LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Alutard SQ Getinggift
(*Vespula* spp.)

SE/H/1638/01-02/MR

This module reflects the scientific discussion for the approval of Alutard SQ Getinggift. The procedure was finalised on 2017-12-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

ALK-Abelló A/S has applied for a marketing authorisation for Alutard SQ Getinggift, up-dosing package (100 SQ-U/ml, 1 000 SQ-U/ml, 10 000 SQ-U/ml and 100 000 SQ-U/ml) and 100 000 SQ-U/ml (maintenance pack), suspension for injection.

The applicant, ALK-Abelló A/S, applies for a marketing authorisation in AT, BE, ES, HU, IT, LU, NO, PT, RO and SI through this mutual recognition procedure with Sweden acting as reference member state (RMS). The product was first approved through a National Procedure.

Alutard SQ Getinggift (wasp venom) is an allergen product with standardised allergen extract of venom from *Vespula* spp. as the drug substance.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3), Known active substance of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The *Vespula* spp. drug substance is derived from venom from wasps/yellow jackets. The wasp venom species included in the drug substance mixture are *Vespula germanica, Vespula alascensis, Vespula maculifrons, Vespula flavopilosa, Vespula pensylvanica* and *Vespula Squamosa.* The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and limits and compliance with Ph Eur monograph on *Allergen Products* has been shown. The analytical methods applied are suitably described and validated.

Stability studies have been conducted and confirm the shelf-life.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Standard animal studies on primary, secondary and safety pharmacodynamics have not been performed with Alutard SQ Venoms.

However, considering the specificity of the pharmacological action, the fact that humans for millennia have been naturally exposed to the allergens contained in Alutard SQ Venoms and the extensive clinical experience with Alutard SQ Venoms no further animal studies are considered necessary to evaluate the pharmacological properties of the Alutard SQ Venoms.

III.2 Pharmacokinetics

The Alutard SQ Venoms are products with high molecular weight and the doses are small in absolute terms of weight (up to 100 µg). They are given subcutaneously in a formulation with aluminium for slow release to reach cells of the immune system.

The main part of the extract is constituted of polypeptides and proteins that are expected to be metabolised and degraded to amino acids and smaller peptides before reaching the blood stream.

For this reason it is evaluated that no further experimental evaluation of pharmacokinetics is necessary.

III.3 Toxicology

Single dose toxicity data demonstrated a wide margin between the maximum human therapeutic dose and the doses inducing adverse effects after intraperitoneal injection in mice and guinea pigs (> 250- and 150-fold, respectively) (Scantox 1986a; Scantox 1986b). Repeated dose toxicity data showed no adverse effects in mice at a dose of venom extract of up to 50 µg per month injected subcutaneously (Jonsson & Falk 1978). This dose is approximately 1250-fold higher than the maximum human therapeutic dose based on body weight.

The non-clinical toxicity studies were performed before the concept of GLP was introduced and can therefore not be judged according to the present standard. However, the studies were performed up to the standard of that time at a quality level considered satisfactory, and the results are judged as reliable. In addition, the data is in light of the clinical safety data base of extremely limited value.

The vast clinical experience does not indicate a genotoxic or carcinogenic potential of venom extracts. Effects on reproduction have not been studied. However, data from the repeated dose toxicity studies and the vast clinical experience does not indicate any risk to male or female reproduction.

In conclusion, no effects except from the expected immunological effects can be demonstrated in connection with the use of Hymenoptera venom extracts and the data indicate that Alutard SQ Venoms does not pose a risk to the patient when administered as intended.

III.4 Ecotoxicity/environmental risk assessment

The active substance (the venom) is a mixture of proteins and therefore not considered to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical part of the dossier for Alutard SQ Getinggift is based upon a bibliographic review of the published literature as well as substantial post-marketing experience with the product with nine key clinical studies (efficacy and safety) performed exclusively with Alutard SQ *vespula spp* (ref 1-9), including in total 517 subjects, and 12 key clinical studies (efficacy and safety) performed using both Alutard SQ *vespula spp* and Alutard SQ *Apis mellifera* (ref 10-21) including in total 1294 subjects. In addition, in total 280 subjects were included in five supportive efficacy studies performed exclusively with Alutard SQ *Apis mellifera* (ref 22-26).

IV.2 Pharmacokinetics

Clinical trials investigating the pharmacokinetic profile and metabolism of Alutard SQ *Vespula spp* have not been performed. This is in accordance with the EMA 2008 guideline on clinical development of products for allergy immunotherapy**.** Alutard SQ *Vespula spp* is formulated as a depot preparation, and hence cause slow release of the allergen extract after subcutaneous injection. Furthermore, the main part of the extract is polypeptides and proteins, which are expected to be broken down to amino acids and small polypeptides. There is no evidence to suggest that the allergens present in Alutard SQ *Vespula spp* are absorbed into the vascular system.

IV.3 Pharmacodynamics

The pharmacodynamic effect of VIT is equivalent to the immunological effect. According to the European Medicines Agency guideline on clinical development of products for AIT for the treatment of allergic diseases (EMEA 2008b), the effect of AIT on the immune system should be evaluated by measuring immunological changes (e.g. changes in allergen-specific Ig levels).

Seven of the studies included in the present dossier investigate the immune modulatory effect of treatment with Alutard SQ*Vespula spp* in terms of changes in serum levels of IgE and IgG (Table 1).

Table 1 Summary of results related to immunology after treatment with Alutard SQ

Study	Treatment	Number of subjects	Immunological results
Key studies performed exclusively with Alutard SQ *Vespula spp.*			
Malling et al 1985 (Malling et al. 1985)	Alutard SQ *Vespula* spp.	25	IgE showed an initial increase then declining to pre-treatment levels. IgG_4 increased during the entire study period.
Mosbech et al 1986 (Mosbech et al. 1986)	Alutard SQ *Vespula* spp. vs. Aquagen vs Pharmalgen	32	IgE descreased with no significant difference between the treatment groups. IgG significantly increased after 6, 12, 18 and 24 months of treatment in the group treated with Alutard SQ.
Möbs et al 2015 (Mobs et al. 2015)	Alutard SQ *Vespula spp.*	39	IgE reduced in subjects having completed immunotherapy 5-12 years ago compared to levels in subjects prior to treatment and subjects undergoing treatment. IgG_4 highest in subjects undergoing treatment but significantly lower in subjects evaluated before or after stopping immunotherapy.
Key studies performed both with Alutard SQ *Vespula spp.* and Alutard SQ *Apis mellifera*			
Wyss et al 1993 (Wyss et al. 1993)	Alutard SQ *Apis mellifera* and/or *Vespula* spp.	35	IgE reduced from 1 year onwards for all subjects treated. IgG and IgG_4 increased by the time maintenance dose was reached and this increase was maintained for the duration of the treatment.
Pasaoglu et al 2006 (Pasaoglu et al. 2006)	Alutard SQ *Apis mellifera* or *Vespula* spp.	18	IgE levels did not differ significantly in treated subjects when comparing values after 1 year of treatment with baseline. IgG_4 significantly increased.
Patella et al 2012 (Patella et al. 2012)	Alutard SQ *Apis mellifera* vs. Aquagen	76	IgE decreased from start of treatment to 2 years after treatment start with no difference between groups.
Supportive studies performed exclusively with Alutard SQ *Apis mellifera*			
Quercia et al 2006 (Quercia et al. 2006)	Alutard SQ *Apis mellifera* vs. Aquagen	70	IgE significantly reduced after 5 years of treatment.
Varga et al 2009 (Varga et al. 2009)	Alutard SQ *Apis mellifera*	20	IgE significantly reduced during treatment and after treatment completion. IgG_4 level significantly increased during treatment compared with after treatment completion and normal controls.

Overall, the studies demonstrated an immune modulatory effect of treatment with Alutard SQ *Vespula spp.* The trend across studies was a rapid increase in IgG antibodies from the onset of treatment, and the increase continued, though at a slower rate, for the duration of the treatment. Concerning IgE, there seemed generally to be an initial raise in the levels at start of treatment followed by a decline so that by the end of the first year of treatment, IgE levels were similar to or below baseline levels. However, it should be mentioned that a single study demonstrated sustained lower levels of IgE even after completion of treatment.

IV.4 Clinical efficacy

Introduction and Method

To support the clinical efficacy of Alutard SQ *Vespula spp.*, a total of 44 studies are included:

- 7 key studies performed exclusively with Alutard SQ *Vespula spp* (ref. 1-7)
- 2 key studies investigating the effect of Alutard SQ *vespula spp*. on quality of life (ref.8-9)
- 7 key studies performed using both Alutard SQ *vespula spp*. and Alutard SQ *Apis mellifera* (including studies where it was not possible to distinguish between these 2 products) (ref. 10-16).
- 4 supportive studies performed exclusively with Alutard SQ *Apis mellifera.* (ref. 22-25).

24 supportive studies investigating the clinical efficacy of Alutard SQ Venom related products (i.e. Pharmalgen and Aquagen) were also submitted in the application.

Most of the studies in the bibliography were published during the last 15 years. The major objectives with the different studies have been either to compare different up-dosing regimens with Aquagen SQ *Hymenoptera venom* (bee and/or wasp) or to compare the effect of the fast release formulations of the venoms (i.e. Pharmalgen and Aquagen) with the slow release formulation (Alutard SQ Hymenoptera Venoms). There are no MAH sponsored clinical trials performed or other un-published data with Alutard SQ *Vespula spp.* included in the presented dossier. In total 16 key efficacy studies has been submitted. These studies all included subjects using Alutard SQ *vespula spp.* alone or subjects using Alutard SQ *vespula spp* and/or Alutard SQ *Apis Mellifera.* In addition 28 supportive efficacy studies have been submitted four with Alutard SQ *Apis mellifera* alone and 24 studies with Alutard SQ Venom related products (i.e. Pharmalgen and Aquagen; studies).

Study design and end-points

Due to the nature of the disease/conditions and ethical aspects all studies had an open, non-controlled design with active treatment for all subjects. Most of the studies had a prospective design. Three of the key efficacy studies were randomised (ref. Malling et al.[ref. 1], Mosbech et al [ref. 2] and Oude Elberink et al [ref.3]). The subjects were randomised to any of the two different formulations of Hymenoptera venoms, “fast release” (Alutard Aqua/Pharmalgen) or “slow release” (Alutard SQ Hymenoptera venom) or to different dose regimes. No data from randomised placebo-studies are available. This should be taken into account when efficacy data are evaluated. The only study exclusively performed in children was an open, non-controlled and retrospective study (Konstantinou et al. 2011 [ref. 14]).

Sting challenge was the most frequently studied endpoint. This was done either by in-hospital sting challenge (“provoked sting”) or more often of the “natural re-sting challenge”. The follow-up time differed from 1 year to 5 years.

Results

Covered population

Both adults and children were selected for the studies based on their history of systemic reactions to Hymenoptera stings, usually combined with a positive skin prick test and/or positive specific IgE to the appropriate allergen(s). Children, adults and elderly were included in the clinical studies. The product is indicated without age restriction (SmPC section 4.2).

Sting challenge

The overall protection rate (i.e. subjects tolerating a sting without having any systemic reactions) offered by Alutard SQ *Vespula spp.* was 52 out of 56 based on 3 clinical studies (ref. 1-3). This protection rate was supported by the studies performed with both Alutard SQ Vespula spp. and Alutard SQ Apis mellifera and by the supportive studies conducted

exclusively with Alutard SQ Apis mellifera and with the Alutard SQ-related product Pharmalgen (**Table 2**).

However, the studies were not placebo controlled this should be taken into consideration when evaluating the results.

In total, a substantial amount of subjects with history of systemic reactions to Hymenoptera stings, usually combined with a positive skin prick test and/or positive specific IgE to the appropriate allergen(s) have been studied and supporting a sufficient evidence regarding a positive effect of VIT with Alutard SQ *Vespula spp* in this population.

Table 2 Summary of results related to systemic reactions to stings after treatment with Alutard SQ

Study	Treatment	Number of subjects	Percentage of subjects without systemic reaction to sting after treatment with Alutard SQ
Key studies performed exclusively with Alutard SQ *Vespula spp.*			
Malling et al 1985 (Malling et al. 1985)	Alutard SQ *Vespula* spp.	25	100%
Mosbech et al 1986 (Mosbech et al. 1986)	Alutard SQ *Vespula* spp. vs. Aquagen vs Pharmalgen	32	100%
Oude Elberink et al 2007 (Oude Elberink HNG et al. 2007)	Alutard SQ *Vespula* spp. vs. Allergoid (Purethal)	66	88%
Poli et al 2001 (Poli et al. 2001)	Alutard SQ *Vespula* spp.	36	100%
Alessandrini et al 2006 (Alessandrini et al. 2006)	Alutard SQ *Vespula* spp. vs. Aquagen	107	100%
Verburg et al 2015 (Verburg et al. 2015)	Alutard SQ *Vespula* spp.	9	100%
Key studies performed both with Alutard SQ *Vespula spp.* and Alutard SQ *Apis mellifera*			
Wyss et al 1993 (Wyss et al. 1993)	Alutard SQ *Apis mellifera* and/or *Vespula* spp.	35	100%

Cadario et al 2004 (Cadario et al. 2004)	Alutard SQ *Apis mellifera* and/or *Vespula* spp. vs. Pharmalgen	45	100%
Pasaoglu et al 2006 (Pasaoglu et al. 2006)	Alutard SQ *Apis mellifera* or *Vespula* spp.	18	100%
Lang & Hawranek 2006 (Lang & Hawranek 2006)	Alutard SQ *Apis mellifera* or *Vespula* spp.	192	86%
Konstantinou et al 2011 (Konstantinou et al. 2011)	Alutard SQ *Apis mellifera*, *Vespula* spp., Polistes spp, mixed Vespid	54	100%
Patella et al 2012 (Patella et al. 2012)	Alutard SQ *Apis mellifera* or *Vespula* spp. vs. Aquagen	76	99%
Stoevesandt et al 2015 (Stoevesandt et al. 2015)	Alutard SQ *Apis mellifera* or *Vespula* spp.	225	93%
Supportive studies performed exclusively with Alutard SQ *Apis mellifera*			
Ruëff et al 2004 (Rueff et al. 2004)	Alutard SQ *Apis mellifera* spp. vs. Pharmalgen	65	84%
Quercia et al 2006 (Quercia et al. 2006)	Alutard SQ *Apis mellifera* spp. vs. Aquagen	70	100%
Bilò et al 2012 (Bilo et al. 2012)	Alutard SQ *Apis mellifera* vs. Aquagen vs Pharmalgen	80	99%

Immunological parameters
Overall, the presented studies demonstrated an immune modulatory effect of treatment with Alutard SQ *Vespula spp*. For furthers results see section Pharmacodynamics and **Table 1** above.

Studies supporting the dosing
In general, subcutaneous immunotherapy is carried out in 2 phases: an *up-dosing phase* and a *maintenance phase*. The reason for having an up-dosing phase with subcutaneous immunotherapy is to gradually improve the immunological tolerance of the patient before administering the recommended maintenance dose.

Up-dosing phase: Different up-dosing schedules have been investigated in 11 studies with Alutard SQ *Vespula spp* or Alutard *SQ Apis mellifera* (
Table **3** and Table 4). The results support similar efficacy and tolerability profiles for the current up-dosing regimens recommended in the SmPC.

The three up-dosing regimens currently recommended for Alutard SQ *Vespula spp* are the 25-week, 15-week and 7-week up-dosing schedules respectively. All schedules are tabulated in SmPC section 4.2 and as reflected in the SmPC, the recommendations given in the tables/schedules are to be considered as a guide and to be adjusted according to the sensitivity of individual subjects. The 25-week up-dosing schedule is recommended to sensitive individuals as the risk of developing allergic reactions should be decreased. The 15-week up-dosing schedule is suitable for the majority of individuals, while the 7-week up-dosing schedule is only recommended in special cases where there is a need for faster protection.

Maintenance phase: In most of the included studies the dose of Alutard SQ is given in µg, i.e., 100 µg venom for maintenance. The dose 100 µg venom corresponds to 100,000 SQ-U and thus supports the recommendations in the SmPC. Maintenance injections should be given every 6-8 weeks for 3-5 years, which is in accordance with clinical guidelines for

immunotherapy (Bonifazi et al. 2005 [ref. 35]). This is supported by results in the studies included in the present dossier.

Dosing in children: No dose adjustment is needed for the paediatric population. For use in the pediatric population see also the section "Clinical studies in special populations" below.

Table 3 Studies investigating up-dosing according to short cluster regimens

Description	Number of subjects exposed to Alutard SQ during up-dosing	Conclusions
Key studies performed exclusively with Alutard SQ *Vespula spp.*		
Alessandrini et al. 2006 (Alessandrini et al. 2006)		
Open, non-controlled study to compare the efficacy and safety of Alutard SQ versus Aquagen SQ according to 3 different protocols for at least 3 years.	Open, non-controlled study to compare the efficacy and safety of Alutard SQ versus Aquagen SQ according to 3 different protocols for at least 3 years.	Open, non-controlled study to compare the efficacy and safety of Alutard SQ versus Aquagen SQ according to 3 different protocols for at least 3 years.
Key studies performed using both Alutard SQ *Vespula spp.* and Alutard SQ *Apis mellifera*		
Konstantinou et al. 2011 (Konstantinou et al. 2011)		
Open, non-controlled study to evaluate retrospectively the efficacy and safety of Alutard SQ administered according to a modified cluster protocol lasting 5 years.	Cluster up-dosing with 31 injections over 5 weeks (14 clusters at 1-2 days intervals). 54 subjects	Cluster up-dosing with Alutard for 5 weeks was safe.
Mellerup et al. 2000 (Mellerup et al. 2000)		
Open, retrospective study to evaluate the practicability and safety of 3 different patient-friendly induction regimens of clustered immunotherapy.	Cluster up-dosing with 16 injections over 8 weeks (8 clusters with 1 week interval). 507 subjects	Cluster up-dosing with Alutard for 8 weeks was an acceptable compromise between safety and time used.
Winther et al. 2006 (Winther et al. 2006)		
This was an open, prospective, multi-centre study to evaluate the safety of VIT and to identify possible risk factors for systemic reactions.	Different cluster regimens investigated: centre 1: 14 injections over 7 weeks; centre 2: 12 injections over 11 weeks; centre 3: 10 injections over 8 weeks; and centre 4: 15 weekly injections. 1038 subjects received treatment of various allergen including wasp and bee venom	Cluster up-dosing with Alutard for 7-11 weeks was safe.
Supportive studies performed exclusively with Alutard SQ *Apis mellifera*		
Quercia et al. 2006 (Quercia et al. 2006)		
Open, non-controlled study to compare the efficacy, safety and modulation of specific immunologic parameter of Alutard SQ versus Aquagen SQ according to 3 different treatment protocols for at least 5 years.	Open, non-controlled study to compare the efficacy, safety and modulation of specific immunologic parameter of Alutard SQ versus Aquagen SQ according to 3 different treatment protocols for at least 5 years.	Open, non-controlled study to compare the efficacy, safety and modulation of specific immunologic parameter of Alutard SQ versus Aquagen SQ according to 3 different treatment protocols for at least 5 years.

Description	Number of subjects exposed to Alutard SQ during up-dosing	Conclusions
Quercia et al. 2001 (Quercia et al. 2001)		
Open, controlled, prospective study to evaluate the safety of up-dosing with Alutard according to a cluster regimen compared with up-dosing with Pharmalgen according to a cluster or rush regimen in subjects sensitised to *Apis mellifera*.	Cluster up-dosing with 12 injections over 5 weeks (5 clusters with 1 week interval). 15 subjects	Cluster up-dosing with Alutard for 5 weeks was safe.

Table 4 Studies investigating up-dosing according to conventional regimens

Description	Number of subjects exposed to Alutard SQ during up-dosing	Conclusions
Key studies performed exclusively with Alutard SQ *Vespula spp.*		
Poli et al. 2001 (Poli et al. 2001)		
Open, retrospective, non-controlled study to evaluate efficacy and safety of Alutard SQ.	Open, retrospective, non-controlled study to evaluate efficacy and safety of Alutard SQ.	Open, retrospective, non-controlled study to evaluate efficacy and safety of Alutard SQ.
Mosbech et al. 1986 (Mosbech et al. 1986)		
Randomised, non-controlled study to compare efficacy and safety of Alutard SQ versus Aquagen SQ versus Pharmalgen treatment for 3 years.	Randomised, non-controlled study to compare efficacy and safety of Alutard SQ versus Aquagen SQ versus Pharmalgen treatment for 3 years.	Randomised, non-controlled study to compare efficacy and safety of Alutard SQ versus Aquagen SQ versus Pharmalgen treatment for 3 years.
Key studies performed using both Alutard SQ *Vespula spp.* and Alutard SQ *Apis mellifera*		
Cadario et al. 2004 (Cadario et al. 2004)		
Open, non-controlled study to compare the efficacy and safety of Alutard SQ versus Pharmalgen treatment for at least 3 years.	Conventional up-dosing with 15 weekly injections. 27 subjects	Conventional up-dosing with Alutard for 15 weeks was safe and effective.
Wyss et al. 1993 (Wyss et al. 1993)		
Open, prospective, non-controlled study to evaluate the efficacy and safety of bee and wasp venom Alutard according to 3 different protocols for 3 years.	Conventional up-dosing with 17 weekly injections. 35 subjects	Conventional up-dosing with Alutard for 17 weeks was safe.

Description	Number of subjects exposed to Alutard SQ during up-dosing	Conclusions
Supportive studies performed exclusively with Alutard SQ *Apis mellifera*		
Rüeff et al. 2004 (Rueff et al. 2004)		
Open, non-controlled study to evaluate efficacy and safety of Pharmalgen versus Alutard SQ according to 3 different protocols for 3 years.	Open, non-controlled study to evaluate efficacy and safety of Pharmalgen versus Alutard SQ according to 3 different protocols for 3 years.	Open, non-controlled study to evaluate efficacy and safety of Pharmalgen versus Alutard SQ according to 3 different protocols for 3 years.

Persistence of Efficacy and/or Tolerance Effects
VIT treatment with Alutard SQ Venom (*Vespula spp* and/or *Apis mellifera*) of 3-5 years demonstrated sustained effect several years (up to 13 years) after end of treatment. This finding was also demonstrated in several of the supportive studies with Alutard SQ Venom related products (i.e. Pharmalgen and Aquagen).

Clinical studies in the paediatric population
Use with Alutard SQ Hymenoptera Venoms in the paediatric population was discussed and assessed in detail in 2010 within a paediatric procedure Article 45 of the Regulation (EC) No. 1901/2006 (DE/W/0010/pdWS/001 and DE/W/0012/pdWS/001). In this procedure paediatric studies completed before 26 January 2007, which had not previously submitted were assessed. The procedure ended up with a conclusion that from available data, at time of assessment, it was not possible to prove efficacy of insect venom immunotherapy in children since no separation of data in children and adults were possible.

However, it was agreed that the same up-dosing schedules and maintenance doses could be used for adults and children due to the fact that the tolerability of the individual patient is the main determinant in the achievement of the maintenance dose and that dose adjustments may be necessary in case of occurrence of side effects**.**

Since age ranges were not clearly stated in any of the studies it was assumed that few subjects were below 5 years of age. There for no conclusions could be drawn for this age group and it was concluded that a risk-benefit analysis must be carefully considered when treating children below 5 years of age. This is reflected in the SmPC section 4.4.

There are three articles (Konstantinou et al. 2011 [ref.14], Golden et al. 2004a [ref. 27] and Gonzalez et al. 2009 [ref. 28]) published after the Article 45 procedure supporting the conclusions in this procedure regarding use of Alutard SQ in the paediatric population.

IV.5 Clinical safety

To support the clinical safety of Alutard SQ *Vespula spp.* the following studies are included in the present dossier:

- 5 key studies performed exclusively with Alutard SQ *Vespula spp* (ref. 1-5). Some of these studies also include efficacy data and are therefore also described in Section III.
- 11 key studies performed using both Alutard SQ *Apis mellifera* and Alutard SQ *vespula spp*. (ref. 10-12 and ref.14-21).
- 4 supportive studies performed exclusively with Alutard SQ *vespula spp*. (ref. 22-23 and 25-26)
- For completeness, 20 studies investigating the clinical safety of the related aqueous products Pharmalgen or Aquagen SQ were also submitted in the application.

Safety was generally assessed based on AE reporting.

Patient exposure
At least 1300 have been exposed to Alutard SQ *Apis mellifera* and/or *Vespula spp* in the submitted key clinical studies. In addition 4800 subjects have been treated with Alutard related products.

Demographic and Other Characteristics of Study Population
The studies have been performed in a mixed population with regards to age varying from young children to elderly (3–79 years). No subjects below 3 years could be identified in the safety studies. It is noticed that in general more males than females were included in the studies. However, approximately 25-40% was females in most of studies. The systemic reactions were most often degreed according to the Muller scale (graded from I-IV) (Table 5).

Table 5

Muller's grading for systemic allergic reactions (Mueller UR 1990):	
I	Generalised urticaria, periorbital oedema, itching, malaise, anxiety
II	Angioedema or two or more of the following: chest or throat tightness, nausea, vomiting, diarrhoea, abdominal pain, dizziness
III	Dyspnoea, wheezing, or stridor, or two or more of the following: dysphagia, dysathria, hoarseness, weakness, confusion, feeling of impending disaster
IV	Hypotension, collapse, loss of consciousness, incontinence, cyanosis

Adverse events
The reported AEs in the clinical trials were all *local injection reactions* and/or s*ystemic allergic reactions* with varied degree. Local reactions in association with Alutard SQ varied between 0% and 79% in the up-dosing phase and 0-47% in the maintenance phase (.Systemic reactions in association with Alutard SQ in the up-dosing phase varied between 0-25% and in the maintenance phase between 0% and 16%. (Table 6)

The systemic allergic reactions was mainly Muller grade I and II. Severe systemic reaction (Muller grade III and IV; see Table 5 for description) were, where specified/graded, in the submitted studies reported in < 3% of the subjects.

The risk for severe systemic allergic reactions is adequately reflected in the SmPC section 4.2, 4.4 and 4.8.

Table 6 Summary of results related to local and systemic reactions to treatment with Alutard SQ

Study	Adverse events			
	Up-dosing		Maintenance	
	Local reactions n/N	Systemic reactions n/N	Local reactions n/N	Systemic reactions n/N
Key studies performed exclusively with Alutard SQ *Vespula spp.*				
Mosbech et al 1986 (Mosbech et al. 1986)	NR	3/12 (25%)	NR	1/12 (8.3%)
Poli et al 2001 (Poli et al. 2001)	2/36 (5.6%)	0736 (0%)	0/36 (0%)	0/36 (0%)
Alessandrini et al 2006 (Alessandrini et al. 2006)	2/34 (5.6%)	2/34 (5.6%)	NR	NR
Verburg et al 2015 (Verburg et al. 2015)	NA	NA	NR	0/9 (0%)
Key studies performed using both Alutard SQ *Vespula spp.* and Alutard SQ *Apis mellifera*				
Wyss et al 1993 (Wyss et al. 1993)	33.3%	3/35 (8.6%)	NR	0/35 (0.0%)
Cadario et al 2004 (Cadario et al. 2004)	4/27 (14.8%)	2/27 (7.4%)	0/27 (0.0%)	0/27 (0.0%)
Pasaoglu et al 2006 (Pasaoglu et al. 2006)	11/14 (78.6%)	1/14 (7.1%)	0/14 (0.0%)	0/14 (0.0%)
Konstantinou et al 2011 (Konstantinou et al. 2011)	NR	1/53 (1.9%)	NR	1/53 (1.9%)
Patella et al 2012 (Patella et al. 2012)	NA	NA	6/76 (7.9%)	8/76 (10.7%)
Stoevesandt et al 2015 (Stoevesandt et al. 2015)	NR	19/225 (8.4%)	20/225 (8.9%)	21/225 (9.3%)
Mellerup et al 2000 (Mellerup et al. 2000)	NR	Grade I: 104/507 (21%) Grade II: 101/507 (20%) Grade III: 17 (3%) Grade IV: 1/507 (0.2%)	NA	NA
Reccardini et al 2004 (Reccardini F et al. 2004)	NA	NA	2/30 (6.7%)	0/30 (0.0%)

Study	Adverse events			
	Up-dosing		Maintenance	
	Local reactions n/N	Systemic reactions n/N	Local reactions n/N	Systemic reactions n/N
Supportive studies performed exclusively with Alutard SQ *Apis mellifera*				
Ruëff et al 2004 (Rueff et al. 2004)	5/23 (21.7%)	3/23 (13.0%)	15/32 (46.9%)	5/32 (15.6%)
Quercia et al 2006 (Quercia et al. 2006)	3/29 (10.3%)	1/29 (3.4%)	0/29 (0.0%)	1/29 (3.4%)
Bilò et al 2012 (Bilo et al. 2012)	NA	NA	NR	0/51 (0.0%)
Quercia et al 2001 (Quercia et al. 2001)	1/15 (6.7%)	0/15 (0.0%)	NA	NA

N = Number of subjects treated with Alutard SQ; n = number of subjects with events; NA: not applicable (e.g. if up-dosing is performed with an aqueous extract); NR: not reported (also including cases where it is impossible to distinguish whether there were no reactions or whether were they were merely not reported).

Serious adverse events and deaths
No fatal events were reported in any of the studies included in this dossier.

For the studies included in the present dossier, AEs have not been categorised as serious or non-serious, since the AEs were not categorised as serious or non-serious in the publications. However, a few severe systemic reactions (Muller grade III, IV) were reported. In the study by Malling et al. 1985 (ref. 1), two subjects were reported to have anaphylactic shock and one subject had a grade III systemic reaction. In the study by Mellerup et al. in 2000 (ref. 18) 3% and 0.2% of subjects were reported to have a grade III and IV systemic reaction after treatment with Alutard SQ Hymenoptera Venoms.

Safety in special populations
Gender: Data from VIT in general has suggested an increased risk of systemic AEs to treatment in females (Mosbech & Muller 2000 [ref. 29]) treated with VIT. This is supported by one study in the bibliography for Alutard *Apis mellifera* (Mellerup et al. in 2000 [ref. 18]). However, the difference only concerned mild and not severe reaction. In addition, supportive studies (Roll et al. 2006 [ref. 30] and Sturm et al. 2002 [ref. 31]) have not demonstrated any gender difference. Thus, it is concluded that even if a small gender difference should be present this should not be of any obvious clinical importance since only mild reactions were concerned.

Age: Limited data from clinical trials on the adverse events in children below 5 years is available. Available safety data from Paediatric Article 45 procedure in 2010 and articles published after this procedure (Konstantinou et al. 2011[ref. 14], Gonzalez et al. 2009 [ref. 28] and Kohli-Wiesner et al. 2012 [ref. 32]) does not indicate additional risks related to the use of Alutard SQ in the paediatric population. This is reflected in SmPC section 4.4 and 4.8.

Use in subjects with mastocytosis: The study by Verburg et al in 2015 (ref. 7) in subjects with mastocytosis suggested that treatment with Alutard seems to be safe in patients with systemic mastocytosis. This issue was assessed in 2014 in procedure 5.4.3-2014-2635 and is thereafter reflected in the SmPC section 4.4**.**

Safety related to drug-drug interactions and other interactions
Drug interactions have not been studied.

Concomitant treatment with Alutard SQ and cardiovascular medication (ACE inhibitors and beta-blockers) was investigated in the study by Stoevesandt et al. in 2015 (ref. 16). This study showed that cardiovascular medication did not impair the safety of immunotherapy. This is reflected in the SmPC.

Use in Pregnancy and Lactation
No clinical data is available for the use of Alutard SQ Apis mellifera during pregnancy or lactation. This is reflected in the SmPC.

Post marketing experience
Post marketing exposure
The cumulative post-marketing exposure covers the period from 01 January 2003 to 29 February 2016. The exposure to Alutard SQ *Vespula spp.* in this period is estimated to 303,223 treatment years (TY). The package specific Conversion Factor multiplied by the number of sold specific packages gives the TY. The overall TY is calculated by adding all the calculated TYs for each certain packages type.

Adverse reactions reported post-marketing
Up to 29 February 2016, a total of 1192 adverse reactions (889 non-serious and 303serious) have been reported in connections with Alutard SQ *Vespula spp.* The overall most common serious reactions were *anaphylactic reactions* (n=17), *dyspnea* (n=15) and *anaphylactic shock* (n=14). The overall most commonly reported reactions were *injections site swelling* (n=53; including 2 serious reactions), *urticaria* (n=48 including 10 serious reactions) and *fatigue* (n=41 including 3 serious reactions).

Basically all serious ADRs reported more than twice in connection with Alutard SQ *Vespula spp.* and all ADRs overall reported 10 or more times are labelled in the SmPC section 4.8.

Paediatric reports
Twenty-five (17 non-serious and 8 serious) reports were received from subjects below 18 years. These included 49 non-serious and 15 serious reactions. The most common serious reaction was *hypersensitivity reaction* (n=3). The overall, most common reaction in the paediatric population was *injection site swelling* (n=4, all non-serious), *injection site erythema* (n=4, all non-serious) and *fatigue* (n=4, all non-serious).

It is noticed that, besides reactions related to allergic reactions, a clinical relevant number of *injection site reactions* have been reported not at least in the paediatric population.

IV.6 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Alutard SQ *Vespula spp*

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	Systemic allergic reactions, including anaphylactic shock
Important potential risks	None identified
Missing information	• Use in children below 5 years • Use in pregnant or lactating women

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Systemic allergic reaction, including anaphylactic reactions	Text in SmPC describing precautions for use and guidance for treatment.	None
Important Potential Risks		
None	N/A	N/A
Missing Information		
Use in pregnant or lactating women	Text in SmPC describing precautions for use and guidance for treatment.	None
Use in children below 5 years	Text in SmPC describing precautions for use and guidance for treatment.	None

Summary of the RMP
The RMP is approved.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Alutard SQ *Vespula spp* is an allergy immunotherapy product indicated for the treatment of specific IgE-mediated allergic diseases caused by bee venom. VIT is currently the only specific treatment available that can prevent morbidity and mortality due to venom allergy and has long been recognised as a viable and effective treatment of individuals sensitised to insect stings and has been found to be satisfactorily safe (Lockey et al. 1990 [ref. 33]; Mosbech & Muller 2000[ref. 29]).
The product was national approved in 1990. Type II variations that affected the clinical aspects were approved in 2013 (Paediatric information; 2122-2010/33642 [Paediatric Article 45 procedure]), 2014 (up-date of SmPC regarding patients with baseline tryptase and mastocytose; 5.4.3-2014-26355, 5.4.3-2014-963) and in 2017 (up-dated dossier inclusively introduction of a RMP; 5.4.3-2016-48009 and up-date of SmPC; 5.4.3-2016-48005).

Efficacy
Based on the results from 16 key efficacy publication with Alutard SQ *Vespula spp.* and 28 supportive studies (4 with Alutard SQ *Apis mellifera* venom and 24 with Alutard SQ related products [Pharmalgen and Aquagen SQ]) it is agreed that the overall data from clinical trials could confirm a sufficient protection against systemic reactions with VIT and positive clinical effect in the majority of cases (ranged from 88%-100%) both in adults and children above 5 years. This is also in accordance with results from meta-analysis demonstrating the efficacy of subcutaneous VIT in general in a Cochran review from 2012 (Boyle et al [ref. 34]). A sustained effect up to 13 years after end of treatment with Alutard SQ Venom (*Apis mellifera* and/or *Vespula spp*.) of 3-5 years was demonstrated. This finding was also demonstrated in several of the supportive studies with Alutard related product (Pharmalgen and Aquagen SQ). In 2010 the Paediatric Article 45 procedure concluded that it was not possible to prove efficacy of insect venom immunotherapy in children since no separation of data in children and adults were possible in the reviewed studies. However, it was agreed that the same up-dosing schedules and maintenance doses could be used for adults and children due to the fact that the tolerability of the individual patient is the main determinant in the achievement of the maintenance dose and that dose adjustments may be necessary in case of occurrence of side effects.

Subcutaneous immunotherapy is carried out in 2 phases: an up-dosing phase and a maintenance phase. Three different schedules with up-dosing recommendations are in the SmPC is given as a guide for the treating physician. Results from clinical studies demonstrated that the three studies could be used with no difference regarding efficacy or tolerability. The different schedules could therefore be used after decision cases by cases with regards to degree of for example previous allergic reactions or risk factors such as other diseases or concomitant treatments.

The presented studies demonstrated a consistent immune modulatory effect of treatment with Alutard SQ *Vespula spp*.

Safety
The major risk with Alutard SQ *Vespula spp* is, as with VIT in general, ADRs related to systemic allergic reactions (including anaphylactic shock/reactions) and/or local allergic reactions. This is clearly demonstrated both from safety results in the clinical studies and from data originating from the MAHs safety database. The risks are sufficiently covered in the SmPC and RMP. Limited data from clinical trials on the adverse events in children below 5 years is available. Available safety data from Paediatric Article 45 procedure in 2010 and articles published after this procedure does not indicate additional risks related to the use of Alutard SQ in the paediatric population. This is reflected in SmPC section 4.4 and 4.8.

Use in children below 5 years
However, since age ranges were not clearly stated in any of the studies it was assumed that few subjects were below 5 years of age. Therefore, no conclusions could be drawn for this age group and it was concluded that a risk-benefit analysis must be carefully considered when treating children below 5 years of age. This is reflected in the SmPC section 4.4 and use in children below 5 years is characterised as missing information in the RMP.

The benefit/risk for Alutard SQ *Vespula spp*. is positive.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Mutual recognition procedure for Alutard SQ Getinggift, up-dosing package (100 SQ-U/ml, 1 000 SQ-U/ml, 10 000 SQ-U/ml and 100 000 SQ-U/ml) and 100 000 SQ-U/ml (maintenance pack), suspension for injection was positively finalised on 2017-12-18.

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LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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