

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

**Leti Pharma:
Depigoid D. pteronyssinus + Milben-Mix
Leti prick and provocation test**

**Allergopharma Joachim Ganzer KG:
Novo-Helisen Depot (D. farinae, D. pteronyssinus, D. mix)
Novo-Helisen Oral (D. farinae, D. pteronyssinus, D. mix)
Intracutaneous Test, Skin Prick test, Provocation Test**

**ALK Abello:
Alutard SQ, (D. farinae, D. pteronyssinus; D. mix)
Aquagen SQ (D. farinae, D. pteronyssinus, D. mix)
Soluprick SQ (D. farinae, D. pteronyssinus, D. mix)**

DK/W/0004/pdWS/001

Rapporteur:	Denmark
Start of the procedure (day 0):	13 May 2009
Date of this report:	22 July 2009
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Date re-start procedure (day 90):	10 February 2010
Deadline for CMS's comments (day 115):	07 March 2010
Finalisation procedure (day 120):	12 March 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Depigoid D. pteronyssinus + Milben-Mix, Leti prick and provocation test Novo-Helisen Depot, Novo-Helisen Oral Intracutaneous Test, Skin Prick test, Provocation Test Alutard SQ, Aquagen SQ, Soluprick SQ
INN (or common name) of the active substance(s):	Dermatophagoides pteronyssinus Dermatophagoides farinae
MAH (s):	Leti Pharma Allergopharma Joachim Ganzer KG ALK Abello
Pharmaco-therapeutic group (ATC Code):	V01AA03
Pharmaceutical form(s) and strength(s):	Solution for injection, prick-test or provocation test and oral formulation.
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I. RECOMMENDATION

Mite allergy in children is common and do occur in early childhood. An International panel of experts, on behalf of the World Health Organisation in the recent “Allergic Rhinitis and Its Impact on Asthma” paper accepted sublingual immunotherapy for routing clinical use in adults and children with the same indications as for subcutaneous immunotherapy and that the WHO statement acknowledge that the use of sublingual immunotherapy in children with respiratory allergies is evidence-based (Paediatric Allergy Immunol 2005; 16: 519-26; BMC Fam Pract 2008; 9: 59). However the quality of most of the earlier conducted clinical trials have been questioned as a Cochrane review focusing on the efficacy of subcutaneous injection specific immunotherapy in patients with seasonal rhinitis (pollen allergy) no accepted studies were conducted exclusively in children and further no specific outcomes were reported in the younger population (Cochrane Database Syst Rev 2007; (i): CD001936).

The efficacy and safety of the products under question in the pediatric population could not be proven by the submitted documents. The PSUR data and the data of open post marketing surveillance studies allow only the assumption that for children up to now no higher risk than for adults was shown. Rapporteur has in agreement with a MS made a recommendation for texts to be implemented in the relevant SmPCs and PLs. The recommendation is included in section V of this report.

II. INTRODUCTION

Immunotherapy with allergen extracts containing *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* or a mixture of these house dust mites has been used in daily clinical practise for years in order to reduce symptoms associated with allergic rhinoconjunctivitis and bronchial asthma or to reduce the risk of developing asthma in children with allergic rhinoconjunctivitis due to these allergens via an immune modulation mechanism. Prior to initiation of immunotherapy extracts of *D. pteronyssinus*/*D. farinae* are used in prick-test in order to verify the diagnosis. Similarly the allergen extracts may be available in solution for nasal or bronchial provocation.

Three MAHs submitted a number of paediatric studies for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* 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 was provided by all MAH.

In addition the MAHs have addressed the point for clarification raised by CMS (DE & NL) in a sufficient way.

The MAHs stated that the submitted paediatric studies do not influence the benefit risk for the products containing *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* and that there is no consequential regulatory action.

All products presented by the MAHs are intended for use in children as allergic rhinoconjunctivitis and allergic asthma caused by dust mites are common in children, and the SPC wording of section 4.1 and 4.2 are related to the paediatric use of the medical products.

III. SCIENTIFIC DISCUSSION

III.1 Information on the pharmaceutical formulation used in the clinical studies

Leti Pharma: Depigoid D. pteronyssinus + Milben-Mix, suspension for subcutaneous injection and Leti prick- and provocation test.

Allergopharma Joachim Ganzer KG: Novo-Helisen (D. farinae, D. pteronyssinus, D. mix) suspension for subcutaneous injection, Novo-Helisen (D. farinae, D. pteronyssinus, D. mix) oral solution, Intracutaneous Test, Skin Prick test, Provocation Test.

ALK Abello: Alutard SQ, (D. farinae, D. pteronyssinus; D. mix) suspension for subcutaneous injection,

Aquagen SQ (D. farinae, D. pteronyssinus, D. mix) suspension for subcutaneous injection and oral sublingual solution and

Soluprick SQ (D. farinae, D. pteronyssinus, D. mix) solution for prick-test,

Studies submitted by Allergopharma (Merck Group Compagny) is the same as for Allergo-Merck Depot Acaros.

Studies submitted by ALK Abello is the same as for ALK-Scherax (DE).

III.2 Non-clinical aspects

Non-clinical studies were not provided by the MAHs.

Discussion on non clinical aspects

The dust mite allergen extracts have been used in clinical practise for several years in a significant numbers of patients and therefore non-clinical studies are not needed.

III.3 Clinical aspects

III.3.1. Introduction

Leti Pharma has submitted the following clinical studies for evaluation (see table below)

Study type / Duration	Description	Report number/Study code	Number of children included
Efficacy and Safety 1 year	Phase IV, randomized, double-blind, placebo-controlled study to evaluate the efficacy of depigmented and polymerised extract of <i>D. pteronyssinus</i> and <i>D. farinae</i> in 66 patients older than 12 years of age with allergic asthma due to IgE mediated hypersensitivity to <i>D. pteronyssinus</i> .	101-PG-PSC-52	Total no. of patients: 64, from those 22 children: <ul style="list-style-type: none"> • 5 between 13 – 14 yrs old • 17 between 15-17 yrs old
Safety 1 year	Phase IV, prospective observational study to evaluate the safety of using standardised depigmented and polymerized allergen extracts (mites and/or pollens) in an ultra-rush schedule of build-up phase in patients with allergic rhinoconjunctivitis and/or asthma due to sensitization to mites and/or pollens. Ultra-rush build-up phase was conducted without premedication or hospitalization.	1300-PG-PSC-119	Total no. of patient: 1068, from those: 199 children vaccinated with Depigoid Dpt or Depigoid mites: <ul style="list-style-type: none"> • 11 between 3 – 5 yrs old • 72 between 6 – 11 yrs old • 116 between 12--17
Safety and Efficacy 6 months	Phase IV, observational cohort study to assess the efficacy and safety of Depigoid in allergic patients with allergic rhinoconjunctivitis, rhinitis and / or bronchial asthma.	Depilate	Total: 768 patients, from those: 210 children <ul style="list-style-type: none"> • 113 between 5 and 11yrs old • 97 between 12- 18 yrs old
Efficacy 6 months	Open label pilot study to assess clinical changes and objective laboratory parameters and evaluate the benefit of house dust mites SCIT in 25 patients with atopic dermatitis with IgE-mediated sensitization against HDM.	No code available since this was an investigator initiated trial	Total: 25 patients <ul style="list-style-type: none"> • 1 < 10 years old • 2 between 10-18 yrs.

In addition the MAH has finalized a multicentre, retrospective study in pollen or mite allergenic children assessing the efficacy and safety of immunotherapy with the Depigoid vaccines. No data has yet been submitted from this study.

Allergopharma has submitted 42 clinical studies (see table below):

Paediatric Studies Submitted to Article 45 of the Regulation No 1901/2006
Dermatophagoides farinae and pteronyssinus

Allergopharma Joachim Ganzer KG, D-21462 Reinbek, Germany Feb. 2008

Product	Study Title	Study Number / Publication	File Identification	Remarks
Novo-Helisen Depot	Retrospective Analysis about Hypersensitivity with Novo-Helisen Depot	Frank E. Allergologie. 1994; 17 (4): 154-159	4810	Age of patients: 9-81 years 494 patients
Novo-Helisen Depot	Successful specific subcutaneous immunotherapy (SCIT) with non-modified semi-depot pollen and mite preparations	Ullrich D, Thum-Oltmer S, Mussler S, Jaeschke B. Allergo J. 2007; 16:193-198	21374	Age of patients: 5-71 years
Novo-Helisen Depot	Post-marketing surveillance study: Novo-Helisen [®] Depot – preparations for mite allergy (November 2002 – December 2005)	Company Report: Post-marketing study 2002-2005	Post-marketing study 2002-2005	NHD Mites in patients with perennial allergic rhinitis, conjunctivitis and possibly asthma symptoms. So far only statistical analysis, publication scheduled
Novo-Helisen oral	Post-marketing surveillance study: Novo-Helisen [®] oral – preparations for mite allergy (September 1998 – October 2001)	Company Report: Post-marketing study 1998-2001	Post-marketing study 1998-2001	Age of patients: 6-61 years
Novo-Helisen oral mite	Retrospective data collection: Novo-Helisen [®] oral mite preparations (July – August 2004)	Company Report: Retrospective data collection: 2004 (year)	Retrospective data collection 2004	Age of patients: 6-80 years
Novo-Helisen oral	What can oral hyposensitization achieve?	Frank E. Allergologie. 1995; 18 (6): 239-245	4461	Results of retrospective analysis about hypersensitivity with Novo-Helisen oral mites Age of patients: 2-37 years

Product	Study Title	Study Number / Publication	File Identification	Remarks
Novo-Helisen Depot	Post marketing Surveillance Study: Novo-Helisen [®] Depot Cluster Schedule (February 2004 through January 2005)	Company Report: Post-marketing study 2004-2005	NHD Cluster Schedule (02.04-01.05)	Age of patients: 5-72 years 175 patients of which 76 were treated with Novo-Helisen Depot mites
Novo-Helisen Depot	Post-marketing surveillance study on specific immunotherapy (SIT) with Novo-Helisen Depot Pollen and Mite Preparations in a cluster dose-escalation-regimen: safety data	Company Report: Post-marketing study 2006-2007	Post marketing surveillance studies (06.07)	Age of patients: 4-65 years 65 patients of which 11 were treated with Novo-Helisen Depot mites
Novo-Helisen Depot	In vitro evaluation of allergen-specific basophils activation may be helpful for assessment of the effectiveness of long-term parenterals and oral specific immunotherapy (SIT) in asthmatic children	Bartkowiak-Emeryk M et al. Allergy. 2001; 56 (68), communication 262: 89-90	16914	Age of patients: 11-18 years 44 patients of which 10 were treated with Novo-Helisen Depot mites
Novo-Helisen Depot	Total IgE and antigen specific IgE in patients with atopic dermatitis and airborne allergy treated with specific immunotherapy	Czarnecka-Operacz M. Int. Rev. Allergol. Clin. Immunol. 2001; 7 (1): 16-26	20163	66 patients aged 5-44 years. 14 patients treated with Novo-Helisen Depot mites
Novo-Helisen Depot	Serum levels of IFN- γ , IL-2R, IL-4, IL-5 and IL-10 in the course of specific immunotherapy of patients with atopic dermatitis	Czarnecka-Operacz M, Silny W, Sobieska M. Int. Rev. Allergol. Clin. Immunol. 2001; 7 (1): 27-33	20164	7 publications for one study.

Product	Study Title	Study Number / Publication	File Identification	Remarks
Novo-Helisen Depot	Immunological parameters in the sera of patients with atopic dermatitis and airborne allergy treated with allergy vaccines	Czarnecka-Operacz M, Silny W. Acta Dermatoverol Croat 2006; 14 (1): 8-20	21230	
Novo-Helisen Depot	Analysis of allergy vaccines in the treatment of atopic dermatitis patients with airborne allergy Part one – clinical evaluation	Czarnecka-Operacz M, Silny W. Acta. Postepy Dermatologii i Allergologii. 2001; 2: 90-105	20166	
Novo-Helisen Depot	Analysis of allergy vaccines in the treatment of atopic dermatitis patients with airborne allergy Part two – clinical evaluation, continuation	Czarnecka-Operacz M, Silny W. Acta. Postepy Dermatologii i Allergologii. 2001; 4: 221-235	20167	
Novo-Helisen Depot	Analysis of allergy vaccines in the treatment of atopic dermatitis patients with airborne allergy Part three – evaluation of immediate skin reactivity towards selected environmental allergens	Czarnecka-Operacz M, Silny W. Acta. Postepy Dermatologii i Allergologii. 2002; 2: 26-37	20168	
Novo-Helisen Depot	Analysis of allergy vaccines in the treatment of atopic dermatitis patients with airborne allergy Part four – serum total and antigen specific IgE in the course of therapy	Czarnecka-Operacz M, Silny W. Acta. Postepy Dermatologii i Allergologii. 2002; 2: 64-78	20169	

Product	Study Title	Study Number / Publication	File Identification	Remarks
Novo-Helisen Depot	Immunotherapy in children with bronchial asthma	Hofman A M. Europ. J. Allergy and Clin. Immunology. 2002; 57 Suppl. 73: 54 XXI Congress of the European Academy of Allergology and Clinical Immunology, Abstract book Naples, Italy, 1-5 June 2002: Abstract No 129.	17686	20 children (4-18 years) with bronchial asthma.
Novo-Helisen Depot	Allergen-specific conventional immunotherapy decreases immunoglobulin E-mediated basophil histamine releaseability	Shim J-Y et al. Clin Exp Allergy. 2003; 33: 52-57	18166	14 Dermatophagoides farinae sensitive children (6-13 years).
Novo-Helisen Depot	Specific immunotherapy in the treatment of patients with atopic dermatitis – results of double blind placebo controlled trial	Silny W S W, Czarnecka-Operacz M C O M. Poster Discussion Sessin 11 – Dermatology / Investigations and Treatment, Abstract No. 262	18368	20 patients (5-40 years, 14 Dermatophagoides sensitive) with atopic dermatitis. 5 children of mean age 5 years. 2 publications for one study.
Novo-Helisen Depot	Spezifische Immuntherapie bei der Behandlung von Patienten mit atopischer Dermatitis, ergebnisse einer plazebokontrollierten Doppelblindstudie	Silny W, Czarnecka-Operacz M. Allergologie. 2006; 29 (5): 171-183	20718	

Product	Study Title	Study Number / Publication	File Identification	Remarks
Novo-Helisen Depot	Safety and Immunogenicity of a Cluster Specific Immunotherapy in Children with Brochial Asthma and Mite Allergy	Schubert R et al. Int Arch Allergy Immunol 2009;148:251–260	22788	
Novo-Helisen Depot	Specific Allergen Immunotherapy: Effect on Immunologic Markers and Clinical Parameters in Asthmatic Children	Cevit O et al. J Investig Allergol Clin Immunol. 2007; 17 (5): 286-291	21786	31 children (6-16 years)
Novo-Helisen Depot	Prevention of New Sensitizations by Specific Immunotherapy in Children With Rhinitis and/or Asthma Monosensitized to House Dust Mite	Inal A et al. J Investig Allergol Clin Immunol 2007; 17(2): 85-91	21414	147 children (6-16 years) with rhinitis and/or asthma; 85 were treated with SIT and 62 with conventional medication.
Novo-Helisen Depot	The safety of subcutaneous immunotherapy	Neziri-Ahmetaj L, Kokollari F, LLeshi L, Zhjeqi V. Congress of the European Academy of Allergology and Clinical Immunology, Göteborg, 9-13 June 2007; Poster Group 1 Allergen Specific Immunotherapy I, No 657	21460	122 patients (5-55 years) with various allergic problems
Novo-Helisen Depot	Basophil activation test using CD63 expression as a tool for monitoring specific immunotherapy: comparison of sublingual and subcutaneous mode of treatment in childhood asthma	Bartkowiak-Emeryk, M et al. Allergy 63 (Suppl. 88): 170. Poster Group 1 – Treatment of Childhood Asthma	22291	24 patients (9-18 years), 10 treated with Novo-Helisen Depot

Product	Study Title	Study Number / Publication	File Identification	Remarks
Novo-Helisen Depot	Treatment of Atopic Dermatitis with a Combination of Allergen-Specific Immunotherapy and a Histamine-Immunoglobulin Complex	Dong-Ho Nahm et al. Int Arch Allergy Immunol 2008;146:235–240	22096	20 patients (7-58 years) with atopic dermatitis
Novo-Helisen Depot	Allergen-specific immunotherapy in Georgia	Rukhadze, M et al. Allergy 63 (Suppl. 88): 529	22293	195 patients with asthma, rhinoconjunctivitis and atopic dermatitis (6-60 years) were treated with aeroallergens (house dust mites, grasses/cereals, weeds, trees, dog epithelia, moulds. 146 patients received Novo-Helisen Depot.
Novo-Helisen Depot	Allergen Specific-Ig-G ₄ in Circulating Immune Complexes in Patients with inhalant Allergy Undergoing Specific Immunotherapy	Rogala B, et al. Wiadomosci Lekarskie. 2005; LVII, 3-4: 123-130 (Polish with English summary)	19344	7 patients (17-34 years) with allergic rhinitis. 27 were treated with Novo-Helisen Depot (grass, cereal, mites)
Novo-Helisen oral	In vitro evaluation of allergen-specific basophils activation may be helpful for assessment of long-term parenterals and oral specific immunotherapy (SIT) in asthmatic children	Bartkowiak-Emeryk M et al. Allergy. 2001; 56 (Suppl 68):89-90 (Abstract)	16914	44 children (11.6 – 17.8 years), 19 treated with subcutaneous Novo-Helisen Depot (mites) and 15 Novo-Helisen oral (mites), 10 treated with conventional medication.
Novo-Helisen oral	Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children	Hirsch T, Sähn M, Leupold W. Pediatr Allergy Immunol. 1997; 8: 21-27	12506	30 children (6-15 years) with mild to moderate asthms, allergic rhinitis or both asthma and rhinitis. All patients were allergic to D.pt. 15 received Novo-Helisen oral.

There is a typing error in the above table in the row Novo-Helisen Depot, File Identification 19344 “7 patients (17-34) with allergic rhinitis. 27 were treated with Novo-Helisen Depot...”. 7 patients is incorrect, it should have been stated 27 patients.

Product	Study Title	Study Number / Publication	File Identification	Remarks
Novo-Helisen oral	Sublingual allergen-specific immunotherapy in allergic rhinitis and related pathologies: Efficacy in a paediatric population	Della Volpe A et al. Int J of Immunopathology and Pharmacology. 2002; 15 (1): 35-40	17705	288 Kinder > 5 Jahre; Milben, Gräser, Parietaria 288 children (>5 years) were treated with Novo-Helisen oral (mites, grass, parietaria)
Novo-Helisen oral	Safety and efficacy evaluation of sublingual allergen-specific immunotherapy – A retrospective, multicenter study	Madonini E et al. Int J of Immunopathology and Pharmacology. 2000; 13 (2): 77-81	16288	302 Patienten; 2-68 Jahre, davon 114 Kinder bis zu 12 Jahren; Grasses; Mites (n=159), Parietaria, Trees; dazu die folgende long-term Studie: 281 Patienten; davon 147 mit HDM therapiert 302 patients (2-68 years), of which 114 were children of up to 12 years, were treated with Novo-Helisen oral (grasses, mites, parietaria, trees). 159 received mites.
Novo-Helisen oral	Long-term and preventive effects of sublingual allergen-specific immunotherapy – A retrospective, multicenter study	Madonini E et al. Int J of Immunopathology and Pharmacology. 2003; 16 (1): 73-79	17991	Long-term-Study of study 16288: 281 patients, 147 with Novo-Helisen oral mites.
Novo-Helisen oral	Allergen-specific immunotherapy in Georgia	Rukhadze, M et al. Allergy 63 (Suppl. 88): 529	22293	195 patients with asthma, rhinoconjunctivitis and atopic dermatitis (6-60 years) were treated with aeroallergens (house dust mites, grasses/ cereals, weeds, trees, dog epithelia, moulds. 20 patients received Novo-Helisen oral.
Novo-Helisen oral	Assessment of clinical effectiveness of 12 month oral specific immunotherapy in children	Emeryk A, Bartkowiak-Emeryk M. Annales Universitatis Mariae	19430	68 children (6-15 years) with rhinitis and asthma.

Product	Study Title	Study Number / Publication	File Identification	Remarks
	with allergic perennial rhinitis and bronchial asthma sensitive to mites	Curie-Sklodowska, Lublin, Poland, Sectio D. 2000; Vol LV (12): 84-90 (Polish)		
Novo-Helisen oral	Assessment of clinical effectiveness of 12 month oral specific immunotherapy in children with allergic perennial rhinitis and bronchial asthma sensitive to mites	Emeryk A, Bartkowiak-Emeryk M. Annales Universitatis Mariae Curie-Sklodowska, Lublin, Poland, Sectio D. 2000; Vol LV (12): 84-90 (English)	19430 english translation	
Novo-Helisen oral	A three-year double-blind placebo-controlled study with specific oral immunotherapy to Dermatophagoides: evidence of safety and efficacy in paediatric patients	Giovane A L et al. Clinical and Experimental Allergy. 1994; 24:53-59	2686	18 children (3-13 years)

ALK Abello has submitted 3 clinical studies (Hedlin G et al. J Allergy Clin Immunology 1999; 103: 609-14, Haugaard L et al. J Allergy Clin Immunology 1993; 91: 709-12 and Panjo GB et al. Clin Exp. Allergy 2001; 31: 1392-7)

III.3.1. Clinical studies

- **Study 101-PG-PSC-52**

Objective

This was a phase-IV, double-blind, placebo-controlled study assessing the efficacy and safety of one year treatment with an extract containing a 50% mixture of *D. pteronyssinus* and *D. farinae* in patients with mild to moderate allergic asthma and rhinoconjunctivitis.

Study design

Placebo-controlled trial of 12 months duration.

Study population/sample size

64 patients including 22 children.

Treatments

LETI depigmented and polymerised extract of *D. pteronyssinus* and *D. farinae*.

Outcomes/endpoints

Bronchial provocation test with a standardized extract of *D. pteronyssinus* (primary endpoint) and prick-test at baseline and at end of study, and assessment of weekly symptom and medication scores as well as safety parameters during the treatment period.

Statistical Methods

Routine statistical tests were applied including Mann-Whitney's test, Wilcoxon's test, Chi-square and Fisher's exact test. A log-log regression analysis was conducted for evaluating the dose-response to skin prick test.

Results

Efficacy

A significant improvement was observed in the primary endpoint at end of study as the active group needed a median of 11.05 times more allergen to achieve a value of PD₂₀FEV₁, whereas the placebo group did not improve ($p > 0.001$). In the dose-response to skin prick-test the active group showed a significant improvement at end of study as 2.04 more of the allergen extract was needed compared to baseline to produce the HEP value ($p=0.029$).

Whereas the placebo group did not improve ($p=0.9$). A mean reduction of overall symptom score of 67% was observed in the active group ($p=0.001$), whereas the placebo group experienced a worsening. Similarly a significant reduction in mean medication score was only detected in the active group ($p=0.013$).

Safety

According to the investigators there were occasional local reactions in both the active and the placebo group. No serious adverse events were recorded and no patients stopped therapy due to adverse reactions.

- **Study 1300-PG-PSC-119**

Objective

This was a phase IV, prospective observational study to evaluate the safety of Depigoid *D. pteronyssinus*/*D. farinae* or pollen extracts in an ultra-rush dose schedule in patients with allergic rhinoconjunctivitis and/or asthma.

Study design

Open label safety study.

Study population/sample size

Total number of patients 1068 with 199 children vaccinated with dust mite extracts.

Treatment

Depigmented and standardized allergen extracts to mites and/or pollens.

Outcomes/endpoints

Safety recordings as recommended by the EAACI. No efficacy data were recorded.

Statistical Methods

Descriptive statistics were used to describe the number and percent of adverse events.

Results

In general the rapid us-scale of immunization was well-tolerated and all patients reached the maximum established dose the first day.

A total of 7 local reactions were recorded and 5 patients experienced a mild to moderate systemic reactions.

- **Depilate study**

Objective

To assess the tolerability and “efficacy” of LITE’s Depigoid vaccines.

Study design

Open label study of 6 month duration.

Study population/sample size

A total of 768 patients including 210 children.

Treatments

Depigoid dust mite or pollen vaccines.

Outcomes/endpoints

Frequency of adverse events and acceptability of the treatments.

Statistical Methods

Descriptive statistics.

Results

Continuation with immunization after 6 months of therapy was decided for 84% of the patients. Allergy related symptoms related to nose and eye improved in more than 67% of all patients.

The tolerability as well as the efficacy was judged “good or very good” by more than 80% of physicians and patients.

- **Allergopharma**

Controlled clinical trials

One controlled clinical trial has been conducted with the approved product containing *D. pteronyssinus* and/or *D. farinae* in children with allergenic rhinoconjunctivitis or allergic asthma (Giovane et al, 1994). However it only included 18 children with allergic asthma that “improved” after 2 years of therapy with oral immunotherapy.

Uncontrolled clinical trials

The MAH has submitted a number of open label and retrospective clinical trials in which children with allergic rhinoconjunctivitis and/or allergic asthma received either subcutaneous or oral/sublingual immunisation with the dust mite extracts.

According to the report a significant proportion of the treated children experienced a clinical significant reduction in symptom scores and in general the therapy was well-tolerated in most children.

- **ALK Abello**

The MAH has not conducted specific clinical trials in children.
The MAH make references to published studies and review articles.

A safety overview indicate that 34% of the total number of reports in PSURs concerns patients below 18 years of age exposed to the ALK dust mite products.

Comments received from other Member states

1. Comment

It does not become clear from the AR whether the SmPC wording regarding the paediatric population is identical for the different products submitted by different MAHs.

Response from ALK

The SmPC wording regarding the paediatric population for the ALK products in different countries is not identical as these products have been approved by national procedure by the national competent authorities.

Assessor's comments:

The response from the MAH is acceptable. Point resolved.

2. Comment

Due to incomplete information a conclusive suggestion for an SPC wording can presently not be made.

Response from ALK

The house dust mite 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 SmPC and PIL throughout Europe. In addition no new clinical findings relevant to children have been presented during this process.

Assessor's comments:

A harmonisation of the different SmPC and PIL is outside the scope of this process. Point resolved.

3. Comment

No differentiation has been made between diagnostic and therapy allergens.

Response from ALK

The executive summary in the PAR recognises diagnostics versus therapeutic products.

Response for Allergopharma

The submitted data referred to therapy only.

Response from LETI Pharma

- ❖ As stated on page 6 of our assessment report (AR) “Clinical overview on paediatric data from 25 February 2009”, in the second paragraph; No concrete studies were performed after December 2003 in order to assess the efficacy and/or safety of either prick test or provocation tests with house dust mites. For this reason the data presented in our AR referred exclusively to treatment with Depigoid® *D. pteronyssinus* and/or Depigoid® Milben Mix. Nevertheless, we also stated on page 6, that information gathered in some of the studies, from the use of prick and provocation allergen extracts to assess the efficacy of treatment with Depigoid®, would be presented specifically within each study. This information is available in the description of such studies.

Assessor’s comments:

These are different allergen products for prick-test diagnosis and for immunotherapy. Point resolved.

4. Comment

In general, no details were provided as to how many children of a certain age and gender have received SIT in the summarized publications and study reports.

Response

The available publications on house dust mites immunotherapy submitted by ALK are mentioned in the Rapporteur’s report. However, none of these studies have been initiated by ALK. Therefore it is not possible to provide more detailed information than given in the publication of these studies regarding the number of children in different age group or the gender.

In Pajno et al publication the children included in the study group were between 6-8 years (mean 7,14 in SIT group and 6.38 in control group) and there are 80 female (42 in SIT group and 28 in control group) and 58 male (33 in SIT group and 25 in control group). (Ref 1)

Concerning the Haugaard et al publication (Ref 2) (children included from age of 10 years) and the Hedlin et al (Ref 3) (children 7-16) it is not possible to provide any further information about the children age group or gender.

ALK has included the pdf’s of the full publications in this response.

Response from Allergopharma

Unfortunately, we do not have free access to the data of publications because we did not sponsor the respective investigations. But we can provide you with data form our own investigations, i.e. three post-marketing surveillance studies concerning effectiveness and overall safety of our mite preparations:

- Post-marketing surveillance study NHD® Mite December 2002 – December 2005
- Post-marketing surveillance study Novo-Helisen® oral (NHO) September 1998 – October 2001
- Post-marketing surveillance study Novo-Helisen® oral (NHO) June 2004 – November 2004

These studies which are available form our database included a total of 228 patients (47 children, 50 adolescents, 131 adults, 103 female and 124 male patients).

Post-marketing surveillance study NHD® Mite 2002 - 2005

Gender * Age Crosstabulation

Count

	Age			Total
	children (2 to 11 years)	adolescents (12 to 18 years)	adults	
Gender female	2	2	11	15
male	8	3	13	24
Total	10	5	24	39

Post-marketing surveillance study Novo-Helisen® oral (NHO) September 1998 – October 2001

Gender * Age Crosstabulation

Count

	Age			Total
	children (2 to 11 years)	adolescents (12 to 18 years)	adults	
Gender male	9	5	6	20
female	3	8	16	27
unknown	0	0	1	1
Total	12	13	23	48

Post-marketing surveillance study Novo-Helisen® oral (NHO) June 2004 - November 2004

Gender * Age Crosstabulation

Count

	Age			Total
	children (2 to 11 years)	adolescents (12 to 18 years)	adults	
Gender female	9	7	45	61
male	16	25	39	80
Total	25	32	84	141

Response from LETI Pharma

On page 12 of the AR submitted on 27th February 2009, Table 1, there is a column with the number of children included in each study. Numbers were also given according to age stratification (children and adolescents). Details on gender distribution were not shown. Information about gender has been added to Table 1 for all studies for which this information could be collected retrospectively. The VIKI study has been included in the table, since the clinical study report was available in May 2009.

- **Study 101-PG-PSC-52:** Data have been enclosed in a separate file: “Study 101-PG-PSC-52-Demographic data of children subpopulation.pdf”.
- **Study 1300-PG-PSC-119:** Data have been enclosed in a separate file: “Study 1300-PG-PSC-119-Demographic data- Age and Gender of children subpopulation.pdf”.
- For the **Depilate study:** See file enclosed separately: “DEP_AWB_SUBAN1.pdf”.

For the **VIKI study**, general information can be obtained from the demographic data for all Depigoid products (tree, grass pollen, mites, etc.). See enclosed files:

- “Viki-Study-Demographic data-Age and Gender-English.pdf”.
- “Supplement on paediatric data to Addendum_CTD_2_5DDp_modif from 27Feb2009-04Jun2009.pdf”.

Taking all clinical studies into account, a total of **1243** children have been treated with Depigoid mites after the marketing authorization. If the children included in the studies which belonged to the CTD submitted in December for the MA are counted, the number of children rises to at least **1275** children.

Assessor’s comments:

No new data have been submitted by the MAHs. However, international consensus among allergologists exists recommending use of subcutaneous immunotherapy (SIT) in children with dust mite induced allergic rhinoconjunctivitis and bronchial asthma. Point resolved.

5. Comment

Sometimes, not even information on doses or the applied allergen as such was provided.

Response from ALK

In the Pajno et al. publication the initial dose is 10 SQ-U and the maintenance dose is 50.000 SQ-U (see table 1 in the publication) (ref 1).

In the Haugaard et al. publication the initial dose is 10 SQ-U (see table III in the publication), but there are 3 different maintenance doses, 10.000 SQ-U, 100.000 SQ-U and 300.000 SQ-U. (ref. 2).

In the Hedlin et al. publication the initial dose is 1 SQ-U and the maintenance dose is 100.000 SQ-U. (ref. 3).

Response from Allergopharma

The preparations were used in accordance with the dosage instructions given in the SPC. The recommended dose for adults is the same dose as recommended for children and adolescents.

Response from LETI Pharma

We provided information on doses (section 2.5.4.3. of AR) and immunotherapy administration for each study. Nevertheless, we have summarized the doses on the right hand column of Table 4 (see page 8) to facilitate an overview of this data.

Additional information has been provided for some studies hereinafter (see next page).

In the studies 101-PG-PSC-52, Depilate, the pilot study in atopic dermatitis and the VIKI study, Depigoid was administered following a conventional regime. In study 1300-PG-PSC-119 Depigoid was administered following a rush regimen (See next page). Tables 2 and 3 show the doses of Depigoid® *D. pteronyssinus* or Depigoid® Milben Mix administered according to the conventional regimen, with a build up and a maintenance phase respectively).

Table 2: Dosage of the study medication during the Initial Build-Up Phase

Vial	Injection interval	Injection no.	Dose in ml	Remarks
1 green	7 days	1		Vial 1: 10 DPP/ml. 1 DPP= result of depigmenting and polymerising 1 HEPL of mites native allergen extract.
			0.2	Dose: 2 DPP
		2	0.5	Dose: 5 DPP
2 blue	7 days	3		Vial 2: 100 DPP/ml. 1 DPP= result of depigmenting and polymerising 1 HEPL of mites native allergen extract.
			0.2	Dose: 20 DPP
		4	0.5	Dose: 50 DPP

Table 3: Dosage of the study medication during the Maintenance Treatment

Vial	Injection interval	Injection No.	Dose in ml	Remarks
2 blue	4-6 weeks	5-16*		
			0.5	Dose: 50 DPP
				* Number of maintenance injections varied depending of study duration.

- No dose reduction was necessary when changing to a new vial no. 2.
- DPP is a biologic unit to measure biologic activity of Depigoid (1DPP=1HEPL [Histamin Equivalent Prick Leti] after de-pigmentation and polymerisation).

❖ **101-PG-PSC-52**

- Vial No. 1: Allergen concentration of 10 DPP/ml. The initial allergenic potency (before the process of depigmentation and polymerisation) was 10 HEP_L. The residual potency after the process of chemical modification was 0.028 HEP_L.
- Vial No. 2: Allergen concentration of 100 DPP/ml. The initial allergenic potency (before the process of depigmentation and polymerisation) was 100 HEP_L. The residual potency after the process of chemical modification was 0.28 HEP_L.

- ❖ **Study 1300-PG-PSC-119:** In this study, a rush administration regimen was used. The first dose was 0.2 ml of vial 2 (20 DPP) and the second dose was 0.3 ml of vial 2 (30 DPP), which was administered 30 minutes after the first dose and only in absence of adverse side effects. The maintenance therapy dose was thus achieved on the first day. In total, each patient received 50 DPP/ per injection.

❖ **Depilate study:** Depigoid was administered in two phases:

- Initiation phase: weekly administration of 0.2 ml (2 DPP) and 0.5 ml (5 DPP) of vial 1 (10 DPP/ml) followed by 0.2 ml (20 DPP) and 0.5 ml (50 DPP) of vial 2 (100 DPP/ml)

- Maintenance phase: Vial 2 (100 DPP/ml): 0.5 ml (50 DPP) every 4-6 weeks.

❖ Pilot study in atopic dermatitis:

The treatment was divided into two courses: the initial build-up phase and the maintenance treatment.

The initial build-up phase during the first 21 days consists of two extract concentrations (vial 1: 10 DPP/ml and vial 2:100 DPP/ml).

The dosage was continuously increased by the investigator, i.e. during the first 21 days the investigator increased the dosage from 0.2 ml to 0.5 ml (vial 1) to 0.2 ml and 0.5 ml of vial 2 on a weekly basis.

During the maintenance treatment phase, i.e. from day 21 onward in 4-6 weeks intervals, the investigator used the higher concentrated medication (vial 2) in a dosage of 0.5 ml for each subsequent injection.

The two vials of the initial build-up phase contained 1.5 ml (vial 1: 10 DPP/ml) and 2.5 ml (vial 2: 100 DPP/ml), respectively.

The vials of the maintenance treatment were each filled with 2.5 ml (for concentration see vial 2 of initial build-up phase).

Based on an average treatment duration of 26 weeks, the patients received an equivalent of 93 µg Der p1 and 58 µg Der p2 with the respective Depigoid extracts. The determination of major allergens was performed in the native extract (before de-pigmentation and modification) using the scanning densitometry method.

❖ Viki study:

This was a retrospective study in which the investigator recorded each patient's immunotherapy administration schema. The administration regimen was the conventional one, with a build up phase of 4 increasing doses at weekly intervals: Vial 1: 0.2 ml (2 DPP), 0.5 ml (5 DPP), Vial 2: 0.2 ml (20 DPP), 0.5 ml (50 DPP). Once the maintenance dose was reached (0.5 ml of vial 2 = 50 DPP), maintenance doses were administered in 4-6 weekly intervals.

In average, 1,398 DPP were administered in children of ages between 5 and 11 years old and 1,380 DPP were administered in children with ages between 12 and 18 years old, over a period of 3 years.

Additionally, these were **the concentrations used for the prick and provocation test** in study **101-PG-PSC-52**, which were performed to assess efficacy, either as the

primary parameter (bronchial provocation test) or as a secondary parameter (titration prick test).

➤ Concentration of Prick Test and Bronchial Provocation with *D. pteronyssinus* Leti¹:

- Prick Test: Titrated skin prick tests were conducted in duplicate on the volar surface of the forearm, using concentrations of 0.002, 0.02, 0.2 and 2 mg of native standardised extract of *D. pteronyssinus* and *D. farinae* per ml. These doses correspond to a biological activity after the lyophilize is reconstituted with the diluent of 0.1, 1, 10 and 100 HEP/ml respectively.
- Bronchial Provocation Solution with *D. pteronyssinus*: Bronchial Provocation Tests (BPT) were conducted in Visit 0 and in Visit 19 (one week after the last injection). The same batch of standardized native unmodified allergen extract of *D. pteronyssinus* at 0.002, 0.02, 0.2, and 2 mg/ml was used throughout the trial. These doses correspond to a biological activity after the lyophilize is reconstituted with the diluent of 0.1, 1, 10 and 100 HEP/ml respectively. The vial of maximum concentration had a potency of 100 histamine equivalent in prick-testing units (HEP)/ml. It was supplied freeze-dried and vacuum closed to be reconstituted just before use.

¹ For further data about prick and bronchial provocations in children in the studies submitted in the CTD in December 2003 please see following documents enclosed separately:

- Demographic data of study 101-PG-PSC-48-Included in CTD 2003.pdf
- Study 101-PG-PSC-62-Demographic data in children-included in CTD 2003.pdf

Table 4: Clinical program of completed studies (with data on allergen doses)

Study type / Duration	Description	Report number/Study code	Number of children included	Doses of allergen (cumulative per patient)
Efficacy and Safety 1 year	Phase IV, randomized, double-blind, placebo-controlled study to evaluate the efficacy of depigmented and polymerised extract of <i>D. pteronyssinus</i> and <i>D. farinae</i> in 66 patients older than 12 years of age with allergic asthma due to IgE mediated hypersensitivity to <i>D. pteronyssinus</i> .	101-PG-PSC-52	Total no. of patients: 64, from those 22 children: <ul style="list-style-type: none"> • 5 between 13 – 14 yrs old • 17 between 15-17 yrs old 	693,5 DPP in 1 year
Safety 1 year	Phase IV, prospective observational study to evaluate the safety of using standardised depigmented and polymerized allergen extracts (mites and/or pollens) in an ultra-rush schedule of build-up phase in patients with allergic rhinoconjunctivitis and/or asthma due to sensitization to mites and/or pollens. Ultra-rush build-up phase was conducted without premedication or hospitalization.	1300-PG-PSC-119	Total no. of patients: 1068, from those: 199 children vaccinated with Depigoid Dpt or Depigoid mites: <ul style="list-style-type: none"> • 11 between 3 – 5 yrs old • 72 between 6 – 11 yrs old • 116 between 12– 17 yrs old 	50 DPP per injection
Safety and Efficacy 6 months	Phase IV, observational cohort study to assess the efficacy and safety of Depigoid in allergic patients with allergic rhinoconjunctivitis, rhinitis and / or bronchial asthma.	Depilate	Total: 768 patients, from those: 210 children <ul style="list-style-type: none"> • 113 between 5 and 11yrs old • 97 between 12- 18 yrs old 	50 DPP/maintenance injection. In average: 327 DPP in 6 months
Efficacy 6 months	Open label pilot study to assess clinical changes and objective laboratory parameters and evaluate the benefit of house dust mites SCIT in 25 patients with atopic dermatitis with IgE-mediated sensitization against HDM.	No code available since this was an investigator initiated trial	Total: 25 patients <ul style="list-style-type: none"> • 1 < 10 yrs old • 2 between 10-18 yrs old 	327 DPP per patient in 6 months.
Efficacy, Safety and Tolerability In average, patients were treated with Depigoid 3 years. Observational period of study: Oct 08/April 09	Phase IV retrospective study to assess the effectiveness and tolerability of the Depigoid® in paediatric patients with hypersensitivity against pollen and mite allergens.	VIKI	Total: 2927 children. Of these 809 children treated with Depigoid® Dpt or Depigoid® Milben Mix. Of these: <ul style="list-style-type: none"> • 470 between 5-11 yrs old • 332 between 12- 18 yrs old 	1.398 DPP for children between 5-11 yrs old 1.380 DPP for children between 12-18 yrs old
Total number of children treated with Depigoid® <i>D. pteronyssinus</i> / Depigoid® Milben Mix:			1243	

Assessor's comments:

In daily clinical practise the doses of applied allergens is in accordance with approved posology which is identical in children and adults. Point resolved.

6. Comment

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 from ALK

It is not possible to evaluate the efficacy and safety for the paediatric patient separately in the Haugaard study (ref. 2). However, the Pajno (ref. 1) and the Hedlin (ref. 3) studies only include paediatric data.

The aim of the Haugaard study was to establish the optimal maintenance dose of house dust mite (*dermatophagoides pteronyssinus*) immunotherapy. 19 patients received dose of 10.000 SQ-U, 20 received a dose of 100.000 SQ-U and 16 patients received 300.000 SQ-U. After 24 months bronchial challenge demonstrated a dose-related increased tolerance to der.p. Immediate systemic reaction occurred in total in 4 cases (0.56%) in the 10.000 SQ-U group, in 25 cases (3.30%) in the 100.000 SQ-U group and in 45 cases (7.10%) in the 300.000 SQ-U group. The conclusion of the study was that this study demonstrated a dose dependence of efficacy and side effects of IT in asthmatic patients and suggested a maintenance dose of 100.000 SQ-U as the appropriate guideline for IT with house dust mite extract.

The aim of the Pajno study was to increase knowledge about the ability of SIT to prevent the onset of new sensitizations in monosensitized subjects. The conclusion of the study was that SIT may prevent the onset of new sensitizations in children with respiratory symptoms that is monosensitized to house dust mite. The aim of the Pajno study was therefore not to evaluate the efficacy and safety for the paediatric patients. However, the investigators reported some adverse events including tiredness after injection, small local reactions and larger local reactions in 12 cases (5 at the same patient). Four systemic reactions occurred, 1 immediately (flushing and chest tightness; treated with adrenaline) and 3 delayed reactions (1 urticaria, 2 shortness of breath).

The aim of the Hedlin study was to investigate the effect of cat or house dust mite immunotherapy on bronchial hyperreactivity and the need for inhaled corticosteroids in children with asthma, cat or dust mite allergy and hay fever. The conclusion of the study was that pollen immunotherapy combined with inhaled corticosteroid results in improvement of both cat/dust mite bronchial sensitivity and hyperresponsiveness to histamine. The combination of cat or dust mite, pollen immunotherapy and inhaled budesonide enhances this improvement. The aim of the Hedlin study was not to evaluate the safety of the therapy. However, the investigators reported some adverse events including mild systemic side effects in 5 children that received cat immunotherapy and recurrent urticaria and asthmatic reactions in one child that therefore was excluded from the study.

Response from Allergopharma

We have to admit that this is true. To compensate this we tried to provide you with the demographic data of three post-marketing surveillance studies (see above). Generally, the preparations demonstrated a sufficient efficacy as well as safety profile in children, adolescents and adults. As an example we mention the publication of Ullrich and co-workers (1) in which the efficacy of different cumulative allergen doses in children up to 14 years compared to adults was measured using a visual analogue scale. In this investigation during the first year of therapy the efficacy in children was even better than in adults: In total, for all subjects included in the three "dose groups" after the first year children showed an amelioration in median VAS from 8 to 3 and adults from 8 to 4, respectively ($p < 0.01$)' (see figure below). Please note that the appropriate literature reference is enclosed as annex Ullrich D et al. Allergo J 2007; 16: 193-8.pdf.

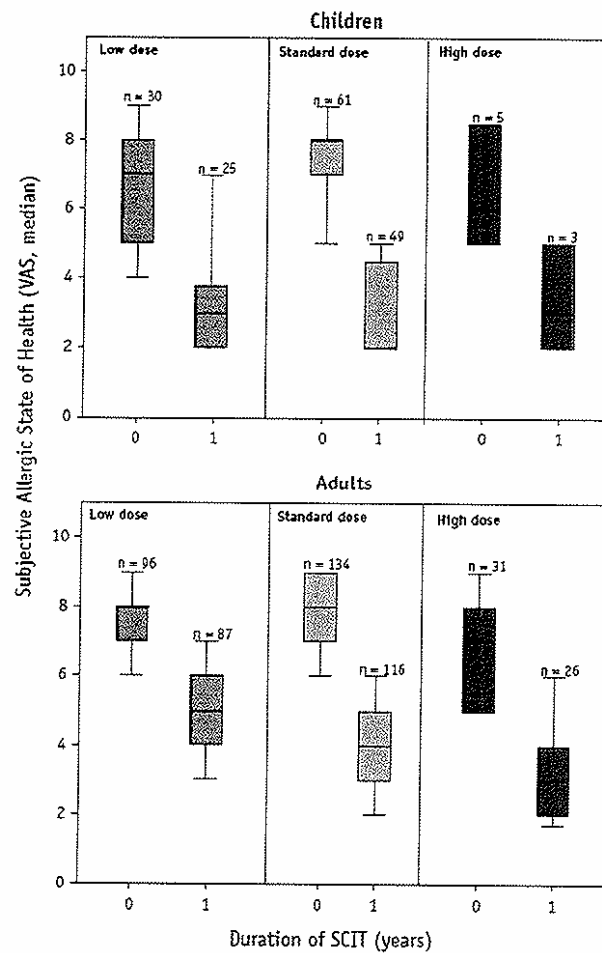


Figure 2. Subjective allergic health status (VAS scores) at the beginning (0) and after 12 months SCIT (1). Top: children (n = 96) up to 14 years; bottom: adults (n = 261). Median values with 25th, 75th (boxes), 5th, and 95th (error bars) percentiles.

Response for LETI Pharma

- Efficacy of SIT, both subcutaneous and sublingual, and for both adults and children, has been shown in separate meta-analyses^{2, 3, 4}.
- Non-interventional studies (NIS) or post-marketing surveillance studies are an indispensable instrument in pharmaceutical research. Due to the fact that clinical phase I-IV trials with pharmaceuticals provide a limited number of data within a selected study population, high-quality post-marketing surveillance studies to receive more information about their use under real life conditions which reflects the medical routine practice, are very valuable. Reliable NIS data enhance the patients' safety.

- The studies belonging to the assessment report for Depigoid® *D. pteronyssinus* and/or Depigoid® Milben Mix were designed to evaluate efficacy and safety in the whole population; children, adolescents and adult patients.
- There were two non-interventional studies (Depilate and Viki studies) in which a large number of children (210 in the Depilate study and 809 in the VIKI study) were treated with Depigoid mites. In both studies, specific sub-analyses were performed separately to assess the efficacy of Depigoid mites in children. Moreover, efficacy in children was assessed independently for two age-stratified groups: children between 5 and 11 and adolescents between 12 and 18.
- Data on efficacy and safety of Depigoid mites for the non-interventional studies (Depilate and VIKI) were submitted on 5th June 2009 as a supplement to the initial AR of 27th February 2009, as soon as the clinical study report of the VIKI study was available. Please find this document enclosed: “Supplement on paediatric data to Adendum_CTD_2_5_DDp_modif from 25Feb2009-

² Metaanalyses of specific immunotherapy trials. Calderon MA. Drugs Today (Barc). 2008 Dec;44 Suppl B:31-4.

³ Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses. Compalati E, Penagos M, Tarantini F, Passalacqua G, Canonica GW. Ann Allergy Asthma Immunol. 2009 Jan;102(1):22-8. Review

⁴ Metaanalysis of the Efficacy of Sublingual Immunotherapy in the Treatment of Allergic Asthma in Pediatric Patients, 3 to 18 Years of Age. Penagos M. CHEST. 2008;133(3):599-609

04Jun2009-final.pdf’. (This supplement was re-submitted on 12th August 2009 for additional consideration in the assessment process after having received the preliminary assessment report on 11th August 2009). It is also attached to this document.

- According to Best Practice Guide, Article 45-Paediatric Regulation: EU Work Sharing Procedure from February 2009, “*there is no need to resubmit data submitted earlier, but in the overview all available information on the paediatric use should be briefly summarized*”. Please find an overview of the studies included in the CTD for MA, in the enclosed document “Summary of clinical trials with Depigoid mites included in CTD submitted for MA in December 2003.pdf”. In addition, two appendixes have been enclosed with a summary of the most relevant information of each study. Moreover, concrete information about demographic data, gender, as well as data on prick and bronchial provocations is available. See appendixes:
 - “Demographic data of study 101-PG-PSC-48-Included in CTD 2003.pdf”
 - “Study 101-PG-PSC-62-Demographic data in children-included in CTD 2003.pdf”

- Study 10-PG-PSC-62 was specifically conducted in children and included in the CTD for MA. Please find demographic data in the document enclosed: “Study 101-PG-PSC-62-Demographic data-Age and Gender of children with Depigoid treatment-Verum.pdf”. A summary as well as data on bronchial provocation test are given in appendix: “Study 101-PG-PSC-62-Demographic data in children-included in CTD 2003.pdf”. The study publication “*Ibero M, Castillo MJ. Significant improvement of specific bronchial hyperreactivity in asthmatic children after 4 months of treatment with a modified extract of Dermatophagoides pteronyssinus. J Investig Allergol Clin Immunol 2006; 16(3): 194-20*” has been enclosed.

Assessor’s comments:

The response from the MAHs is acceptable. There is international consensus that these products are effective and safe in both the diagnostic procedures and in the immunotherapy of children with dust mite allergy. Point resolved.

7. Comment

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

Response from ALK

ALK has included the company position on this issue in the clinical expert statement already submitted. “In established use the same up-dosing schedules and maintenance doses have been used in both adults and children. The only difference between adult and children is that a smaller size of local reaction should lead to consideration about possibly lowering of the dose for the next

injection. Further the choice of dose and adjustment is done in accordance with the physician’s evaluation of the individual patient, and is not determined based on age or age group”.

Response from Allergopharma

The demographic data listed above gives the numbers of children, adolescents and adults as well as male and female patients that were included in three post-marketing surveillance studies.

Response from LETI Pharma

The results pertaining to efficacy and safety have shown no differentiation between children and adults when performing prick and provocation tests. Therefore, the dosage schedules for both prick and provocation tests (nasal and bronchial), as well as the safety information of these diagnostic tests, do not differ between adults and children.

The efficacy of specific immunotherapy (SIT) has been shown to be dose-dependent⁵. SIT has been shown to be efficacious in both children and adults by using the same immunotherapy doses. With doses that are too high, systemic and even serious adverse reactions do occur in SCIT and SLIT, making safety a determining factor for the maximum dose. This maximum dose tolerated does not seem to be lower for small children in comparison with older ones^{6, 7}.

Since children older than 5 years old have not shown to suffer from more adverse events than adults, the use of SIT in children with lower allergen content or with lower biological activity than in adults, therefore, would not be justified.

See following documents enclosed: “Justification of SmPC and PL of Depigoid Mites.pdf” and “Justification_of_SmPC_and_PL_of_Diagnostics.pdf”.

⁵ Allergy 2006; 61 (Suppl. 82): 1–20. Standards for practical allergen-specific immunotherapy. Alvarez-Cuesta E., Bousquet J., Canonica G. W., Dirham S. R., Malling H.-J., Valovirta E.

⁶ Rienzo VD, Minelli M, Musarra A, et al. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. Clin Exp Allergy 2005;35:560-564

⁷ Fiocchi A, Pajno G, La Grutta S, et al. Safety of sublingual swallow immunotherapy in children aged 3 to 7 years. Ann Allergy Asthma Immunol 2005;95:254-258

Assessor’s comments:

According to international clinical guidelines the doses used in children are identical to those used in adults. Point resolved.

8. Comment

The MAH should provide detailed information on age and gender in the studied paediatric population. This may not be possible for each referenced report. But as some of the studies may have been initiated by the MAH, data should be available from the company’s database.

Response from ALK

See response to comment 4.

None of these studies were initiated by ALK.

Response from Allergopharma

Please refer to our response given for question 2 above.

Response from LETI Pharma

See response to second comment on page 2 and the corresponding attachments:

- “Study 101.PG-PSC-52. Age and Gender children subpopulation.pdf”
- “Study 1300-PG-PSC-119. Demographic data- Age and Gender of children subpopulation.pdf”
- “Study 101-PG-PSC-62-Demographic data-Age and Gender of children with Depigoid treatment-Verum.pdf”
- “DEP_AWB_SUBAN4.pdf”
- “Viki-Study-Demographic data-Age and Gender-English.pdf”

Assessor’s comments:

No further information has been submitted by the MAHs. The numbers of children assessed in clinical trials are limited as previously stated. However, a significant numbers of children have received the products for years indicating that in common practise they are both effective and safe.
Point resolved.

9. Comment

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 from ALK

As requested all events (662 for adults and 326 for children) data are presented by distribution on MedDRA System organ Class (SOC) and Preferred Term (PT), for children and adults respectively in appendix 1. The data apply to 366 individual reports. 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 17 years, 33% are females and 67% are males. Regarding severity of the adverse events 29 % of reports in paediatric patient were assessed as serious and also 29% of reports in adults. In general the adverse events resolved. –See response to Q 10.

Overall the events reported are very similar in the two age groups. The reporting of anaphylactic shock (15/ 8) as well as anaphylactic reaction is fairly low (10/9) in both children and adults.

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.

From this data there is nothing to suggest any difference between children and adults regarding the safety profile of ALK HDM products.

Response from Allergopharma

Please refer to our consolidated answering scheme, enclosed as annex Alpha – Consolidated answering scheme.pdf.

Response from LETI Pharma

There has not been any notification of adverse reactions related with the administration of either Prick Test or Provocation Test *D. pteronyssinus* / *D. farinae* Leti in any clinical study. Moreover, no spontaneous notification through the pharmacovigilance system has been reported either. Both prick and provocation test of mite allergens are safe. At recommended doses, and with the correct use of the preparations, no additional adverse reactions are expected other than those elicited by the provocation test *per se* in order to establish the diagnosis. Caution is nevertheless recommended, and is stated in the SmPC and patient leaflet. See following PSURs enclosed:

- PSUR_PRICK_PROV_N.1_MITES_060106.pdf.
- PSUR Prick-Provo Mites n°4 01Jan06-31Dec08 - Final 27-02-2008.pdf.
- PSUR D. MiteMix n°7 22dec04-21apr09 FINAL -18jun09.pdf.
- PSUR D. Dpt n° 7 22Dec04-22Apr09 FINAL 18jun09.pdf.

In the last 5 years there were only three spontaneous reports of allergic reactions in children. No anaphylactic shock has been communicated to date either with Depigoid® *D. pteronyssinus* or with Depigoid® Milben Mix. Safety reporting gathered from clinical trials and post-marketing studies also showed that Depigoid mites is safe and very well tolerated in children. In addition to the good safety profile and excellence tolerance of Depigoid mites showed in the clinical trials, when we compare the high number of Depigoid mites administered in Germany with the very low number of spontaneous communications of adverse drug reactions (which refers to the pharmacovigilance in all countries where these two products are sold), we can conclude that the safety of Depigoid® *D. pteronyssinus* and Depigoid® Milben Mix is indeed very high.

Assessor's comments:

The safety profile of the products is identical in children and adults according to available safety data bases. Point resolved.

10. Comment

For one MAH, PSUR data with regard to children has been briefly mentioned. However, no details were given as to the severity and the outcome of the reported events

Response from ALK

On page 4 of the ALK expert statement the overall cases for adults and children are presented by serious and non-serious.

In the period two cases have had a fatal outcome – both cases concerned adult patients.

One case from 1996 (ADR 46) in a 28-year old female after an overdose of 10 times the planned dose was given, and the other from 2003 (ADR 1151) in a 39 year male where there was a suspicion of injection technique failure, which lead to a severe asthma attack.

Assessor's comments:

The response from the MAH is acceptable. Point resolved.

11. Comment

The clinical studies submitted by ALK Abello do not provide the number and gender of children grouped into a certain age range. Also, efficacy and safety has not been evaluated for children in particular.

This information should be submitted as the respective data should be available from the ALK Abello database

Response

See comment to response 4.

Assessor's comments:

The response form the MAH is acceptable. Point resolved.

Miscellaneous

12. Comment

At point II. Recommendation of the PdPAR: it has been stated that immunotherapy has been used "in order to reduce symptoms associated with allergic rhinitis.". It should be added "via an immune modulating mechanism"

Assessor's comments:

Agreed. Will be added accordingly.

13. Comment

On page 7 Table 2, third line "Remarks" of the PdPAR: There must a typing error: "...7 patients had allergic rhinitis, 27 were treated..." This study population has, by the way, been treated with different inhalant allergens so that no information is available on how many children have received house dust mite allergens

Assessor's comments:

Agreed. Will be added accordingly.

14. Comment

According to the "List with studies_MAH-contact_points" provided by the CMD(h) secretariat by 28 January 2009 there are more products included as mentioned in the Assessment Report (e.g. products from the MAH ALK Scherax (DE) and Merck (PT)-Alergo_Merck Depot Ácaros) – see in the attached table yellow marked. Please clarify why these products were not included in the assessment

Assessor's comments:

Studies submitted by Allergopharma (Merck Group Company) is the same ad for Allergo-Merck Depot Acaros. Studies submitted by ALK Abello is the same as for ALK-Scherax (DE).
Point resolved.

MS Comments

The English translations of the SPCs of all concerning products are requested for the purpose of a discussion within the involved countries. The wordings of section 4.1 and 4.2 of the SPCs concerning the use in children can be assessed and be updated to the current guideline on summary of products.

Response from ALK

Please find attached a list (attachment 3) containing English translation the wording of section 4.1, 4.2, 4.3, 4.4 and 5.2 for the concerned products.

Response from Allergopharma

Please find enclosed English translations of our concerned SmPCs. See attachment {date}-de-spc-{product name}-en.pdf.

Response from LETI Pharma

English translations of SmPCs are attached to this document.

Assessor's comments:

The MAHs have provided the requested documents. Point resolved.

Comment 2

No proposal concerning including the results of the studies in section 5.1 were made. Since this is one of the goals of the paediatric worksharing a proposal is requested so a discussion can be started.

Response from ALK

The 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 SmPC and PIL throughout Europe

In addition no new clinical findings relevant to children have been presented during this process and therefore ALK does not see the need to include further data in section 5.1 in the SPC.

Response from Allergopharma

We assume that this question refers to rapporteur DK only.

Response from LETI Pharma

We have sent, in the submission of the report on 27.02.2009, a justification to outline the reasons why we considered that there was no need to change the wording of the SmPC regarding the use of diagnostic tests - prick and provocation Leti – and regarding the use of Depigoid on the paediatric population.

Please see documents enclosed:

- “Justification_of_SmPC_and_PL_of_Diagnostics.pdf”
- “Justification_of_SmPC_and_PL_of_Depigoid_Mites.pdf”

Should the competent authorities still think that a change of SmPC might be necessary, we would kindly appreciate being expressly instructed about the desired changes. Similarly, we would kindly appreciate obtaining any suggestion for a suitable wording.

Assessor’s comments:

As no new information was submitted by the MAHs further information in SPC 5.1 is not needed at the moment. Point resolved.

Comment 3

As no studies were conducted exclusively in children and no specific outcomes were reported, the reason for this conclusion is unclear. Please comment.

Response from ALK

The publications by Pajno et al and by Hedlin et al submitted by ALK contain only data about immunotherapy in the paediatric population.

Response from Allergopharma

We assume that this question refers to rapporteur DK only.

Response from LETI Pharma

We have sent, in the submission of the report on 27.02.2009, a justification explaining the reasons why we considered that there was no need to change the wording of the SmPC regarding the use of diagnostic tests, either for prick and provocation Leti, or for Depigoid® *D. pteronyssinus* and Depigoid® Milben Mix on the paediatric population.

Assessor’s comments:

The clinical experience gathered during decades of use of these products in common daily practise in children outweighs the lack of specific clinical studies in children. Point resolved.

Discussion on clinical aspects

House dust mite extracts have been used in daily clinical practise for years for diagnosis and immunotherapy in children with allergic rhinoconjunctivitis and mild-to-moderate asthma and that immunotherapy according to international position papers have a clearly defines role in treating these children.

The products were introduced and marketed at a time where the requirements were significantly less restrictive and therefore specific controlled clinical studies in children are lacking.

Post-marketing surveillance data have documented the safe use of these products with current labelling that is identical in children and adults.

Day 115 MS comments

A MS does not agree with the overall conclusions of the Rapporteur for the following reasons:

The efficacy and safety of the products under question in the pediatric population could not be proven by the submitted documents. The fact, that specific allergen immunotherapy with subcutaneous injection of the allergen is widely used in pediatric patients with perennial allergy due to house dust mites did not allow the assumption of the Rapporteur that it is an efficacious treatment in children. The PSUR data and the data of open post marketing surveillance studies allow only the assumption that for children up to now no higher risk than for adults was shown.

Further comment 12 and 13 on the PPdAR were agreed by the Rapporteur, but the corrections have not been made in FPdAR accordingly.

IV. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall Conclusion

Dust mite extracts containing *D. pteronyssinus* and *D. farinae* have been used in daily clinical setting for several years for diagnosis and immunotherapy in children with allergic rhinoconjunctivitis and mild-to-moderate allergic Asthma and according to international position papers have a role in treating these children. There is no difference in the responds to treatment in adults and children.

➤ Recommendation

For all therapeutic allergens the following statement should be implemented:

SmPC section 4.2:

“Children under 5 years of age are normally not considered suitable candidates for hyposensitization because acceptance and cooperation problems are more likely in this age group than for adults. For children >5 years of age clinical data of efficacy are sparse and cannot prove efficacy, however data on safety do not reveal a higher risk as for adults.”

And the corresponding section in the PL:

“[Name] is normally not recommended for treatment of allergy in children under the age of 5 years.”

For the prick-test allergens the following text should be implemented in SmPC section 4.2 and the corresponding section in the PL:

"Prick testing in children is already possible after the first year of life depending on the child's constitution, but in general should not be performed before the age of 4."