

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

**Felis Domestius**

**Canis Familiaris**

**Dog and cat hair allergen for diagnosis and treatment of  
Type-I allergy**

**DK/W/006/pdWS/001**

<b>Rapporteur:</b>	Denmark
<b>Start of the procedure (day 0):</b>	22.07.2009
<b>Date of this report:</b>	21.05.2010
<b>Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70):</b>	30.09.2009
<b>Deadline for CMS's comments (day 85):</b>	15.10.2009
<b>Date re-start procedure (day 90):</b>	21.04.2010
<b>Deadline for CMS's comments (day 115):</b>	15.05.2010
<b>Finalisation procedure (day 120):</b>	21.05.2010

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	<b>Alutard SQ (ALK 553, ALK 555)</b> <b>Aquagen SQ (ALK 553, ALK 555)</b> <b>Soluprick (ALK 553, ALK 555)</b>
INN (or common name) of the active substance(s):	Canis familiaris Felis domesticus
MAH (s):	ALK-Abelló A/S
Pharmaco-therapeutic group (ATC Code):	V 01 AA 11
Pharmaceutical form(s) and strength(s):	Suspension for injection Powder and solvent for solution for injection Solution for pricktest
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## I. EXECUTIVE SUMMARY

The MAH for the approved products for diagnosis and treatment of Type-I allergy to dog and cat (ALK-Abelló) has submitted a clinical expert statement documenting that the products used for diagnosis (Soluprick SQ and Aquagen SQ for provocation) and immunotherapy (Alutard SQ and Aquagen SQ) are commonly used in children as well as adults and that the diagnostic procedure and treatment modality are identical in both children and adults.

However the clinical documentation for the use of the product is sparse and for that reason the following statement should be implemented in SPC 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.*

### **Proposal for PIL**

*The product is normally not recommended for treatment of allergy in children under the ages of 5 years.*

For the prick-test allergens the following statement should be implemented in the current SPC 4.2.

*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.*

## II. RECOMMENDATION

It is recommended to modify the approved SPC as stated above.

## III. INTRODUCTION

The MAH (ALK-Abelló) has submitted a clinical expert statement with international position papers, PSUR and clinical studies.

Diagnosis and immunotherapy in general has wide use in paediatric patients from age 5 and above and the present products have seen used in clinical practice for years. The diagnosis of allergy in children against cat and dog hair and dander allergens depend on specific allergen extract from dog (*Canis Familiaris*) and cat (*Felis domesticus*) for prick testing and occasionally bronchial provocation. Similarly immunotherapy against cat and dog allergy is an established treatment modality using the same allergen extracts in an up dosing schedule and maintenance dosing both in children and adults.

*Malling et al. EACCI Position Paper. Allergy 1993; 14: 1- 46*

*Bousquet et al. WHO Position Paper. Allergy 1998; 53: 1 – 42*

*Scheinmann et al.: Immunotherapy in young children. Allergens and Immunotherapy 2006; 3: 567 – 83.*

The approved dose-regiments for immunotherapy are the same in children and adults.

No studies have been conducted to address effect and safety specifically in children.

## IV. SCIENTIFIC DISCUSSION

### Clinical studies

*Gunilla Hedin et al. Immunotherapy in children with allergic asthma: Effect on bronchial hyper reactivity and pharmacotherapy. J Allergy Clin Immunol. 1999; 103: 609 – 14.*

This placebo-controlled study was designed to investigate the effect of 3 years of cat or dust mite immunotherapy in children with moderate asthma with specific forms on the effect on bronchial hyper reactivity and the influence on concomitant use of inhaled corticosteroids.

A total 32 paediatric patients (7 – 16 years) were enrolled and 29 completed. Of the children 28 were allergic to cat hair and dander, 4 allergic to house dust mite and all were allergic to birch and/or grass pollen. Immunotherapy with Alutard SQ allergen extract and placebo both resulted in significant decreased bronchial hyper reactivity and hyper responsiveness to histamine, but more pronounced in the active immunotherapy group. There was no significant change in dose of inhaled budesonide needed for symptom control in either of the groups. There were no unexpected safety findings.

*Bo Sundin et al. Immunotherapy with partially purified and standardised animal dander extracts. Clinical results from a double-blind study in patients with animal dander asthma. J Allergy Clin Immunol 1986; 77: 478 – 87.*

The purpose of this study was to evaluate the clinical and immunologic effect of immunotherapy with standardised cat or dog - dander extract (Alutard SQ) relative to placebo in patients with cat dander or dog dander induced asthma. A total of 41 patients (21 adults and 20 children (aged 0,5 – 47 years) were included. Twenty two received active immunotherapy (15 with cat allergen and 7 with dog allergen) for 1 year. In the cat allergen – treated patients the bronchial sensitivity toward cat and histamine decreased significantly ( $p < 0.001$ ) and  $p < 0.05$ , respectively) measured by bronchial challenge, the cat allergen – treated patients could tolerate 11 times more allergen at the end than at the start of the study. No significant changes were observed in the dog allergen – treated or placebo treated groups. No unexpected adverse events were reported.

### Discussion on clinical aspects

The submitted clinical trials in children are small and no specific trials have been conducted in children with allergy to cat and/or dog hair /dander.

In the submitted PSURs and the company safety database, the reports that concern patients below 18 years constitute 24 % of the total number of reports from patients exposed to ALK-Abelló' s animal air diagnostics and immunotherapy. There is nothing to suggest that children differs neither regarding adverse event profile nor efficacy. However the clinical documentation is sparse in children and a modification of the approved SPC and PIL are suggested (see Executive Summary).

Comments raised by the RMS and from concerned Member States

## **A. Rapporteurs overall conclusion and recommendation**

### **Overall conclusion**

*The product approved for diagnosis and immunotherapy of cat and/or dog allergy are often used in children sensitized to these animal dander and the approved diagnostic procedure and the immunotherapy dose regime is identical in adults and children.*

### **Recommendation**

*The SPCs for the relevant products – as approved in all countries, where the products are on the market – should be submitted for evaluation, especially with regard to any information on use in children. A harmonisation procedure might be a way forward, probably including some information in 5.1. on the scanty clinical data.*

### **Response**

A table containing paediatric information in the SPCs for the different products in different countries is attached (Appendix 1).

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. The current SPCs in EU do not either mention clinical data for adults.

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.

### **Assessor’s comments**

The actual procedure, as pointed out by the MAH, is not to harmonise approved SPC in CMS and therefore the arguments presented is accepted. Although the diagnostic procedure and immunotherapy are identical in children and adults, we suggest a statement in the SPC 4.2 relating to the use of the products in children (See Executive Summary).

## **B. Comments received from other member states**

### **B.1 Comment from MS1**

*The MS1 does basically agree with the overall conclusions of the Rapporteur for the following reasons:  
As the Rapporteur pointed out, it does not become evident whether the SmPC wording regarding the paediatric population is identical for the different products as approved in all countries. Due to incomplete information a conclusive suggestion for an SPC wording can presently not be made.*

**As far at the information provided by the AR is concerned:**

#### **1. Comment**

*No differentiation has been made between diagnostic and therapy allergens.*

### **Response**

To be answered by the rapporteur

The overall conclusion in the PAR recognises diagnostics versus therapeutic products.

**Assessor's comments**

According to approved SPC there are specific products for both diagnosis and immunotherapy.  
Point resolved.

**2. Comment**

*In general, no details were provided in the summarized publications and study reports as to how many children of a certain age and gender have received SIT with Canis and/or Felis extract as the allergens in question or had been in the active treatment group (see study published by Bo Sundin et al., 1986).*

**Response**

The available publications on Canis and Felis allergen specific immunotherapy are assessed 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 the study published by Sundin et al. 12 children received an active treatment, 8 received Felis allergen and 4 received Canis allergen (see table III, page 482 in the publication) (ref 1 in Appendix 2).

In the study published by Hedin et al. 13 children with Felis allergy received an active treatment (ref 2 in Appendix 2).

**Assessor's comments**

The MAH has presented available efficacy and safety data in children exposed to products. No further data on children received SIT with Canis and/or Felis extract can be generated.

Point resolved.

**3. 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 have been investigated in parallel in the same study because no data was provided as to how many children of which age group were treated with the active substance of which allergen.*

**Response**

Two of the publications ALK submitted, Sundin et al and Hedlin et al. included only paediatric patients, but unfortunately the number of children treated with Canis/Felis allergens is limited and the results have not been analyzed for different age groups. The aim and the results of the studies are summarized below.

Sundin et al study included 21 adults and 20 children, and 8 children were treated with Felis allergen and 4 with Canis allergens.

The aim of the Sundin et al study was to study the clinical and immunologic effect of immunotherapy by use of standardized Felis or Canis extracts (Alutard SQ) relative to placebo in patient with Felis or Canis induced asthma. The conclusion of the study was that in the Felis allergen treated group the bronchial sensitivity toward Felis and histamine decreased. Measured by bronchial challenge, the Felis allergen-treated patients could tolerate 11 times more allergen at the end than at the start of the study. No significant changes were observed for the Canis allergen treated- or placebo treated groups.

Sundin et al registered the side effects and concluded that the adverse effects in general were negligible except for some systemic side effects during rush hypo sensitization, especially among the children, but these were mild and responded promptly to treatment.

It was not possible to evaluate if the side effects are more frequent within the paediatric population compared to adults in this study as the up-dosing was different in these two groups.

The Hedlin study included only paediatric patients and 13 children with Felis allergy received an active treatment.

The aim of the Hedlin study was to investigate the effect of cat or dust mite immunotherapy on bronchial hyper reactivity 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 hyper responsiveness to histamine. The combination of cat or dust mite and pollen immunotherapy and inhaled budesonide enhances this improvement. The aim of the Hedlin study was not to evaluate the safety of the treatment. However, the investigators reported some adverse events including mild systemic side effect in 5 children that received cat immunotherapy and recurrent urticaria and asthmatic reactions in one child that therefore was excluded from the study.

**Assessor's comments**

The MAH has presented all available efficacy and safety data in their assessment. The lack of publications and other data in children exposed to cat and/or dog extracts is compensated by the extensive clinical use of Felis and Canis extracts in children that receive SIT.  
Point resolved.

**4. Comment**

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

**Response**

ALK has already included the company position on this comment 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".

In the Sundin et al study the immunotherapy of the adults was carried out with Alutard SQ extracts with weekly injections starting at a dose of 30 SQ units. The dose was then increased stepwise to an ideal maximum dose of 100,000 SQ units. The injections were administered every fourth week after the individual maximum dose was reached, which was considered as the maintenance dose. The up-dosing for children was made differently but after one year of treatment the total dose of cat or dog allergen (SQ units) were about the same for children as for adults (Table 111)

The doses used in the study performed by Hedlin et al are given below:

The starting dose of allergen was 1 SQU and the maintenance dose was 100.000 SQU.

Two children in the active group had 80.000 SQU as their maintenance dose of cat allergen.

**Assessor's comments**

The MAH has presented both the Company position as well as the position of clinical experts on SIT with Felis and Canis extracts. No further clinical data in children can be generated at the moment.  
Point resolved.

**5. Comment**

*The MAH should provide detailed information on age and gender in the studied paediatric population.*

**Response**

See response to comment 2.

**Assessor's comments**

The MAH has responded in a satisfactory way (see previous comments).  
Point resolved.

## 6. 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**

As requested all events (149 individual cases for adults and 46 individual cases for children)- data are presented by distribution on MedDRA System organ Class (SOC) and Preferred Term (PT), for children and adults respectively in appendix 3. The data apply to 195 reports. They are based on all reports available to the MAH, from 1995 to 01 June 2009

The age range for the reported cases related to children was from 4 to 17 years, 41% are females and 56 % are males, sex not reported for 2% (1 case). There was one case where SoluPrick (diagnostic 10 species was used in an 8 month old girl, who experienced skin symptoms which resolved.

Regarding severity of the adverse events 28 % of reports in paediatric patient were assessed as serious and also 28 % 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 (17/ 3) as well as anaphylactic reaction is fairly low (19/1) in both children and adults Urticaria (30/16) and asthma (46/16) are the most frequently reported events 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 products. Market research indicates that about one third of sales of ALK grass pollen products are for children.

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

### **Assessor's comments**

The MAH has submitted all available safety data on the products. There is no signal of specific safety issues in children exposed to Canis and/or Felis extracts.

Point resolved.

### **Day 115 comments from MS1:**

1. It is the clear aim of the EU work sharing to harmonize the SmPCs regarding the wording according to the use in children. Thus, the statement of ALK and the Assessor's comment to point "A. Rapporteurs overall conclusion and recommendation" that the intention is not to be a harmonization process for SmPC and PIL is from our point of view not totally correct. It is correct, that not the full SmPC should be harmonized; however, the issues regarding children should be harmonized across the EU. This should be reflected in the Assessor's comments.
2. To the Answer to the 6. comment of MS1:According to the response of ALK in the table in Appendix 3 all adverse events are reported for adults and children. However, the headings of the columns with the number of cases read "Total" and "Paediatric". Since sometimes the number in column "Paediatric" is higher than in column "Total" it is assumed that column "Total" should read "Adults". This should be commented in the Assessor's comments or should be corrected by ALK.
3. To the Answer to the 6. comment of MS1:ALK stated that in general the adverse events resolved and refers to response to Q10. However, there is no question 10 and consequently no

answer to question 10. This should be at least commented in the Assessor's comments or ALK should be asked to which documents they refer to.

#### **Assessor's comments**

1. We agree that the SPC and PIL text should be harmonised concerning the pediatric indication. As previously stated the following text should be added in SPC section 4.2:

*Children under 5 years of age are normally not considered candidates for hyposensitization because of 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.*

In the PIL the following should be implemented:

*“(Name) is normally not recommended for treatment of allergy in children under the age of 5 years”*

For prik-test allergens the following statement should be implemented in SPC section 4.2.

*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.*

The above proposal is in line with that agreed upon with D. pteronyssinus and D. farinae allergens.

2. We agree with the CMS that the labelling of the column in the ALK Appendix 3 should be changed as suggested.

The MAH has confirmed that the column “total” should be named “adults”. The MAH has submitted an updated appendix 3. Point resolved.

3. In the ALK statement on the adverse events the reference to Q 10 (see response to Q 10) should be deleted.

#### **Comments on FPdAR from MS2:**

Please be informed that MS2 does not consider harmonisation the goal of PdWS. In MS2 SmPC children younger than 5 years are now contra-indicated for treatment with Alutard SQ 553. On the basis of this PdWS the MS2 does not see data to remove this contra-indication. Therefore the company is not requested to submit a variation to change the SPC.

For the SPT in MS2 the SPC already contains the sentence:

*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.*

Therefore the company is not asked to submit a variation.

#### **Assessors comment**

It will not be possible to achieve a fully agreed recommendation, see below. Rapporteur recommends implementation of the proposed recommendation.

## **V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**

### **Overall Conclusion**

The product approved for diagnosis and immunotherapy of cat and/or dog allergy are often used in children sensitized to these animal dander and the approved diagnostic procedure and the immunotherapy dose regime is identical in adults and children.

However the submitted clinical documentation is sparse and as a consequence a modification of the approved SPC text relating to the use of the products is needed (see suggested changes in Executive Summary).

### **Recommendation**

Based on the available sparse clinical documentation and the response from Concerned Member States the approved SPC text need to be revised taken into account the limited experience with the use of the product in children.

The suggested modifications are shown in the Executive Summary Section.

### **V.1 DISCUSSIONS ON SmPC FOLLOWING CIRCULATION OF FINAL AR**

Following circulation of the final assessment report, comments were received from one MS that the harmonised paediatric recommendation as proposed by the Rapporteur could not be accepted. It is the Rapporteurs opinion that agreement on a fully EU harmonised paediatric recommendation can not be achieved in this particular case, because of differences in the already approved paediatric use among MS.

The procedure will be finalised in accordance with the Rapporteur's final recommendation for paediatric use (see above) and implementation of the harmonised use in MS via appropriate regulatory procedures is recommended. However, we acknowledge that one MS is not in agreement with the proposed changes.

The Rapporteur recommends that the MAH achieve full harmonisation with regard to paediatric use through use of appropriate regulatory procedures.