venom therapy as provided by ALK Abello upon request*

2. Clinical study(ies)

CLINICAL STUDY TITLE

1. *Higher frequency of early local side effects with aqueous versus depot immunotherapy for Hymenoptera venom allergy;*

➤ **Description: An original article published in 2004**

Cadario G et al., J Invest Allergol Clin Immunol 2004; 14: 127-133

➤ **Methods**

• **Objective(s)**

To investigate the side effects related to the use of depot versus aqueous venom extracts.

• **Study design**

An open, uncontrolled study where Hymenoptera venom-sensitized subjects with a history of systemic reactions were treated with commercially available preparations of either aqueous or depot venom extracts and carefully monitored over at least 3 years for side effects and efficacy. Eight centres in Northern Italy participated.

• **Study population /Sample size**

Table I. Patients (N = 45): demographic data of patients included in the study.

| group | N = | sex (M/F) | age (range) | age (mean) |
|--------------|-----------|--------------|--------------|------------|
| depot | 27 | 19/8 | 15-68 | 39.0 |
| aqueous | 18 | 15/3 | 19-69 | 42.6 |
| Total | 45 | 34/11 | 15-69 | |

- **Treatments**

The allergen-enriched extracts that were used in the 2 cohorts for aqueous and depot immunotherapy (IT) (Pharmalgen and Alutard, respectively) were prepared from the same source by the supplier (ALK Abellò). An 8-week, 12-dose induction modified rash schedule was used for aqueous IT, in the first and in the second visit at the medical unit the patients received two doses, at 30 minutes interval, of 0.01 and 0.1 µg and of 1 and 2 µg, respectively. In the third and fourth visits patients received 2 doses, at 60 minutes interval, of 4 and 8 µg, and of 10 and 20 µg, respectively. Forty, 60, 80 and 100 µg were administered subsequently in single doses at weekly intervals. This phase was followed by the monthly administration of 100 µg of venom extract per dose, for at least 3 years. For depot IT, a progressive schedule was used for induction, consisting of 15 weekly injections of increasing doses of venom extracts (0.02, 0.04, 0.08, 0.2, 0.4, 0.8, 2, 4, 8, 10, 20, 40, 60, 80 and 100 µg). Subsequently, for maintenance therapy, a monthly administration of 100 µg venom extract per dose per 3 years was used. No premedication was used.

- **Outcomes/endpoints**

Systemic and local side effects were recorded according to previously described criteria, with minor modifications. Specifically, local erythematous and swelling reactions were recorded if erythema and swelling were > 10 cm diameter.

In Italy it is not allowed to perform intentional challenge sting tests under medical control. Therefore, patients were asked to report of any sting they were subjected to during the course of IT or after its discontinuation, as well as of the reactions they observed. This information was used to evaluate the protection they had achieved.

- **Statistical Methods**

The one-tailed probability of the chi-squared distribution was used to compare the number of side effects (considered both on a "per patient" and on a "per dose" basis) in the cohort subjected to aqueous venom IT versus the cohort receiving depot IT. The confidence interval was used to evaluate the overall proportion of individuals who were protected after vaccination, as it could be extrapolated on the basis of the number of individuals who were re-stung. All analysis was done with standard statistical software (GraphPad software Inc., San Diego, CA). Values of $p < 0.05$ were considered statistically significant.

➤ **Results**

Side effects were less frequent with the depot extract both on a "per patient" (22.2% versus 50.0%) and on a "per dose" (2.9% versus 10.2%) basis ($p=0.026$ and $p<0.0001$, respectively). Better tolerance was mainly due to the lower frequency of local side effects occurring at early times after vaccination. The efficacy of vaccination was comparable in the 2 cohorts, as expected.

- **Recruitment/ Number analysed**

The study was performed on 45 subjects sensitized to either *Apis mellifera*- or *Vespula*-venom. Patients were assigned to either a depot (N=27) or an aqueous (N=18) immunotherapy regimen.

- Baseline data

Table II. Patients (N = 45): severity of reactions to *Hymenoptera* stings and exposure risk.

| N = | Grade | Expos. risk | Exposure risk | Treatment (aqueous/depot) |
|--------------|-------|-------------|---------------------------------|---------------------------|
| 4 | IV | low | previous anaphylactic shock | 3/1 |
| 1 | IV | medium | resident in the countryside | 1/0 |
| 8 | IV | high | professional exposure | 5/3 |
| 1 | IV | unknown | unknown | 0/1 |
| 2 | III | low | severity of reactions to stings | 0/2 |
| 5 | III | high | professional exposure | 0/5 |
| 2 | III | unknown | unknown | 0/2 |
| 6 | II | low | severity of reactions to sting | 1/5 |
| 5 | II | medium | resident in the countryside | 6/2 |
| 3 | II | high | professional exposure | 0/3 |
| 5 | II | unknown | unknown | 2/3 |
| Total | | | | 18/27 |

Grades of severity are expressed according to Mueller [15].

- Efficacy results

Six (22.2 %) and 5 (27.7%) patients who had received the depot and the aqueous extracts, respectively, were stung one or more times 3 years since the beginning of IT. In all these patients the reaction to each subsequent sting consisted of a limited local reaction which did not require any treatment. The confidence interval of a proportion for 6 and 5 events is similar (56.2 to 100% and 51.6 to 100%, respectively). The patients who were re-stung were differently graded in terms of severity of their systemic reactions before IT (Table IV). Five patients were also stung before completion of the IT (3 who were treated with depot extracts and 1 with aqueous extracts); none of them experienced any systemic reaction.

- Safety results

Table III. Side effects (induction phase).

| | | DEPOT per patient (N = 27) | per dose (N = 405) | AQUEOUS per patient (N = 18) | per dose (N = 216) |
|--------------|------------------|----------------------------------|-----------------------|------------------------------------|-----------------------|
| SR | Grade I | 0 | 0 | 0 | 0 |
| | Grade II | 2 (L) | 7 (L) | 2 (E) | 9 (E) |
| | Grade III and IV | 0 | 0 | 0 | 0 |
| | <i>Total</i> | 2 | 7 | 2 | 9 |
| LR | Local pruritus | 0 | 0 | 1 (L) | 1 (L) |
| | Edema / erythema | 4 (1E + 3L) | 5 (1E + 4L) | 6 (1E + 5L) | 12 (1E + 11L) |
| | <i>Total LR</i> | 4 | 5 | 7 | 13 |
| Total | | 6 | 12 | 9 | 22 |

Figure 1. Frequency of side effects in subjects who received either depot or aqueous IT. Results are grouped in “systemic” (top panel) versus “local” (bottom panel) and shown as percent both on a “per patient” as well as on a “per dose” basis. Results of the chi square analysis are shown.

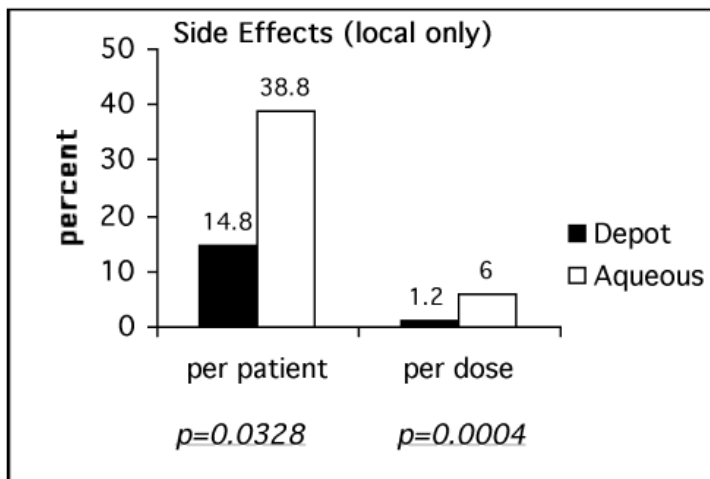
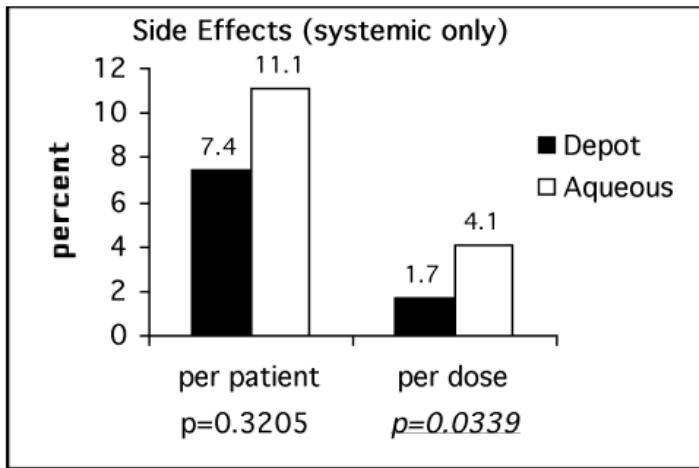


Figure 2. Frequency of side effects in subjects who received either depot or aqueous IT. Results are grouped in “early” (i.e., occurring within 60 minutes from injection) (top panel) versus “late” (i.e. occurring in the 6-24 hours following injection) (bottom panel). Results are shown as percent both on a “per patient” as well as on a “per dose” basis. Results of the chi square analysis are shown.

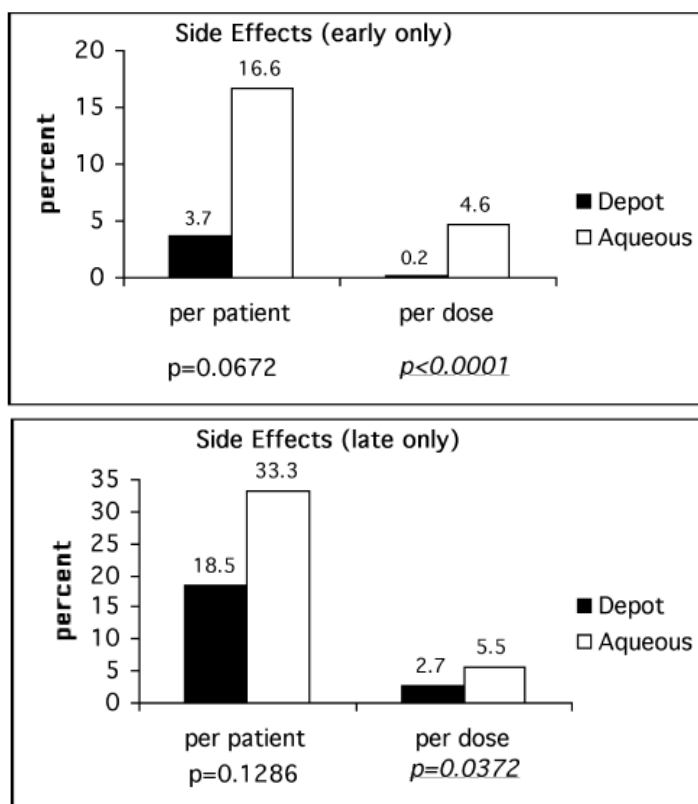


Table IV. Efficacy of venom IT at three years. All patients who were naturally re-stung after 3 years from the beginning of venom IT suffered only a mild local reaction. Results of efficacy of depot versus aqueous IT are listed according to the known grade of severity of the reaction before the beginning of IT.

| | Depot | Aqueous |
|-----------|-------|---------|
| grade IV | 2 | 2 |
| grade III | 2 | 2 |
| grade II | 2 | 1 |

Rapporteur’s comment:
 Comparable to the majority of published studies also this one has been performed on both groups of hymenoptera venom allergic subjects, honey bee and *Vespula*-venom-allergic individuals. In addition, the age of hymenoptera venom-allergic patients has not been mentioned. It has not been documented, how many out of 45 insect sting-allergic patients were wasp or bee venom-allergic children (of what gender) and had received wasp or bee venom, respectively. Valuable data on *hymenoptera*-venom-therapy in children cannot be extracted from this study. Therefore, its relevance to the specific requirements of the article 45 procedure cannot be assessed in detail.

2. *Insect sting allergy. A study from 1980 to 2003 Insect sting allergy. A study from 1980 to 2003 of patients who started treatment with venom immunotherapy between 1980 and 1998.*

➤ **Description: An original article published in 2005**

Haye R & Dosen LK. Clinical and Molecular Allergy 2005; 3:12-19

➤ **Methods**

• **Objective(s)**

The purpose of this study was to examine the short and long term effectiveness; side effects; causes for cessation of immunotherapy; the serological data and the skin prick test (SPT) results and quality of life of insect sting allergic patients, in order to improve treatment.

• **Study design**

This is an open, single centre study on patients treated with hymenoptera venom IT **14 years or older** with a history of a systemic allergic reaction to an insect sting, a positive skin prick test (SPT) or a positive RAST and willingness to comply with five years of IT. Clinical and laboratory data were registered prospectively at the start of IT and after five years of treatment until 2003 on patients who started IT between 1980 and 1998. Questionnaires were answered in 1989, 1993 and 2003.

• **Study population /Sample size**

The patients started immunotherapy between 1980 and 1998. Three hundred and fifteen patients were included in the study, 151 males (48%) and 164 females (52%). The age varied from 14 to 73 with a mean of 41.1 years. Forty four patients (14%) were given bee, 248 (79%) common wasp (*Vespula* sp.) and 23 (7%) both venoms.

• **Treatments**

The IT was performed with Pharmalgen (ALK) venoms. The injections were given subcutaneously on the lateral part of the upper arm. Aspirations were done at the beginning and during the injection. A rush regimen of five days duration was used with a starting dose of 0.1 microgram venom, doubling this every 2 hours for three days. The dose was increased more slowly on day four and five aiming for 50 micrograms or more for the last injection. Thereafter the venom was given at weekly intervals gradually increasing the dose to 0.1 mg and the interval to six weeks. Seven patients received Alutard (ALK) venoms. Many patients were referred back to their general practitioner to continue the IT after having reached 0.1 mg as their maintenance dose. A few patients who only tolerated 50 micrograms venom used this as their maintenance dose even if this is less effective. If they did not tolerate 50 micrograms of venom after up to three years of IT, the treatment was ended.

• **Outcomes/endpoints**

Duration of treatment: Efficacy of treatment after treatment cessation; feeling of safety / precautionary steps taken by the patients; SPT results before and after treatment.

• **Statistical Methods**

Statistical analysis was done with Pearson's chi square, Fisher's exact or the t-test. For the duration of IT two samples t-test was used.

➤ **Results**

• Recruitment/ Number analysed

315 patients were treated

- Baseline data

Table 1: Main Symptom

| Insect/Symptom | Vascular and respiratory | Vascular | Respiratory | Angioedema head/neck | Skin + gastrointest. | Total |
|-----------------|--------------------------|----------|-------------|----------------------|----------------------|-------|
| Bee | 12 | 18 | 13 | 1 | | 44 |
| Common wasp | 87 | 110 | 46 | 3 | 2 | 248 |
| Bee/common wasp | 6 | 8 | 6 | 3 | | 23 |
| Total | 105 | 136 | 65 | 7 | 2 | 315 |

- Efficacy results

Table 8: Reaction to sting after adequate immunotherapy of 5 or more years' duration in common wasp. Number of times stung

| Type of reaction | 0–5 years after cessation | More than 5 years after cessation | Total |
|--------------------------|---------------------------|-----------------------------------|----------|
| No / local swelling | 61 (3) | 14 | 75 (3) |
| Itching / urticaria etc. | 5 (2) | 0 | 5 (2) |
| Sedation | 7 (3) | 1 | 8 (3) |
| SAR | 19 (11) | 7 (5) | 26 (16) |
| Joint pain | 0 | 0 | 0 |
| Tachycardia | 4 (1) | 0 | 4 (1) |
| Total | 96 (20) | 22 (5) | 118 (25) |

In parenthesis: Number of times adrenaline was administered.

Table 9: SPT at start and after 5 years in bee and wasp allergic patients

| Bee-allergic | SPT grading | | | Total |
|---------------|-------------|-------------|--------------|------------|
| | Year | Neg. | Pos. | |
| 0 | | 0+0 | 40+23 | 40+23 = 63 |
| 5 | | 29+11 | 10+11 | 39+22 = 61 |
| Wasp-allergic | | SPT grading | | |
| Year | Neg. | Pos. | Total | |
| 0 | 1 | 208+43 | 209+43 = 252 | |
| 5 | 142+18 | 67+25 | 209+43 = 252 | |

Italics: Number of patients incompletely treated.

This study has shown that ongoing IT for common wasp is efficient when the maintenance dose is 0.1 mg, as also seen in other studies and for bee venom even better than others. After cessation of IT the results for inadequately treated patients are unfavourable compared to adequately treated ones.

- Safety results

Of 315 patients treated, 44 were given bee, 248 common wasp and 23 both venoms. Of the common wasp sting incidents 5.5 % resulted in a severe allergic reaction (SAR) during adequate IT and 22% after cessation. SAR occurred in 45 patients 14.2% (12 males, 33 females) (33 allergic to wasp, and 12 to bee) during increasing dosing.

During maintenance dosing the following SAR occurred: 1. SAR in one bee allergic patient occurred when an attempt was made to increase the dose above 0.1 mg; 2. in one wasp allergic patient due to a higher than planned dose after a prolonged interval of IT; 3. in one patient who received both venoms at the second maintenance dose; 4. in one wasp allergic patient after a few maintenance doses, and 5. in one case there was an unexplained syncope one day later.

In three of these cases there was a change in allergic sensitivity so that it was impossible later to reach an adequate maintenance dose again, and IT was discontinued. The most serious reaction causing cessation occurred in a female patient who had a cardiac arrest without prior warning at day four, 20 minutes after receiving 30 microgram common wasp venom as the second dose that day. It was difficult to resuscitate her, but she has recovered completely. However, the adequately treated wasp allergic patients experienced a SAR to sting after cessation of IT more frequently than has been found in other studies. The investigator stated that no explanation can be provided. The investigator reasoned that some of the patients should, therefore, preferably continue IT indefinitely.

Table 2: Number of patients reacting to immunotherapy

| Type of reaction | During incremental dosing | During maintenance dosing |
|--------------------------------------|---------------------------|---------------------------|
| Large local reaction | 14 | 5 |
| Itching in throat or nose / vomiting | 18 | 1 |
| Urticaria | 11 | 2 |
| Sedation | 51 | 25 |
| SAR | 45 | 5 |
| Joint / muscle pain | 21 | 26 |
| Tachycardia | 10 | 1 |
| Total | 170 | 65 |

**Table 3: Causes for cessation of immunotherapy before 5 years.
Number of patients**

| | |
|--|----|
| Problems due to work or change of domicile | 15 |
| Reactions to immunotherapy | 36 |
| Other serious illness | 7 |
| Death of other causes | 1 |
| Own initiative | 11 |
| Tolerated multiple stings | 1 |
| Others | 6 |
| Total | 77 |

Besides the allergic reactions the investigators found sedation (fatigue) and particularly joint and muscle pain to be an obstacle to further IT. Headache and fatigue is well known but did not lead to cessation of IT in this study, although some patients had to abstain from work on the day of injection and sometimes also the next day.

Little attention has been paid to joint/muscle pain which in this study led to cessation of IT in some cases. Although the investigators suspected this to be an immune disease, they were unable to confirm it.

Rapporteurs's comment:

This study has been performed on both groups of hymenoptera venom allergic subjects, honey bee- and *Vespula* venom-allergic individuals. The age range of the patients who received treatment was 14 to 73; 44 patients were given honey bee venom, 23 were given both venoms, however, a differentiation with regard to age (particularly in children) has not been made in all treatment groups. The gender of patients between 14 and 18 years of age was not mentioned. Valuable data on hymenoptera-venom-therapy in children cannot be extracted from this study. Therefore its relevance to the specific requirements of the article 45 procedure cannot be assessed.

As the investigators discussed critically, little attention has been paid to joint/muscle pain which in this study led to cessation of IT in some cases. Although the investigators suspected this to be an immune disease, they were unable to confirm it. This is also of relevance for the paediatric population.

Request for supplementary information:

In the study from Hays and co-workers (2005) the potential induction of autoimmune reactions (joint and muscle symptoms) was discussed critically. When re-organising the PSUR data this aspect should be considered as well.

Response ALK:

Using MedDRA PT arthralgia, arthropathy, musculoskeletal pain and myalgia (21 events all in adults) these terms constitute below 3% of the reactions reported in adults, thus the post-marketing data do not support this to be an issue of concern.

Rapporteur's comment:

The issue has been solved.

3. Anwendungsbeobachtung mit VENOMENHAL bei Patienten mit einer Allergie gegen Bienen- oder Wespengift. (Non-investigational study with VENOMENHAL in patients with allergy to bee or wasp venom).

➤ **Description: An original article published in 2000**

Sager A. LUFT 2000; 5: 823-828

➤ **Methods**

• **Objective(s)**

The objective of this study was to compare the safety of VENOMENHAL containing an allergenic extract of bee or wasp venom with alternative immunotherapy in adult patients suffering from an IgE-mediated sensitisation against bee or wasp venom. The study was not interventionally designed but rather documenting the treating physician's daily situation.

• **Study design**

Controlled prospective open study.

• **Study population /Sample size**

In total, 137 patients were treated; 106 patients were treated with VENOMENHAL[®] and 31 were treated with alternative immunotherapy. 12 patients received bee venom and 125 patients received wasp venom. Diagnosis and main criteria for inclusion: Allergic reaction following bee or wasp stings proven by patient's history, skin prick test and RAST: 3
Age in years VENOMENHAL (4 - 78), other treatments (12 - 68).

• **Treatments**

VENOMENHAL was administered subcutaneously according to a 5-day rush protocol with increasing doses of the allergenic extract.

Duration of treatment: 4 to 10 days

Reference therapy, dose and mode of administration: Commercially available standard immunotherapy to be administered within a rush protocol according to the specific scientific information provided by the manufacturer.

• **Outcomes/endpoints**

Primary safety criterion:

Any systemic or local reaction following each injection had to be documented. All measurements to resolve the adverse events had to be documented.

Secondary safety criterion was the duration to reach the 100 µg dose.

The safety of VENOMENHAL[®] was compared with the safety of alternative standard immunotherapy.

- **Statistical Methods**

Multicentre observational cohort study in hospitalised patients.

The sum of local reactions was calculated in both treatment groups as area under the curve (AUC) and compared using the Wilcoxon rank-sum test. The change of the size of local reactions in relation to the increasing dose applied was evaluated and compared for both groups by the Wilcoxon rank-sum test. The difference in change of the size of local reactions between both treatment groups was evaluated using the two-tailed Wilcoxon rank-sum test with a significance level of $\alpha=0,05$ with the statistical hypothesis H_0 : there is no difference of AUC for both treatment groups.

➤ **Results**

- Recruitment/ Number analysed

222 patients planned, 137 patients analysed; 137 patients were treated totally; 106 patients were treated with VENOMENHAL[®] and 31 were treated with alternative immunotherapy. 12 patients received bee venom and 125 patients received wasp venom. **5/125 wasp-venom treated patients were children. 2 children have been treated with bee-venom**

- Baseline data

None stated.

- Efficacy results

None stated.

- Safety results

The mean value for the AUC of local reactions was 207.1 cm² in the VENOMENHAL[®] group and 338.4 cm² in the group treated with alternative immunotherapy. Only in patients treated with VENOMENHAL no local reactions were observed in 7 cases at all. The co-variance analysis revealed no statistically significant difference between both treatment groups. The change of the size of local reaction in relation to the increasing dose was of special interest for the last two days of the rush protocol since for VENOMENHAL[®] the dose applied was much higher compared to alternative immunotherapy. Despite being statistically not significant there was a trend even in favour for VENOMENHAL[®] resulting in less and smaller local reactions. There were 16 systemic reactions reported: 15 in the VENOMENHAL[®] group and 1 in a patient treated with Reless[®], 9 systemic reactions were of grade 2 (8 VENOMENHAL[®] and 1 Reless[®]) and 7 of grade 1. The mean time to reach the 100 µg dose was in both treatment groups 6.9 days. In conclusion the available data verify that VENOMENHAL[®] can be applied safely within the recommended rush protocol of 5 days. The observed local reactions were even less and smaller compared to alternative immunotherapy.

No specific conclusions regarding the paediatric population were drawn from this investigation.

Rapporteur's comment:

This study has been performed on both groups of hymenoptera venom-allergic subjects, honey bee- and Vespula venom-allergic individuals. 125 patients received wasp venom, 12 bee venom.

Age has been documented (4-78 yrs for VENOMENHAL-treated patients), however, generally, no details are provided as to how many children of a certain age (of what gender) have received bee venom or wasp venom. According to the critical expert opinion no specific conclusions regarding paediatric population were made.

Valuable data on hymenoptera-venom-therapy in children cannot be extracted from this study. Therefore, its relevance to the specific requirements of the article 45 procedure cannot be assessed. Minor aspect: The alternative immunotherapy has not been specified.

4. A comparison of the diagnostic properties of VENOMENHAL® and Reless®.

➤ **Description: not given**

➤ **Summary as provided by the MAH**

The aim of this study was to find out how VENOMENHAL® Bee and Wasp compare with other commercially available venom preparations. In this study, 20 patients aged 15 to 69 years were tested (15 males and 5 females). In total 19 patients were treated with Wasp venom. One of them was 15 years old. From the results of this study the MAH concluded that VENOMENHAL®Bee and VENOMENHAL®Wasp are safe and efficient for diagnostic purposes. However, no conclusions regarding children are possible.

(P.J. Blaauw A A comparison of the diagnostic properties of VENOMENHAL® and Reless® AMKlh95432)

5. A clinical study on the safety and efficacy of VENOMENHAL®.

➤ **Description: not given**

➤ **Summary as provided by the MAH**

The aim of the study was to establish the efficacy and safety of VENOMENHAL®. Overall forty patients with IgE mediated hypersensitivity to insect stings were included in the study and treated with VENOMENHAL® or Reless® for one year. From them, 25 patients aged 14 to 73 years were treated with VENOMENHAL®Wasp. The actual number of children treated with VENOMENHAL®Wasp was not reported. From the results of this study it had generally been concluded that VENOMENHAL® is safe and efficient and comparable to other commercially available venom extracts. However, no specific conclusions regarding children were drawn.

(2 L. Jager, W. Wenz. A clinical study on the safety and efficacy of VENOMENHAL® AMKlh95435[klinstud])

6. Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial

➤ **Description: An original article published in 2000**

Reimers A, Hari Y, Müller U in Allergy 2000; 55: 484-488.

Methods

- **Objective(s)**

Pretreatment with antihistamines has been proposed as an effective way to reduce the side effects of allergen immunotherapy. Only a few controlled studies on this method are available.

- **Study design**

A double-blind, placebo-controlled trial of the preventive effect of a new, potent, well tolerated, and non-sedating antihistamine, fexofenadine, during ultrarush immunotherapy with bee venom (BV).

- **Study population /Sample size**

57 adult patients aged [16 to 72] with history of a moderate to severe systemic allergic reaction to a honeybee sting, All had a positive intracutaneous skin test to BV at 10^{-4} g/l (0.1 µg/l) or less, and BV-specific serum IgE antibodies (\geq CAP class 1).

- **Treatments**

Treatment and premedication. All patients were started on immunotherapy with BV (Pharmalgen, ALK Hørsholm, and Denmark) according to an ultrarush protocol. A cumulative dose of 111.1 µg divided into six subcutaneous injections was administered over 3.5 h under intensive care conditions on day 1. Further injections were given on days 8 (2 x 50 µg with an interval of 30 min) and 22 (100 µg), and thereafter at intervals of 4 weeks (100 µg maintenance dose). All injections were applied subcutaneously to the outside of the upper arm, at least 10 cm above the elbow. Patients were randomly assigned to pretreatment with either fexofenadine 180 mg or placebo, one tablet on the evening before and one tablet 2 h before the first injection on days 1, 8, 22, and 50. On day 80, the injection was performed without pretreatment. The cumulative dose of BV from day 1 to 50 was added up to a maximum of 411.1 µg per patient. If the protocol had to be changed to Alutard, it was added up to the last dose of aqueous venom applied.

- **Outcomes/endpoints**

I.c. skin tests with BV (Pharmalgen, ALK Hørsholm, and Denmark) were performed as described previously. The lowest concentration resulting in a weal of 5 mm or more in diameter with erythema was defined as the end-point concentration (EPC). BV-specific IgE was estimated by the CAP System of Pharmacia-Upjohn (Uppsala, Sweden). The incidence of systemic allergic side-effects and the extension and duration of local reactions also was an endpoint.

- **Statistical Methods**

Clinical parameters between groups were compared by unpaired t-test, and diagnostic parameters by the Mann-Whitney U-test. The incidence of systemic allergic side-effects and the extension and duration of local reactions were compared by chi-square test; mean cumulative dose, rescue medication, and local reaction scores by the Mann-Whitney U-test.

➤ **Results**

- Recruitment/ Number analysed

57 study patients were originally included, 3 had to be excluded later. Two received systemic corticosteroid treatment for unrelated disease one curious patient opened her capsule.

The age range was 16 to 72 years.

- Summary of results

Local reactions: On day 1, extended local reactions of more than 6 cm in diameter were observed more frequently in placebo-treated than in fexofenadine treated patients ($\chi^2=4.31$, $P<0.05$). Local reactions also lasted longer in placebo patients. The combined extension/duration score was significantly lower for the fexofenadine group (Mann-Whitney U-test, $P<0.025$). The extension of local reactions on days 1-80: In both groups, local reactions decreased fast. The between-group difference at day 1 was no longer present afterwards. The small increase on day 80 in the fexofenadine group was not significant.

Systemic reactions: No significant difference between groups was found in the overall occurrence of subjective and/or objective systemic allergic symptoms that were observed in 12 patients on fexofenadine and nine on placebo. The majority of these reactions, eight in the fexofenadine and five in the placebo group, occurred already on day 1. Analysis according to type of reaction showed that typical cutaneous histamine-related symptoms such as pruritus, urticaria, and angioedema were significantly reduced under fexofenadine pretreatment ($\chi^2=4.55$, $P<0.05$), whereas other skin, gastrointestinal, respiratory, and cardiovascular symptoms occurred at similar frequencies in both groups. The rescue medications used in the two groups: Most side-effects could be dealt with by oral antihistamines alone. While the mean cetirizine dose per patient was somewhat higher in the placebo group, this difference did not reach significance. Other medications were used so infrequently that statistical analysis seemed useless. Adherence to treatment protocol: The cumulative dose of 111.1 μg on day 1 was reached in 26 of 28 patients on fexofenadine and 25 of 26 on placebo; the total cumulative dose of 411.1 μg was reached on day 50 by 24 on fexofenadine and 23 on placebo. The mean cumulative dose for days 1-50 was 371 μg for fexofenadine and 383.3 μg for placebo. In four patients in the fexofenadine group and in one in the placebo group, it was decided to change the schedule to weekly injections with Alutard. None of the treatment adherence parameters reached statistical significance between groups.

Table 1. Clinical data of study patients

| Parameter | Pretreatment with | | P value |
|--|---------------------|----------------|---------|
| | Fexofenadine (n=28) | Placebo (n=26) | |
| Sex (F/M) | 10/18 | 16/10 | NS |
| Age (years), arithmetic mean value (range) | 37.04 (16-64) | 38.5 (17-72) | NS |
| Grade of systemic reaction | | | |
| I-II | 2 | - | |
| III-IV | 26 | 26 | NS |
| Skin test (-log EPC) arithmetic mean value | 5.43 | 5.54 | NS |
| Specific IgE (kU _A /l) geometric mean value | 7.98 | 10.06 | NS |

Rapporteur's comment:

Age has been documented, however, generally, no details are provided as to how many children of a certain age have received bee venom or wasp venom. Only an age-range of 16 to 72 yrs was provided. The investigators considered 16-year-old patients as adults. No information was given on gender. Valuable data on *Apis mellifera*-venom therapy in children cannot be extracted from this study. Therefore, its relevance to the specific requirements of the article 45 procedure cannot be assessed.

7. Another study on honey bee- and Vespula-venom therapy as provided by HAL Allergy upon request

A clinical study on the safety and efficacy of VENOMENHAL[®]

The aim of the study was to establish the efficacy and safety of VENOMENHAL[®]. In total, forty patients with IgE-mediated hypersensitivity to insect stings were included in the study and treated

with VENOMENHAL[®] or Reless[®] for one year. Out of these, 15 patients aged 15 to 53 years were treated with VENOMENHAL[®] Bee.

The actual number of children treated with VENOMENHAL[®] Bee was not reported. From the results of this study it was concluded that VENOMENHAL[®] is safe and efficient and comparable to other commercially available venom extracts. However, no specific conclusions regarding children were possible.

Rapporteur's comment:

The study has been performed on both groups of hymenoptera venom allergic subjects, honey bee- and *Vespula*-venom-allergic individuals. Age has been documented, however, generally, no details are provided as to how many children of a certain age have received bee venom or wasp venom. No information on gender has been provided.

Valuable data on *Apis mellifera*-venom-therapy in children cannot be extracted from this study. Therefore, its relevance to the specific requirements of the article 45 procedure cannot be assessed.

8. A table representing a synopsis of published studies on honey bee- and Vespula-venom therapy as provided by ALK Abello upon request

Alutard[®], Aquagen[®] and Pharmalgen[®] Literature Search, Venom

| Reference | Material /Species | Treatment Groups | Dose Regime | Comments/conclusions |
|--|---|---|---|---|
| Arnaldo E et al. Ann Allergy Asthma & Immunol. 2006;97:92-97 | Hymenoptera venom (<i>Vespula</i>) allergic patients. N = 106 M/F = 68/38 Age 12-78 years | Induction/Maintenance Depot/Depot: N = 34 M/F = 26/8 Age 41 years (12-77) Aqueous/Aqueous: N = 43 M/F = 27/16 Age 51 years (17-77) Aqueous/Depot: N = 29 M/F = 15/14 Age 39 years (15-78) | Aquagen (A) and Alutard SQ (D) Up-dosing: 6-week, 14-dose induction Maintenance: Monthly (3-8 weeks) 100µg per dose for at least 3 years | No dose differentiation adults/children No specific comments on dose use or adverse events in children. No pre-medication. Systemic reactions occurred with similar frequency in depot and aqueous cohorts. Local adverse events occurred more frequently in the aqueous cohort. Early events (< 1 hour) occurred more frequently in the aqueous cohort |
| Bimbaum J et al. Clin Exp Allergy 2003;33:58-64 | Hymenoptera allergic patients. N = 51 children Age ≤ 15 years: Age 9.20 years ± 3.41 N = 207 adults Age 40.62 years ± 14.00 Bee: Children/Adults: 17/73 Yellow jacket: Children/adults: 38/148 Wasp: Children/Adults: | Bee: N = 69 Yellow jacket: N = 123 Children/Adults: 38/148 Wasp: N = 3 Yellow jacket and Wasp: N = 42 Yellow jacket and Bee: N = 17 Bee , Yellow jacket and Wasp: | Unspecified Ultra-rush up-dosing All groups: Day 1: 0.1µg, 1µg, 10µg and 20µg at 30 min interval, 30µg and 40µg at 60 min interval Booster: Day 15 50µg and day 45 100µg. Maintenance: 100µg monthly | No dose differentiation adults/children. No pre-medication. Systemic reactions: Mild (grade 1-2) cutaneous symptoms, localized urticaria, and/or angio-oedema, and/or erythema : Children/Adults: 3/21 Severe (grade 3-4): Children/Adults: 3/6 Severe cardiovascular symptoms were not seen in children. Significant correlation between ultra-rush up-dosing and severe reactions in children as well as in adults. |

| | | | | |
|---|---|--|--|---|
| | 10/39 | N = 4 | | Higher incidence of severe reactions in Bee immunotherapy compared to Wasp. The safety of venom immunotherapy is comparable in children and adults. |
| Brehler R et al J Allergy Clin Immunol 2000;105:1231-1235 | Hymenoptera allergic patients N = 1055 Age 2-84 years | Bee: N = 122 M/F = 70/52 Age 37 years (4-76) Wasp N = 933 M/F = 428/505 Age 39 years (2-84) | Alutard SQ Group 1: N = 317: 20 inj 7-9 days Group 2: N = 335: 10-14 inj 3-6 days Group 3: N = 403: 9 inj. In 2 days | No dose differentiation adults/children. No specific comments on use in children. Risk factors for occurrence of adverse events: - Woman > men - Age > 50 years |
| Cadario G et al J Invest Allergol Clin Immunol 2004;Vol.14(2):127-133 | Hymenoptera allergic patients N = 45 sensitized to Apis mellifera or Vespula spp | Depot: N = 27 M/F = 19/8 Age 39.0 years (15-68) Aqueous: N = 18 M/F = 15/3 Age 42.6 years (19-69) | Alutard SQ Depot: 15 weekly inj: 0.02µ, 0.04µ, 0.08 µ, 0.2 µ, 0.4µ, 0.8µ, 2 µ, 4µ, 8µ, 10µ, 20µ, 40µ, 60µ, 80µ and 100µ Maintenance: 100µ monthly Pharmalgen Aqueous, 8 week 12-dose induction. Visit 1: 0.01µ and 0.1µ with 30 min interval Visit 2: 1µ and 2µ with 30 min interval Visit 3: 4µ and 8µ with 60 min interval Visit 4: 10µ and 20µ with 60 min interval Visit 5, 6, 7: 40µ, 80µ and 100µ, respectively Maintenance: 100µ monthly | No dose differentiation adults/children. No specific comments on use in children Less frequent side effects with depot compared to aqueous (No of patients with side effects 6/27 versus 9/18). |

| | | | | |
|---|---|--|---|---|
| Carballada F et al. J Invest Allergol Clin Immunol 2003;Vol. 13(1):43-49 | Hymenoptera allergic patients N = 241 M/F = 88/153 Age 41.9 years (4-81) N = 7 < 14 years | Bee: N = 208 Wasp: N = 33 | Pharmalgen Up-dosing: One or twice weekly 9 inj: 0.1µ, 1µ, 5µ, 10µ, 20µ, 40µ, 60µ, 80µ and 100µ Maintenance: 100µ monthly (200µ in two patients) | No dose differentiation adults/children. No specific comments on use in children |
| Haye R, Dosen LK. Clinical and Molecular Allergy 2005, 3:12 | N = 315 M/F = 151/164 Age 41.1 years (14-73) | Bee: N = 44 Wasp: N = 248 Bee and Wasp: N = 23 | Pharmalgen Rush up dosing: Start dose 0.1µ, doubling every 2 hours for 3 days. Day 4 and 5, slow up-dosing aiming for ≥ 50µ as last inj. Further dose increase once weekly to 100µg Maintenance: 100µg every 6 week. | No information on doses provided. No specific comments on use in children |
| Lang R, Hawranek J Invest Allergol Clin Immunol 2006;Vol. 16(4):224-231 | N = 192 M/F = 121/71 Age 31.7 years (3-78) | Bee: N = 95 M/F = 61/34 Age 25.1 years (5-68) Yellow jacket: N = 64 M/F = 38/26 Age 39.9 years (5-76) Bee and Yellow jacket: N = 33 M/F = 22/11 Age 34.8 years (3-78) | Bee and Yellow jacket, ALK-Abelló Up-dosing: Up to 3 rd day 6µg Increase every 1 to 2 weeks to Maintenance dose 100µg after 7 to 14 weeks. Maintenance 100µg every 4 to 8 weeks for > 3 years | No dose differentiation adults/children. No specific comments on use in children Results concern outcome of field sting, not adverse events related to VIT. |
| Lerch E, Müller UR J Allergy Clin Immunol; Vol 101:606-612 | N = 385 N = 200 re-stung | Bee: N = 120 M/F = 85/35 Age 38.9 years (11-70) Vespula: N = 80 M/F = 49/31 Age 43.4 years (12-78) | Pharmalgen Up-dosing not provided Maintenance 100µg every 4 weeks | No dose differentiation adults/children. No specific comments on use in children Results concern outcome of field sting, not adverse events related to VIT. |

| | | | | |
|--|--|---|---|--|
| Mosbech H, Müller U Allergy 2000;55:1005-1010 | N = 840 M/F = 457/383 Age 5-77 years N = 782 treated with one venom extract alone N = 58 treated with two venom extracts | Bee: N = 212 Vespula: N = 557 Polistes: N = 13 | Venom Depot/aqueous solution ALK-Abelló Up dosing: Weekly Clustered Rush/ultra rush Mixed Doses not provided Maintenance: 100µg (min 20µg, max 200µg) | No dose differentiation adults/children. No specific comments on use in children No pre-medication |
| Poli F et al' Allergol et Immuno pathol 2001; 29(5): 191-196 | Patients sensitized to Vespula N = 36 M/F = 20/16 Age 6-73 years 3 children 6, 111 and 16 years | | Alutard SQ Up dosing: Gradual increase to 50 µg Maintenance: 50 µg after 2, 3 and 4 weeks, and hereafter every 4 weeks | No dose differentiation adults/children. No specific comments on use in children |

| | | | | |
|---|--|---|---|--|
| Quercia O et al Allergy and Asthma Proceedings 2006, Vol 27:151-158 | Sensitized to Hymenoptera venom N = 70 M/F = 58/12 Age 41.4 years (12-76) | Aqueous Rush: N = 20 M/F = 16/4 Age 42.1 years (18-75) Aqueous Cluster: N = 20 M/F = 16/4 Age 43.8 years (28-76) Depot Cluster: N = 30 M/F = 26/4 Age 41.4 years (12-68) | Aquagen/Alutard SQ <u>Rush dose</u> aqueous: Day 1: 0.01µg, 0.1µg, 1µg and 2µg Day 2: 4µg, 6µg, 10µg and 20µg Day 3: 40µg and 40µg Day 4: 60µg, 50µg and 50µg <u>Cluster dose</u> aqueous : Week 1: 0.01µg, 0.1µg, 3µg and 6µg Week 2: 20µg Week 3: 40µg Week 4: 60µg Week 5: 40µg and 40µg Week 6: 50µg and 50µg <u>Cluster dose</u> depot: Week 1: 0.03µg, 0.1µg, 0.3µg and 1µg Week 2: 2µg and 4µg Week 3: 10µg and 20µg Week 4: 40µg and 40µg Week 5: 50µg and 50µg Maintenance: 100µg week 2, week 3 and week 4 and hereafter every 4 weeks | No dose differentiation adults/children. No specific comments on use in children Occurrence of side effect was significantly lower in the up-dosing phase of the depot cluster compared to aqueous rush. Side effects in the maintenance phase were lower in the depot cluster as compared to aqueous rush group. |
| Roll A et al J Investig Allergol Clin Immunol 2006; Vol. 16(2):79-85 | Sensitized to Hymenoptera venom N = 67 M/F = 44/23 Age 40.4 years (15-66) Age 0-20 years: N = 9 | Bee: N = 20 Wasp: N = 34 Bee and Wasp: N = 13 | Pharmalgen Ultra rush µg induction: Day 1: 0.01µg, 0.1µg, 10µg and 20µg at 30 min interval, followed by 30µg and 50µg at 60 min intervals Day 7 and day 14 : 100µg Booster every 4-6 weeks: 100µg | No dose differentiation adults/children. Age had no influence on side effects. |

| | | | | |
|---|---|--|--|---|
| Schiavino D et al Anna Allergy Asthma & Immunol. 2004;92:409-413 | Sensitized to Hymenoptera venom N = 57 M/F = 40/17 Age 11-68 years Children: 11 years: N = 2 12 years: N = 2 15 years: N = 2 16 years: N = 1 M/K = 6/1 | Bee: N = 9 M/K = 7/2 Age 11-62 years Wasp: N = 48 M/F = 30/15 Age 11-68 years | Pharmalgen Ultra rush induction: Day 1: 0.1µg, 1µg, 10µg, 20µg, 30µg and 40µg with 30 min interval Day 15: 100µg Maintenance: 100µg once a month | No dose differentiation adults/children. No specific comments on use in children |
| Sturm G et al J Allergy Clin Immunol 2002, Vol. 110:928-933 | Sensitized to Hymenoptera venom N = 101 M/F = 57/44 Age 4-71 years | Bee: N = 51 M/F = 31/21 Age 5-71 years Yellow jacket: N = 47 M/F = 25/22 Age 4-61 years European hornet venom N = 2 M/K = 1/1 Age 41-61 years | Aquagen/Alutard SQ Rush induction: Day 1: 0.001µg, 0.01µg, 0.1µg, 0.2µg and 0.4µg Day 2: 0.8µg, 1µg, 2µg, 4µg and 6µg Day 3: 8µg, 10µg, 20µg, 40µg and 60µg Day 4: 80µg and 100µg | No dose differentiation adults/children. No specific comments on use in children |
| Wenzel J et al Allergy 2003;58:1176-1179 | N = 178 Age 41.18 years (10-76) | Wasp one cycle: N = 149 Wasp 2 cycles: N = 3 Bee: N = 24 Wasp and Bee: N = 2 | ALK Scherax Rush induction: Day 1: 0.000002µg, 0.000002µg, 0.00002µg, 0.0002µg Day 2: 0.002µg, 0.004µg, 0.008µg, 0.02µg Day 3: 0.04µg, 0.08µg, 0.02µg | No dose differentiation adults/children. No specific comments on use in children |
| Winther L et al Clinical and Experimental Allergy 2006; 36:254-260 | N = 1038 M/F = 522/516 Age 35 years (7-84) SIT > 2 with 1709 allergens Subgroup: N = 625 Age 37.7 years (8-84) M/F = 319/306 SIT = 1 allergen (686) | | Alutard Q Individual modified cluster regimens Centre 1: 7 weeks and 14 injections Centre 2: 11 weeks and 14 injections Centre 3: 8 weeks and 10 injections | No dose differentiation adults/children. No specific comments on use in children |
| Wyss et al Allergy 1993;48:81-86 | Hymenoptera allergic patients N = 55 Age 43 years (10-75) M/F = 17/18 | Bee: N = 17 Yellow jacket: N = 13 Bee and Yellow jacket: N = 5 | Alutard Q Conventional up-dosing: 17 injections Maintenance: 1 injection every 4 weeks | No dose differentiation adults/children. No specific comments on use in children |

Rapporteur's comment:

Total age range of these studies: 0 to 84 years of age

Total number of children treated: at least 68

Number of children treated with wasp venom: at least 41

Number of children treated with bee venom: at least 17

The majority of published studies have been performed on both groups of hymenoptera venom-allergic subjects, honey bee- and *Vespula*-venom-allergic individuals. Age has been documented, however, generally, no details are provided as to how many children of a certain age have received bee venom or wasp venom. Mostly, no information on the gender was provided.

There was no separation in the presentation of efficacy and safety for paediatric patients (versus adult patients). Sometimes not even a differentiation between hymenoptera venoms as such was made.

There was no dose differentiation between adults and children.

No specific comments on use in children were documented. Sometimes, not even information on doses was provided.
The MAH discussed these tabulated additional data extracted from original publications critically with regard to their information on the paediatric population. However, these publications had not been submitted as copies of the original papers.
Valuable data on hymenoptera-venom-therapy in children cannot be extracted from these studies. Therefore its relevance to the specific requirements of the article 45 procedure cannot be assessed.

Request for supplementary information:

The information given in the table (tabulated list of published studies) has not been submitted as original publications, which should be provided by the MAHs.

Response ALK:

The publications have been submitted.

Rapporteur's Comment:

The issue has been solved

General request for supplementary information for studies 1, 2, 3, 6, 7 and tabulated summary (8)

In the submitted publications and study reports, age (age range) has been documented, however, generally, no details were provided as to how many children of a certain age and gender have received bee venom or wasp venom. The MAH should provide detailed information on age and gender in the paediatric population.

- a. The summarized publications and study reports do not allow evaluating efficacy and safety for paediatric patients separately, not even with regard to adult patients who mostly have been investigated in parallel in the same study.*

Response HAL:

A comparison of the diagnostic properties of VENOMENHAL® and Reless®. No further data were available for review besides these mentioned in the clinical expert statement previously submitted.

Response ALK:

ALK has submitted the available publications on *Vespula* spp. venom for allergen specific immunotherapy. However, none of these have been initiated and/or sponsored by ALK. Therefore it is not possible to provide more detailed information regarding:

- 2a) Separation of efficacy and safety for paediatric patients versus adult patients
- 2b) Differentiation between hymenoptera venoms
- 2c) Dose differentiation between adults and children
- 2d) Information on doses

Vespula spp.venom product have obtained marketing authorisation and launched in several countries since the early 1980-ties. Efficacy of ALK *Vespula* spp.venom has according to the Applicant been demonstrated in the publications although the above requests raised by the Rapporteur have not been addressed. There is nothing to suggest that the safety profile in children, when used at the same doses as in adults, differs from that of adults. For support for the safety profile the Applicant refers to the response to question nr. 3 regarding the post marketing safety data.

Furthermore, allergen-specific immunotherapy was first used nearly one hundred years ago and remains in use worldwide for treatment of allergic diseases. It has been recognised as the only effective treatment for type I allergic diseases when the appropriate quantities of allergens are used.

ALK has submitted the available publications on *Vespula* spp venom for allergen specific immunotherapy. However, none of these have been initiated and/or sponsored by ALK. Thus ALK has no access to raw data / clinical databases, and it is not possible to provide more detailed information

b. Sometimes not even differentiation between hymenoptera venoms as such was documented.

Response HAL:

A clinical study on the safety and efficacy of VENOMENHAL®(2). No further data were available for review besides these mentioned in the clinical expert statement previously submitted.

Rapporteur's comment:

It is acknowledged that the MAH have tried to provide additional (partially published) information.

c. There was no dose differentiation between adults and children or an according comment given.

d. Sometimes, not even information on doses was provided.

Response HAL:

There is no dose differentiation between adults and children. Both in children and adults, the aim of specific immunotherapy is to increase the tolerability of an allergen, by administering increasing amounts of the particular allergen with a recommended maintenance dose of 100 µg. See also the answer to question 7/8.

The aim of the VENOMENHAL® Bee/Wasp Observational Cohort Study was to compare the safety of VENOMENHAL® containing an allergenic extract of bee or wasp venom with alternative immunotherapy in patients suffering from an IgE mediated sensitization against bee or wasp venom. A total of 137 (106 allocated to VENOMENHAL® following a rush protocol and 31 to alternative immunotherapies) patients were included in this study. The results of the study showed no differences in the extent of the local reactions between VENOMENHAL® and the comparator group.

In total, 16 systemic reactions (9 grade 2 and 7 grade 1) were reported, 15 of them in relation to VENOMENHAL® and 1 with the comparator. It was concluded that VENOMENHAL® is safe when applied with a rush protocol. The paediatric population included 2 girls and 6 boys aged between 4 and 17 years. Six of them were children treated with VENOMENHAL® Wasp and two with VENOMENHAL® bee. Among these children, six experienced local reactions at the injection site. None of the children included in the study reported a systemic reaction following one of the administered injections. Most commonly reported local reactions were redness erythema/redness. Two paediatric patients withdrew from the study without providing a specific reason. Specific data on the paediatric population included in this study is provided in Table 1 below.

| Patient ID | 202 | 404 | 408 | 1006 | 1108 | 1115 | 705 | 5 |
|---|-------------------------|-----------------------------------|-------------------------|---|----------------------|--------------------------|---|------------------------------|
| Age at baseline (years) | 4 | 17 | 16 | 17 | 9 | 12 | 17 | 17 |
| Gender | Male | Female | Male | Female | Male | Male | Male | Male |
| Treatment | Bee | Wasp | Wasp | Bee | Wasp | Wasp | Wasp | Wasp |
| Injection number (dose)/Local reactions with diameter > 5cm | Inj 26 (100µg): Redness | Inj 14 (20 µg): 8 x 11 cm | Inj 12 (8 µg): 7 x 8 cm | Inj 7 to 18 (0.4 to 80 µg): Redness, swelling | Inj 17 (70 µg): 6 cm | Inj 13 (10 µg): 8 cm | None | None |
| Treatment for local reaction | None | Inj. 14, 17, 19: Lisino 1 tablet. | Inj 12 Lisino 1 tablet | None | None | Inj 14 Fenistil 1 tablet | Tavegil 1 Tbl Inj 8,11,14 Fenistil Gel Inj. 9,12 | None |
| SAE | None | None | None | None | None | None | None | None |
| Comment | | | | | | | Withdraw. No reason given | Withdraw. No reason given |

Abbreviations: ID: identification number; Inj: injection; (S)AE: (Serious) Adverse Event

Table 1. Clinical data paediatric patients included in VENOMENHAL® Bee/Wasp Observational Cohort Study(3)

Rapporteur's Comment:

It is acknowledged that study data on children is sparse.

Other Database-Results

a) ALK safety database

In the ALK safety database the reports that concerns patients below 18 years constitute 10 % of the total number of reports for patients exposed to the ALK products venom immunotherapy and venom diagnostics.

From the post-marketing safety data there is no signal that the safety profile in children when used at the same doses as in adults, differs from that of adults.

In established use the same up-dosing schedules and maintenance doses have been used in both adults and children. The only established difference between adults and children is that a smaller size of local reaction should lead to a consideration about possibly lowering the dose for the next injection and this is included in the listings of relevant sections of National SmPCs submitted in 2008.

PSUR Pharmalgen 2008:

There have been 2 reports of adverse events in children during the reporting period.

The patients in the 2 reports were 6 and 10 years old.

PSUR on prick-test solutions (Soluprick)

There have been no reports of adverse events in patients aged 18 years or younger during the reporting period.

PSUR 2003-2008 Alutard und Aquagen:

No differentiation was made between adults and children.

PSUR 2007-2008 Alutard und Aquagen:

There has been no case with wasp venom in the Injury, Poisoning and Procedural Complications SOC.

There have been 0 reports of adverse events in children aged 12 years or younger during the reporting period.

PSUR august 2008-January 2009:

In the period from data lock point of the most recent PSUR (31 July 2008) and up to 25 January 2009, ALK-Abelló has received 9 non-serious ADR reports for Alutard SQ and Aquagen SQ.

The 9 reports do not change the overall conclusions made in the PSURs. Of the 9 reports, 6 were on Alutard SQ and 3 on Aquagen. Amongst the non-serious events two occurred in children.

Rapporteur's comment:

A table of PSUR data was submitted providing valuable data on the treated paediatric population. However, its time range in years has not been documented.

As PSUR data are available, a synopsis of all available data on the paediatric population should be provided, preferably as a table similar to the submitted one.

No information was provided as to the severity of the symptoms in the 2 reports about Pharmalgen. Were they serious? Have they resolved completely?

Request for supplementary information:

In addition, it is advised to provide a synopsis of all PSUR data available and present them in a tabulated format. Although submission of PSURs and safety reviews are recommended but not compulsory according to Art. 45-requirements, this is nevertheless strongly suggested. The data exist in MAH data bases, which are probably the most reliable source of safety data on the paediatric population available.

Response ALK:

As requested all events (731 for adults and 87 for children) for the ALK venom products (*Apis mellifera* and *Vespula* spp) are now presented by distribution on MedDRA System Organ Class (SOC) and Preferred Term (PT), for children and adults respectively in appendix 2. The data apply to 312 suspected ALK venom products in 299 individuals. They are based on all reports available to the MAH, from 1995 to April 2009.

The age range for the reported cases related to children was from 5 to 16 years, 33% are females and 67% are males. Regarding severity of the adverse events 22% of reports in paediatric patient were assessed as serious and 35% of reports in adults. In general the adverse events resolved. Only one case of anaphylactic reaction in 39 year old female with a medical history of cardiac problems had a fatal outcome.

Overall the events reported are very similar in the two age groups, and the only trend is that the most severe systemic reactions primarily are reported in adults; Anaphylactic shock is only reported in adult patients (25); however both the number of anaphylactic shock and anaphylactic reaction (17/4) is fairly low in both adults and children

The most common event for both age groups is 'urticaria' (50/8)

Reporting frequencies in children cannot be calculated since information about how sales is distributed on adults and children respectively is not available for venom products.

Please note that there were some mistakes in the calculation in the table on page 2 in the clinical expert statement submitted in April 2009. A revised table has been submitted together with this response.

Rapporteur's Comment:

In total, more information on safety in children was provided showing that children do not seem to be at a higher risk to develop severe side effects when compared with adults.

In the ALK Abello expert opinion it is not clearly stated whether the table regarding PSUR data is a synopsis of the attached report from January 2008 to December 2008. This should be clarified.

Response ALK:

The period covered in the table on page 2, clinical expert statement as well as the data listed in Appendix 2 of this document includes all cases in the ALK database entered from 1995 to April 2009.

A number of PSURs were attached with the clinical expert statement. Individual reports were included for Pharmalgen (Jan 08 – Dec 08) and Alutard SQ/Aquagen SQ (Aug 05 – Jan 09) venom products. The PSURs include ALK venom products from all species (*Apis mellifera* and *Vespula* spp.) for the respective formulations.

Rapporteur's Comment:

The data documented in the respective table have been re-calculated and additional data has been added.

The issue has been solved.

b) HAL Allergy safety database

Post marketing surveillance data

A. For an overview of the post-marketing data of VENOMENHAL[®] Bee, reference is made to the Periodic Safety Update Report (PSUR). The PSUR covers the analysis period of March 2002 up to February 2007. Within this report, nine adverse events were reported in six patients. Three patients were treated with VENOMENHAL[®] Bee, one of them aged 8 years.

All adverse events were considered as listed and not serious. After February 2007 no additional events in relation to VENOMENHAL[®] Bee have been reported to HAL Allergy.

Sales figures in Germany from 1999 up until March 2009 showed that 225 children received at least one prescription of VENOMENHAL[®] Bee. No additional adverse events were reported in association with VENOMENHAL[®] Bee in the same period besides those already mentioned in the current section of this document.

Until now there is very limited clinical data regarding the use of VENOMENHAL[®] Bee in children. However, according to the MAH, post-marketing data suggest that VENOMENHAL[®] Bee has been used in children without safety concerns for more than 10 years.

B. For an overview of the post-marketing data of VENOMENHAL[®] Wasp, reference is made to the Periodic Safety Update Report (PSUR).

The PSUR covers the analysis period of March 2002 up to February 2007. Within this report, nine adverse events were reported in six patients. Three patients were treated with VENOMENHAL[®] Wasp, two of them were aged 10 and 12 years respectively. All adverse events were considered as listed and not serious.

After February 2007 an additional event in relation to VENOMENHAL[®] Wasp has been reported to HAL Allergy, however, it concerned a 48-year-old female patient.

A more detailed look into the sales figures in Germany showed that from 1999 up until March 2009, more than 200 children received at least one prescription of VENOMENHAL[®] Wasp. No additional adverse events were reported in association with VENOMENHAL[®] Wasp in the same period besides those already mentioned.

Rapporteur's comment:

A synopsis of all available PSUR data has not been submitted. Generally, no details are provided as to how many children of a certain age have received bee venom or wasp venom. No information on the gender has been given.

Request for supplementary information:

In addition, it is advised to provide a synopsis of all PSUR data available and present them in a tabulated format. Although submission of PSURs and safety reviews are recommended but not compulsory according to Art. 45-requirements, this is nevertheless strongly suggested. The data exist in MAH data bases, which are probably the most reliable source of safety data on the paediatric population available.

Response HAL:

An overview of the post-marketing data of VENOMENHAL® Bee/Wasp, reference is made to the Periodic Safety Update Report (PSUR) from March 2007. The PSUR covers the analysis period of March 2002 up to February 2007. Within this report, nine adverse events were reported in six patients. From all the reported adverse events, three patients were aged less than 18 years. Full details are provided in the Table 2:

| VENOMENHAL | Age | Sex | Adverse Event | Seriousness | Labelling |
|------------|-----|-----|---------------------|-------------|-----------|
| Bee | 8 | F | Hypersensitivity | Not serious | Labelled |
| Wasp | 10 | M | Dyspnea | Not serious | Labelled |
| | | | Angioneurotic edema | Not serious | Labelled |
| | | | Swollen tongue | Not serious | Labelled |
| Wasp | 12 | F | Dyspnea | Not serious | Labelled |
| | | | Angioneurotic edema | Not serious | Labelled |

Table 2. Data concerning paediatric patients presented in the PSUR covering period from March 2002 up to February 2007.

After February 2007 no new adverse events in association with VENOMENHAL in children have been reported.

Rapporteur's Comments:

In total, more information on safety in children was provided showing that children do not seem to be at a higher risk to develop severe side effects when compared with adults.

The MAHs propose not to alter the following wording of the SmPCs.

SmPC-wording concerning paediatric population (Citations)

ALK Abello:

Posology and method of administration

Dose reduction: In the event of swelling at the injection site for one or more days after the injection, the following dose reduction is recommended:

| Maximum diameter of swelling | | |
|------------------------------|----------|--|
| Children | Adults | Recommended dose reduction |
| < 5 cm | < 8 cm | Continue upward titration according to Table 1 |
| 5-7 cm | 8-12 cm | Repeat dose last given |
| 7-12 cm | 12-20 cm | Reduce dose to dose given the time before last |
| 12-17 cm | > 20 cm | Reduce dose to dose given 2 times before last |
| >17 cm | | Reduce dose to dose given 3 times before last |

Pharmalgen wasp venom, powder and solvent solution

“Local reactions

If swelling occurs at the injection site, the next dose is reduced in relation to the table below.

In cases of *immediate local reactions*, no further injections are administered the same day.

It should be noted that late reactions may occur within 24 hours of the injection in the form of diffuse swelling”.

| Maximum diameter of swelling | | |
|------------------------------|--------|----------------------------|
| Children | Adults | Next dose |
| < 3 cm | < 5 cm | Continue up dosing |
| 3-7 cm | 5-8 cm | Repeat last dose |
| 7-9 cm | > 8 cm | Reduction of dose, 1 stage |

After dose reduction, the patient must be up dosed again.

The extent of the dose reduction depends on the severity of the allergic reaction, time interval, etc.

The safety of the patient is paramount and if in doubt, it is recommended that the dose be reduced.

Rapporteur’s comment:

No particular SmPC wording was provided for the diagnostic test allergen (prick-test solution – e.g. ALK 802 Wasp Venom, ALK 802 Bee venom)

No age limit given in English SmPC wordings.

ALK Scherax:

Wording of the German SmPC and Package leaflet (Fach-und Gebrauchsinformation):

“...Was ist bei Kindern und älteren Menschen zu berücksichtigen? Eine feste untere Altersgrenze lässt sich nicht generell bestimmen. Die Behandlung von Kindern unter 5 Jahren sollte nur nach strenger Indikationsstellung erfolgen.“

HAL Allergy

SmPC VENOMEMHAL:

“...The end dose of 1 ml of the 100 µg venom/ml concentration level is the target and should be reached if possible, even in highly sensitised patients and children. Exceptionally the tolerance threshold may be reached at a lower dose (e.g. 0.7 ml of the 100 µg venom/ml concentration level). This dose must then be considered as the end dose, at which maintenance treatment may

commence.”...” When treating children, the dose must always be reduced in accordance with the patient’s age and body weight.”

Wording of the German SmPC and Package leaflet (Fach- und Gebrauchsinformation)

“...Die Erhaltungsdosis von 1 ml in der Konzentrationsstufe 100 µg Insektengift/ml sollte angestrebt und möglichst erreicht werden, auch bei hoch sensibilisierten Patienten und Kindern.“

„...Kinder unter 5 Jahren: Es liegen keine ausreichenden Erfahrungen über die Anwendung bei Kindern unter 5 Jahren vor.“

Rapporteur’s comment:

The SmPC (-wording) relevant for the paediatric population used in all Member states except Germany has not been provided in English by all the MAHs.

Therefore a detailed overall assessment with regard to the wording of points 4.1 to 4.4 of the SPC was not possible.

Request for supplementary information:

There is a contradiction in the wording of the SmPC for VENOMENHAL: A reduction of the dose in accordance with the patient’s age and body weight is recommended, but it is also advised to reach a maintenance dose of 100 µg in children. Additionally, no example has been provided with regard to the calculation of the dose based upon age and body weight.

Response HAL:

After reviewing the data currently available on VENOMENHAL Bee/Wasp, there is insufficient evidence to support the statement “When treating children, the dose must always be reduced in accordance to the patient’s age and body weight.”

Both in children and adults, the aim of specific immunotherapy is to increase the tolerability of an allergen, by administering increasing amounts of the particular allergen. In general, the recommended maintenance dose is 100 µg. According to the susceptibility of every patient this dose is achieved after two to three weeks following a rush protocol or four to six weeks following a conventional protocol. In consequence, this statement in the Core SmPC was replaced by “The tolerability of the individual patient is the main determinant in the achievement of the maintenance dose. Therefore, dose adjustments may be necessary in case of occurrence of side effects”.

Rapporteur’s comment:

The assessor agrees. The issue has been solved.

The MAHs are requested to:

- *Provide a list of the current wording (in English) relevant for paediatric patients in the SmPCs from all MS in which wasp and bee venom is an approved medical compound (including section 4.1).*
- *In case of divergences between Member States, the MAHs should provide a proposal in English for a harmonised SPC text in sections 4.1 to 4.4 and 5.2 (if considered applicable) regarding paediatric use. The proposal should be justified by supporting data from the MAHs’ databases and relevant published data*

Response HAL:

A list of the current wording relevant for paediatric patients in the SmPCs was provided.

HAL proposed the following wording for the relevant sections:

4.2.2

“...The end dose of 1ml of the 100 µg venom/ml concentration level is the target and should be reached if possible, even in highly sensitized patients and children. Exceptionally the tolerance threshold may be reached at a lower dose (e.g. 0.7 ml of the 100 µg venom/ml concentration level). This dose must then be considered as the end dose, at which maintenance treatment may commence...”

4.3 Contraindication

4.3.2

- Children below the age of 5.

4.8

“...The tolerability of the individual patient is the main determinant in the achievement of the maintenance dose. Therefore, dose adjustments may be necessary in case of occurrence of side effects”.

Response ALK:

The requested list was provided in an appendix with the answer document for the Alutard SQ products and for the Pharmalgen products. However, since there are a lot of national SmPCs they are not listed here in the assessment report.

ALK did not provide a proposal for a harmonised SmPC wording relevant for paediatric patients, due to the following reason:

“The venom immunotherapy products in question have obtained national approvals in a number of the EU member states. The “EU work sharing project assessment of paediatric data of existing products” is an initiative from CMDh in Europe and the intention for this initiative is not to be a harmonisation process for SPC and PIL throughout Europe

In addition no new clinical findings relevant to children have been presented during this process.

As stated in the executive summary of the PdAR that “The allergen-specific –immunotherapy was first used nearly one hundred years ago and remains in use worldwide for treatment of allergic rhinitis, asthma and the life-treating hymenoptera venom allergy. It has been recognized as the only effective treatment for type I allergic diseases when the appropriate quantities of allergens are used”.

Conclusion

It is the opinion of ALK-Abelló that the current national SmPCs are adequate to ensure safety and efficacy for the paediatric patients and that no harmonisation of the SmPCs and PILs in Europe is considered necessary.

In addition, it should be noted that the data from post-marketing surveillance included in the response document confirm the safe use of the products with the current label in children as well as in adults.”

Rapporteur’s comment:

A new and adapted proposal for the wording was explicitly required, however was only provided by one applicant (HAL). The justification of ALK not to provide a harmonised SmPC wording relevant for paediatric patients cannot be accepted because a harmonised SmPC in the European Community is a key issue in the Article 45 procedures.

According to the proposed wording of HAL and the provided SmPCs of ALK the Rapporteur provided the Wording for the SmPC in Section II. Recommendation of this Assessment Report.

Comments from The Netherlands (Day 85):

Specific comments (as required)

Following the comment from The Netherlands the MAH of Pharmalgen (Alk-Albello) was requested to comment on the differences between the Danish SmPC and the Dutch SmPC.

Citation of the Danish SmPC:

Pharmalgen wasp venom, powder and solvent solution

“Local reactions

If swelling occurs at the injection site, the next dose is reduced in relation to the table below.

In cases of immediate local reactions, no further injections are administered the same day.

It should be noted that late reactions may occur within 24 hours of the injection in the form of diffuse swelling”.

| Maximum diameter of swelling | | |
|------------------------------|--------|----------------------------|
| Children | Adults | Next dose |
| < 3 cm | < 5 cm | Continue up dosing |
| 3-7 cm | 5-8 cm | Repeat last dose |
| 7-9 cm | > 8 cm | Reduction of dose, 1 stage |

end of citation –

Response ALK:

The MAH pointed out that *Vespula* spp venom (e.g. Pharmalgen) has obtained national marketing authorisations in the EU and that the above SmPC citation is from the SmPC approved by the Danish Medicine Agency only.

Due to the nature of the SmPC approvals in the national marketing authorization procedures, with communication with each national competent authority, differences between the SmPC text of the Danish nationally approved and the Dutch SmPC text is unavoidable, reflecting the national clinical practice and not necessarily prompted by data available.

Rapporteur’s comment:

Differences in the SmPCs between the national SmPCs of one MAH are not the scope of this procedure as long as no paediatric issues are concerned. However, a harmonised SmPC in the wording relevant for paediatric patients in the European Community is a key issue in the Article 45 procedures, the Rapporteur provided a proposal for a harmonised SmPC concerning this issue in Section II of this Assessment Report.

9. Discussion on clinical aspects at day 90

Mostly, no discussion of paediatric aspects was provided in the original submitted studies or by the MAH who submitted the publications as study data. However, one MAH discussed additional tabulated data extracted from original publications critically with regard to their information on the paediatric population. The majority of published studies have been performed on both groups of hymenoptera venom-allergic subjects, honey bee- and *Vespula*-venom-allergic individuals. Age has been documented, however, generally, no details are provided as to how many children of a certain age have received bee venom or wasp venom. Mostly, no information on the gender was provided. There was no separation in the presentation of efficacy and safety for paediatric patients (versus adult patients), sometimes not even a differentiation between hymenoptera venoms as such was

made. There was no dose differentiation between adults and children. No specific comments on use in children were documented. Sometimes, not even information on doses was provided.

Valuable data on hymenoptera-venom-therapy in children cannot be extracted from the original provided study data. Therefore its relevance to the specific requirements of the article 45 procedure cannot be assessed without supplementary information. As not all available SmPCs had been provided, a final assessment cannot be made.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

V.1. Rapporteur's Overall Conclusion and Recommendation at Day 90

➤ Overall conclusion

Presentation of the data in the original submission was insufficient. Therefore, a recommendation for a harmonized SmPC-wording could not be provided due to the lack of data.

➤ Recommendation

Based on the data submitted, the MAHs were requested to provide additional information as part of this worksharing procedure. The questions and responses were included in the section IV. The MAH have submitted additional information as well as a critical discussion together with the SmPC-wording in different countries

As harmonization of the paediatric relevant wording is to be achieved, the Rapporteur suggests an alteration as documented above under II. Recommendation.

V.2 Discussions on SmPC/PIL following circulation of the final Day 90 Assessment Report

Day 115 Comments of The Netherlands authority:

The Dutch MEB does not agree with the overall conclusions of the Rapporteur.

There are differences within the EU member states regarding the exact wording of the SmPC. Harmonization of the paediatric related information in the SmPCs throughout Europe was intended in the worksharing procedure. The Dutch MEB do not agree with the proposals of the Rapporteur because the proposed changes of the SmPC are not supported by the submitted studies and/or submitted publications. The Rapporteur refers to not further mentioned position papers of Research Groups.

In the Dutch SmPC of Alutard a stronger decrease in dosing is advised after swelling observed during the previous injection: Children > 17 cm maximum diameter swelling after the previous injection dose-reduction given 4 times before last in stead of the proposed 3 times before last.

In the NL children younger than 5 years are contra-indicated.

Aim of the paediatric worksharing was that on submitted data a decision can be made to adjust the SmPC. Based on the review of the presented paediatric data the Rapporteur considers that from the available data and supplementary information as provided by the MAHs it is not possible to prove efficacy of insect venom immunotherapy in children.

Therefore no specific indication for the use in children can be given and an extension to use honey bee or wasp venom in the paediatric population younger than 5 years is not considered acceptable, since there is

no evidence that Wasp and Bee venom is safe under age 5 years and if dosing scheme of the older children is applicable to children aged younger than 5 years.

It is not made clear to which specific position papers of Research Groups the RMS is referring to.

On the basis of the data the NL does not support harmonization of the SmPC.

Answer of the Rapporteur to the Day 115 NL Comments

Following the day 115 comments by Dutch MEB which could not agree with the overall conclusions the Rapporteur provided the following comments.

Section 4.2

The dose reduction scheme of the Dutch SmPC of Alutard to which the Dutch MEB refers was not included in the documentation ALK send as answer to the list of questions. In appendix 5 “Current wording relevant for the paediatric patients in the SmPC’s from MS” of ALK’s answer for the SmPC of Alutard SQ Venoms in the Netherlands “No information” is mentioned to this issue. In most other MS the table as now proposed by the Rapporteur is used. Therefore, the Rapporteur used this table as proposal for harmonization. In a harmonization procedure it may be useful to harmonize the paediatric relevant SmPC wording on the basis of the majority of SmPCs and not on the basis of one SmPC in one MS especially if the SmPCs are as in this case is of the same MAH.

NL is therefore asked to agree on the SmPC wording based on the majority of SmPCs.

Section 4.3

According to the relevant position papers an absolute contra-indication for children younger than 5 years is not justified.

According to U. Müller and H. Mosbech (EAACI Position Paper: Immunotherapy with Hymenoptera venoms. Allergy, 1993, 48 (Suppl. 14), 37-46) “during infancy and early childhood, severe allergic reactions are extremely rare, and fatalities are almost unknown. Only in heavily exposed cases with severe reactions, as in the children of beekeepers, should VIT be started before the age of 5.” Thus no contra-indication is given for children younger than 5 years in this position paper. This is also reflected in the position paper of the DGAKI (Deutsche Gesellschaft für Allergologie und klinische Immunologie (German Society for Allergology and Clinical Immunology) (Rueff, F et al. Diagnose und Therapie der Bienen- und Wespenigallergie. Allergo J 2000;9:458-472) which states that for children between the age of 2 – 16 years with systemic reactions restricted to the skin it is - due to a study of Valentine et al. (The value of immunotherapy with venom in children with allergy to insect stings. N Engl J Med 1990;323:1601-3) - unlikely that in following stings the reaction is worse. However, if it cannot be excluded that the reaction may be worse in a following sting the question of performing immunotherapy with insect venom should be discussed with the parents under consideration of the individual risk factors and the behaviour of the child. Thus according to this position paper, the treatment of children below an age of 5 years is possible if severe systemic reactions including respiratory and cardiovascular symptoms occur and even in children with systemic reactions restricted to the skin in individual cases.

Moreover, the agreed revised **Standard PIP for allergen products for specific immunotherapy** <http://www.ema.europa.eu/pdfs/human/paediatrics/73760509en.pdf> define for insect venom preparations the study population as “children and adolescents **from 3 years to less than 18 years**” ...” with a documented clinical history of **severe** systemic reaction, including respiratory and cardiovascular symptoms, to <insect> stings”. Thus, in the opinion of the Rapporteur a contraindication for children below the age of 5 years is not justified but venom immunotherapy should only be performed in selected and justified cases in this age group. Therefore the warning “Special care should be given to the risk-benefit assessment with regard to treatment of children younger than 5 years of age.” was given.

NL is therefore asked to agree on the conclusions of the Rapporteur.

Answer of the Dutch MEB on the Rapporteur's answer to the Day 115 NL comments

For the above mentioned procedures the NL is not prepared to endorse the Rapporteur's conclusion. Harmonization is not the aim of the paediatric procedure; normally a decision will be based on data solely.

On the matter of harmonization of section 4.2 (dose-reduction):

An immediate local reaction > 17 cm after the previous injection leads in the NL to 4 steps backwards while in other countries this is 3 steps. The limited data do not support revision of the SPC and the NL is not prepared to follow the Rapporteur.

On the matter of harmonization of section 4.3 (Contra-indication < 5 years):

In this procedure no safety data is available. Since both anaphylactic shock in children < 5 years is almost unknown and more safety data are needed NL is not prepared to remove the absolute contra-indication < 5 years on the basis of this procedure.

No comments were received from further Member States.

V.3 Member states Final Day 120 Overall Conclusion and recommendation

➤ Overall conclusion

1) Rapporteurs Position

The presentation of the data was partly insufficient but it does not seem that the submitted publications and non-published studies reveal so far unknown aspects. Details on pre-clinical studies were provided by the MAHs as requested.

It is acknowledged that the MAH have provided information on specific immunotherapy as far as possible and that study data on children are sparse.

Therefore, from the available data and supplementary information as provided by the MAHs it is not possible to prove efficacy of insect venom immunotherapy in children. Therefore no specific indication for the use in children can be given and an extension to use honey bee or wasp venom in the paediatric population younger than 5 years is not possible.

However according to the published relevant position papers (see under VI and references) and the agreed Standard PIP for allergen products for specific immunotherapy <http://www.ema.europa.eu/pdfs/human/paediatrics/73760509en.pdf> which includes children below 5 years in the study population for insect venom preparations the Rapporteur considers that an absolute contra-indication for children younger than 5 years is not justified but venom immunotherapy should only be performed in selected and justified cases in this age group. Therefore the warning "Special care should be given to the risk-benefit assessment with regard to treatment of children younger than 5 years of age." is given.

In conclusion, based on the review of the available data/publications and the different SmPCs the Rapporteur recommends that all SmPCs contain the harmonised paediatric related statements as presented under "Recommendation"

2) Position of NL

No consensus could be reached with NL. The Dutch MEB does not agree with the proposals of the Rapporteur because the proposed changes of the SmPC are not supported by the submitted studies and/or submitted publications. Harmonization is not the aim of the paediatric procedure; normally a decision will be based on data solely. On the basis of the data the NL does not support harmonization of the SmPC

➤ Recommendation

1) Rapporteurs Recommendation

Typ IB variation is recommended for following changes in the SmPCs/PILs **except for the medicinal products authorised in NL**.

4.1 Therapeutic Indication

No change

4.2 Posology and method of administration

Recommended Dose-reduction in case of local adverse events:

| Maximum diameter of swelling | | Recommended dose reduction |
|------------------------------|----------|---|
| Children | Adults | |
| < 5 cm | < 8 cm | Continue upward titration according to up-dosing schedule |
| 5-7 cm | 8-12 cm | Repeat dose last given |
| 7-12 cm | 12-20 cm | Reduce dose to dose given the time before last |
| 12-17 cm | > 20 cm | Reduce dose to dose given 2 times before last |
| >17 cm | | Reduce dose to dose given 3 times before last |

4.3 Contraindication

Treatment of children younger than 5 years should not be stated as contraindication

4.4 Special warning and precaution for use

Special care should be given to the risk-benefit assessment with regard to treatment of children younger than 5 years of age. For children ≥ 5 years of age clinical data of efficacy are sparse, however data on safety do not reveal a higher risk as for adults.

Proposed paediatric related wording in the PIL:

None of the MAH provided data on the current PILs nor on a harmonised PIL.

In the case that a PIL is provided, the rapporteur proposes the following wording:

WHAT XXX IS AND WHAT IT IS USED FOR

No specific indication for children can be made.

BEFORE YOU TAKE XXX

Take special care with XXX

Special care should be given if children younger than 5 years of age are treated with XXX. The physician must carefully weigh the risk-benefit for the individual child.

For children ≥ 5 years of age clinical data of efficacy are sparse, however data on safety do not reveal a higher risk as for adults

HOW TO TAKE XXX

The Dosage Reduction Scheme in case of swelling after the administration should be as proposed for the SmPC.

No differentiation on the recommended up-dosing or maintenance dose between adults and children should be made.

2) Recommendation of NL

No change of the SmPC/PIL

References

A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS

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Golden DBK, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. *N Engl J Med* 2004;351:668-674.

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VI. MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Wasp venom Products

| MAH | MS | Name of the medicinal product | Strength | Pharmaceutical form | Active Substance | Marketing Authorisation Number |
|----------------|----|---|----------------|---|------------------|--------------------------------|
| ALK-Abelló | DK | Alutard SQ | 100000 SQ | Suspension for injection | Vespula spp. | 59/526/92-S |
| ALK-Abelló | FR | Pharmalgen Extrait allergenique de venin de guepe | 100µg/ml | Powder and Solvent for solution for injection | Vespula spp. | NL12945 |
| ALK-Abelló | PL | Alutard SQ | 100000 SQ-U/ml | Suspension for injection | Vespula spp. | (6177) 3595 |
| ALK-Abelló | PL | Pharmalgen Hymenoptera venoms | 100µg/ml | Powder and Solvent for solution for injection | Vespula spp. | (5359) 0104 |
| ALK-Abelló | SE | Alutard SQ Getinggift | 100000 SQ-U/ml | Suspension for injection | Vespula spp. | 90161 |
| ALK-Abelló | UK | Pharmalgen Wasp Venom | 100µg/ml | Powder and Solvent for solution for injection | Vespula spp. | PL 10085/0004 |
| ALK-Abelló A/S | CZ | Alutard SQ | 100000 SQ-U/ml | Suspension for injection | Vespula spp. | 59/526/92-S/C |
| ALK-Abelló A/S | DK | ALK 802 Hvepegift (Alutard SQ) | 100000 SQ-U/ml | Suspension for injection | Vespula spp. | 12497 |
| ALK-Abelló A/S | DK | Pharmalgen Hveps | 100µg/ml | Powder and Solvent for solution for injection | Vespula spp. | 10284 |
| ALK-Abelló A/S | EE | Alutard SQ Hymenoptera Venoms | 100000 SQ-U/ml | Suspension for injection | Vespula spp. | 318600 |
| ALK-Abelló A/S | FI | Alutard SQ Hyönteismyrkyt 802 Ampiaisen myrkky (Vespula spp.) | 100000 SQ-U/ml | Suspension for injection | Vespula spp. | 10407 |
| ALK-Abelló A/S | PL | Alutard SQ | 100000 SQ-U/ml | Suspension for injection | Vespula spp. | (6177) 3595 |
| ALK-Abelló A/S | SK | Alutard SQ | 100000 SQ | Suspension for injection | Vespula spp. | 59/526/92-S |

| MAH | MS | Name of the medicinal product | Strength | Pharmaceutical form | Active Substance | Marketing Authorisation Number |
|-------------------------------|----|---|--|---|------------------------|--------------------------------|
| ALK-Abelló bv | BE | Pharmalgen Wasp (Wespengif, Venin de guépe, Wespengift) | 100 µg/ml | Powder and Solvent for solution for injection | Vespula spp. | 3040 IE 8 F 17 |
| ALK-Abelló bv | NL | Alutard SQ Venoms | 100000 SQ-U/ml | Suspension for injection | Vespula spp. | RVG 16490 |
| ALK-Abelló bv | NL | Pharmalgen | 100µg/ml | Powder and Solvent for solution for injection | Vespula spp. | RVG 16436 |
| ALK-SCHERAX Arzneimittel GmbH | DE | ALK-depot SQ Wespengift | 100 SQ-U/ml 1000 SQ-U/ml 10000 SQ-U/ml 100000 SQ-U/ml | Suspension for injection | Vespula spp. | 113a/91a-113a/91d |
| ALK-SCHERAX Arzneimittel GmbH | DE | Reless Wespengift | 100µg/ml | Powder and Solvent for solution for injection | Vespula spp. | 209a/89 |
| HAL Allergie GmbH | DE | VENOMENHAL [®] Wespe | 120 µg/vial | Lyophilisate and solvent for subcutaneous injection | Lyophilised wasp venom | 192a/96b |
| Halcis | RO | VENOMENHAL [®] Viespe | 120 µg/vial | Lyophilisate and solvent for subcutaneous injection | Lyophilised wasp venom | 7921/2006/01-02 |

Honey Bee Venom products

| MAH | MS | Name of the medicinal product | Strength | Pharmaceutical form | Active Substance(s) | Marketing Authorisation Number |
|----------------|----|--|----------------|---|-----------------------|--------------------------------|
| ALK-Abelló bv | BE | Pharmalgen Bee (Bijengif, Venin d'abeille, Bienengift) | 100µg/ml | Powder and Solvent for solution for injection | Apis mellifera | 3040 IE 7 F 17 |
| ALK-Abelló A/S | CZ | Alutard SQ | 100000 SQ-U/ml | Suspension for injection | Apis mellifera | 59/526/92-S/C |
| ALK-Abelló | DK | Alutard SQ | 100000SQ | Suspension for injection | Apis mellifera | 59/526/92-S |

| MAH | MS | Name of the medicinal product | Strength | Pharmaceutical form | Active Substance(s) | Marketing Authorisation Number |
|----------------|----|---|----------------|---|---------------------|--------------------------------|
| ALK-Abelló A/S | DK | ALK 801 Bigift (Alutard SQ) | 100000 SQ-U/ml | Suspension for injection | Apis mellifera | 12491 |
| ALK-Abelló A/S | EE | Alutard SQ Hymenoptera Venoms | 100000 SQ-U/ml | Suspension for injection | Apis mellifera | 318600 |
| ALK-Abelló A/S | FI | Alutard SQ Hyönteismyrkyt 801 Mehiläisen myrkky (Apis melifera) | 100000 SQ-U/ml | Suspension for injection | Apis mellifera | 10407 |
| ALK-Abelló | FR | Pharmalgen Extrait allergenique de venin d'abeille | 100µg/ml | Powder and Solvent for solution for injection | Apis mellifera | NL12924 |
| ALK-Abelló bv | NL | Alutard SQ Venoms | 100000 SQ-U/ml | Suspension for injection | Apis mellifera | RVG 16490 |
| ALK-Abelló bv | NL | Pharmalgen | 100µg/ml | Powder and Solvent for solution for injection | Apis mellifera | RVG 16436 |
| ALK-Abelló | PL | Alutard SQ | 100000 SQ-U/ml | Suspension for injection | Apis mellifera | (6177) 3595 |
| ALK-Abelló | PL | Pharmalgen Hymenoptera venoms | 100µg/ml | Powder and Solvent for solution for injection | Apis mellifera | (5359) 0104 |
| ALK-Abelló | SE | Alutard SQ Bigift | 100000 SQ-U/ml | Suspension for injection | Apis mellifera | 90155 |
| ALK-Abelló A/S | SK | Alutard SQ | 100000SQ | Suspension for injection | Apis mellifera | 59/526/92-S |
| ALK-Abelló | UK | Pharmalgen Bee Venom | 100µg/ml | Powder and Solvent for solution for injection | Apis mellifera | PL 10085/0003 |

| MAH | MS | Name of the medicinal product | Strength | Pharmaceutical form | Active Substance(s) | Marketing Authorisation Number |
|-------------------------------|----|-------------------------------|--|---|-----------------------|--------------------------------|
| ALK-SCHERAX Arzneimittel GmbH | DE | ALK-depot SQ Bienengift | 100 SQ-U/ml 1000 SQ-U/ml 10000 SQ-U/ml 100000 SQ-U/ml | Suspension for injection | Apis mellifera | 112a/91a-112a/91d |
| ALK-SCHERAX Arzneimittel GmbH | DE | Reless Bienengift | 100µg/ml | Powder and Solvent for solution for injection | Apis mellifera | 208a/89 |
| HAL Allergie GmbH | DE | VENOMENHAL® Biene | 120 µg/vial | Lyophilisate and solvent for subcutaneous injection | Lyophilised bee venom | 191a/96b |
| HAL Allergy BV | EE | VENOMENHAL® Biene | 120 µg/vial | Lyophilisate and solvent for subcutaneous injection | Lyophilised bee venom | 402002 |
| HAL Allergy BV | HU | VENOMENHAL® Méh | 120 µg/vial | Lyophilisate and solvent for subcutaneous injection | Lyophilised bee venom | OGYI-T-8398/01 |
| HAL Allergy BV | PL | VENOMENHAL® Pszczoła | 120 µg/vial | Lyophilisate and solvent for subcutaneous injection | Lyophilised bee venom | 97022P |
| Halcis | RO | VENOMENHAL® Albina | 120 µg/vial | Lyophilisate and solvent for subcutaneous injection | Lyophilised bee venom | 7971/2006/01-02 |