NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Pharmalgen for the treatment of venom allergy

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

1 Background

1.1 The condition

When bees or wasps sting people, they inject venom (on average 174 and 17 micrograms respectively). Bee and wasp stings typically produce an intense, burning pain followed by erythema (redness) and a small area of oedema (swelling) at the site of the sting, which usually subsides within a few hours. Some people experience allergic reactions, which can be local or systemic, can vary in severity, and are typically of rapid onset. A small number of people may experience a severe, generalised type I allergic reaction, known as anaphylaxis.

Initial symptoms of anaphylaxis are usually cutaneous, followed by hypotension, with light-headedness, fainting or collapse. Some people develop respiratory symptoms as a result of either concomitant asthma or laryngeal oedema. However, a few people have little or no warning before collapsing and losing consciousness. The enzyme tryptase is generally markedly elevated in sting-induced severe anaphylaxis and baseline levels of tryptase may predict the severity of a response to a sting in people with bee or wasp venom allergy. Less common allergic reactions are conjunctivitis, rhinitis and gastrointestinal reactions.

Severity of systemic reactions to bee and wasp venom can be measured using the Mueller grading system. Severity ranges from grade 1 (symptoms limited to skin and mucous membranes) to grade IV (cardiovascular symptoms). See page 14 of the assessment report for further details of the Mueller grading system.

The primary method for diagnosing bee and/or wasp venom allergy is venom skin testing. Another less-sensitive method is the direct measurement of allergen-specific IgE antibodies in serum.

In the UK, insect stings are the second most frequent cause of anaphylaxis outside of medical settings. It is estimated that of all deaths from anaphylaxis between 1992 and 2001, 61.7% were due to reactions to wasp stings, and 8.5% were due to reactions to bee stings.

1.2 Current management

People considered to be at risk of anaphylaxis because of venom allergy are typically provided with an emergency kit to be used if stung. The kit includes an adrenaline autoinjector and one or more other emergency treatments, including a high-dose antihistamine, a corticosteroid, and/or a bronchodilator. Preventative measures include advice on how to avoid bee and/or wasp stings (avoidance advice), and/or advice on recognising the early symptoms of anaphylaxis.

Venom immunotherapy is considered for people with a history of systemic allergic reaction to bee venom and/or wasp venom. It aims to prevent severe reaction to future bee and/or wasp stings. Venom immunotherapy consists of subcutaneous injections of increasing amounts of venom and therefore carries a significant risk of systemic allergic reaction (adverse reaction). The effectiveness of is primarily assessed by the rate of reactions to subsequent stings, or changes in health-related quality of life. There are 44 centres across the UK that provide venom immunotherapy to people with bee or wasp venom allergy. It is thought that there are substantial variations in clinical practice across the country in terms of delivery of venom immunotherapy.

2 The technologies

The technologies in this appraisal are Pharmalgen bee venom extract and Pharmalgen wasp venom extract. Pharmalgen bee venom extract is indicated for the treatment of IgE-mediated allergy to bee venom and Pharmalgen wasp venom extract for treatment of IgE-mediated allergy to wasp venom. Pharmalgen bee venom extract or wasp venom extract (from now on referred to as Pharmalgen) are also indicated for the diagnosis of IgE-mediated allergy to bee or wasp venom, however the assessment related to this appraisal only evaluates Pharmalgen for the treatment of IgE-mediated allergy to (bee or wasp) venom.

Treatment with Pharmalgen is in two phases: the initial phase and the maintenance phase (see table 1). Before people can receive Pharmalgen, IgE-mediated allergy to bee or wasp venom must be confirmed by case history and by in vivo and/or in vitro diagnosis. Pharmalgen must be given by subcutaneous injection. Intravenous administration must be avoided because of an increased risk of potentially fatal anaphylactic reactions. The dosage of Pharmalgen must be individually adjusted, and should depend on the person's general health, the allergenic anamnesis and the person's sensitivity to the specific allergen used.

Pharmalgen is the only bee or wasp venom extract with a UK marketing authorisation for the treatment of IgE-mediated allergy to bee or wasp venom. Other bee or wasp venom extracts include Aquagen, Alutard SQ, Alyostal, Venomenhal or Venomil, but none of these has a UK marketing authorisation. Pharmalgen, Aquagen and Alutard SQ are manufactured by ALK-Abello.

Table 1 Summary description of technologies

Non-proprietary name	Bee venom extract	Wasp venom extract
Proprietary name	Pharmalgen (bee venom extract)	Pharmalgen (wasp venom extract)
Manufacturer	ALK-Abello	ALK-Abello
Dose		
Initial phase	Initial dose increased stepwise until a maximum dose of 0.01 microgram of venom per millilitre is reached. Conventional dosage schedule: one injection every 3–7 days; Modified rush schedule: two to four injections per week at intervals of 30 minutes, or Rush schedule: one injection every 120 minutes with a maximum of four injections per day	
Maintenance phase	Maintenance dose of 100 micrograms of venom per millilitre, in weeks 0, 2, 5 and 9, then every 4 weeks for at least 3 years. If allergic reactions persist, dose can be increased to maximum of 200 micrograms of venom per millilitre.	
Acquisition cost (BNF edition 61)	Initial phase: £54.81 treatment set Maintenance phase: £63.76 treatment set	Initial phase: £67.20 treatment set Maintenance phase: £82.03 treatment set

3 The evidence

The manufacturer of Pharmalgen, ALK-Abello, did not provide a submission for this appraisal. The Assessment Group (Liverpool Reviews and Implementation Group, LRiG) produced an assessment report of the clinical effectiveness and cost effectiveness of Pharmalgen within its licensed indication for the treatment of bee and wasp venom allergy.

3.1 Clinical effectiveness

The Assessment Group conducted a systematic review of the evidence on the clinical effectiveness of Pharmalgen (used within its licensed indication, see table 1) compared with other treatment options in people with bee and/or wasp venom allergy. Nine studies reported in 11 publications were identified

that met the inclusion criteria of the systematic review (see table 2). All the studies compared Pharmalgen with an active treatment, five compared Pharmalgen used within its licensed indication with a differing dose or protocol of Pharmalgen, one compared Pharmalgen with a modified form of Pharmalgen, and three compared Pharmalgen with other venom immunotherapy. Of the nine studies identified, four were randomised controlled trials (RCTs), and five were quasi-experimental studies. The Assessment Group explored the possibility of conducting a mixed-treatment comparison or an indirect comparison, but neither was deemed appropriate.

Table 2 Studies included in the Assessment Report

Study reference	Country	Duration of study	Venom allergy of participants	Severity of systemic reactions to stings
RCTs				
Golden et al. (1980)	US	20 weeks	Bee and/or wasp venom allergy	Sting-related anaphylaxis
Mosbech et al. (1986)	Denmark	2.5–3 years	Wasp venom allergy only	Not reported
Muller et al. (1987)	Switzerland and South Africa	14 weeks	Bee venom allergy only	Not reported
Quercia et al. (2001)	Italy	4 days to 6 weeks	Wasp venom allergy only	Grade 2, 3 or 4 Mueller grade
Non-RCTs				
Cadario et al. (2004)	Italy	At least 3 years	Bee and/or wasp venom allergy	Grade 2, 3 or 4 Mueller grade
Golden et al. (1981a)	US	20 weeks	Bee and/or wasp venom allergy	Not reported
Golden et al. (1981b)	US	2.5–3 years	Bee and/or wasp venom allergy	Not reported
Patriarca et al. (2008)	Italy	2 years	Wasp venom allergy only	Not reported
Thurnheer et al.	Switzerland	3 years	Bee and/or wasp venom	Grade 1, 2, 3 or 4 Mueller

(1983)			allergy	grade

As shown in table 2, the type of allergy and the severity of systemic reactions to stings were specified in four of the studies. None of the studies was conducted in the UK. The number of people recruited in each study ranged between 30 and 65. The average age of participants was similar across studies and ranged between 35 and 49 years. All studies reported results for a higher percentage of men than women. All studies recruited people who were shown to be allergic to bee or wasp venom by skin tests, and seven studies confirmed this with IgE testing. The initial phase protocols differed between studies and varied between 6 and 35 doses, over 3 hours to 16 weeks. The maintenance dosing protocols were more similar across the studies, with most studies reporting a maintenance dose of 100 micrograms every month or 4 weeks. The studies measured outcomes at different time points from 4 days to more than 3 years.

3.1.1 Systemic reactions to stings

Of the nine studies, all but one (Quercia et al. 2001) reported systemic reaction to re-stings.

Table 3 Systemic reactions to re-stings

Study reference	Interventions	re-sting	Systemic reaction to stings
Golden et al. (1980)	Pharmalgen (slow therapy – conventional dose increases at less frequent intervals)	19/19 (100%)	0 (%)
	Pharmalgen (step therapy – stepwise dose increases)	19/19 (100%)	0 (%)
	Pharmalgen (rush therapy)	18/18 (100%)	0 (%)
Mosbech et al. (1986)	Pharmalgen	3/3 (100%)	0 (%)
	Alutard	7/7 (100%)	0 (%)
	Aquagen	9/9 (100%)	0 (%)
Muller et al. (1987)	Pharmalgen	14/14 (100%)	2/14 (14.3%)
	Pharmalgen	17/17 (100%)	4/14 (23.5%)

	(monotherapy polyethylene glycol-coupled)		
Cadario et al. (2004)	Pharmalgen (aqueous therapy)	5/18 (27.8%)	0 (%)
	Alutard (depot therapy)	6/27 (22.2%)	0 (%)
Golden et al. (1981a)	Pharmalgen (50 micrograms maintenance)	19/19 (100%)	4/19 (21.1%)
	Pharmalgen (100 micrograms maintenance)	18/18 (100%)	0 (%)
	In-house venom (100 micrograms maintenance)	19/19 (100%)	Not reported
Golden et al. (1981b)	Pharmalgen (4-weekly maintenance)	42/42 (100%)	1/42 (2.4%)
	Pharmalgen (6-weekly maintenance)	29/29 (100%)	1/29 (3.4%)
	Pharmalgen (4-weekly maintenance)	56/56 (100%)	1/56 (1.8%)
Patriarca et al. (2008)	Pharmalgen (ultra rush therapy)	9/20 (45%)	1/9(11.1%)
	Aquagen (ultra rush therapy)	4/17 (23.5%)	1/4 (25.0%)
Thurnheer et al. (1983)	Pharmalgen (conventional therapy)	24/40 (60%)[a]	4/11 (36.4%)
	Pharmalgen (rush therapy)		3/11 (23.1%)

[a]Of the 24 people stung, 11 people's stings were confirmed to be from a bee or wasp

Table 3 shows that the incidence of systemic reaction to re-sting ranged from 0% to 36.4%. Two studies (Golden et al. 1981a and Golden et al. 1981b) compared the rate of systemic reaction across the arms and neither reported a significant difference between arms. Large local reactions were reported by Muller et al. (1987) and Patriarca et al. (2008). The frequency of large local reactions ranged from 33.7% to 41.2% in the study of Muller et al. (1987), and 50% to 88.9% (depending on route of administration) in the study of Patriarca et al. (2008).

The Assessment Group presented data on systemic reaction to stings from observational non-comparative studies. The Assessment Group found 17 studies that assessed the rate of systemic reaction to stings before, during or after venom immunotherapy. The reported rates of systemic reaction to stings

ranged from 0.0% to 32.7%. There were no reported systemic reactions after venom immunotherapy in any study. Further details can be found on pages 48–51 of the assessment report.

3.1.2 Systemic adverse reactions to venom immunotherapy

Venom immunotherapy carried a significant risk of systemic allergic reaction (adverse reaction). Adverse reactions were reported in eight of the studies: in one study during the initial phase only, in five studies during the initial or maintenance phase, and in two studies during maintenance only.

Table 4 Systemic reactions to venom immunotherapy

Study reference	Interventions	Phase of treatment	Adverse reaction
Golden et al. (1980)	Pharmalgen (slow therapy – conventional dose increases at less frequent intervals)	Initial or maintenance phase	4/22 (18.2%)
	Pharmlagen (step therapy – stepwise dose increases)		2/20 (10%)
	Pharmalgen (rush therapy)		4/22 (18.2%)
Mosbech et al. (1986)	Pharmalgen	Initial and maintenance phase	0/10 (0%)
	Alutard		3/10 (33.3%)
	Aquagen		0/12 (0%)
Muller et al. (1987)	Pharmalgen	Initial and maintenance phase	4/14 (28.6%)
	Pharmlagen (monotherapy polyethylene glycol-coupled)		2/17 (11.8%)
Cadario et al. (2004)	Pharmalgen (aqueous therapy)	Early (within 60 minutes of receiving therapy) Late (60 minutes or more after receiving therapy)	Early 2/18 (11.1%) Late 0/18 (0%)
	Alutard (depot therapy)		Early 0/27 (0%) Late 2/27 (7.4%)
Golden et al. (1981b)	Pharmlagen (4-weekly maintenance)	Maintenance phase	Not reported
	Pharmlagen (6-weekly		0/30 (0%)

	maintenance)		
	Pharmlagen (4-weekly maintenance)	Not reported	Not reported
Quercia et al. (2001)	Pharmalgen (cluster therapy)	Maintenance phase	1/20 (5%)
	Pharmalgen (rush therapy)		7/20 (35%)
	Alutard (depot cluster therapy)		0/15 (0%)
Patriarca et al. (2008)	Pharmlagen (ultra rush therapy)	Initial or maintenance phase	1/20 (5%)
	Aquagen (ultra rush therapy)		2/21 (9.5%)
Thurnheer et al. (1983)	Pharmlagen (conventional therapy)	Initial or maintenance phase (3-year treatment)	8/21 (38.1%)
	Pharmlagen (rush therapy)		8/21 (38.1%)

Table 4 shows that the frequency of adverse reaction during the initial and maintenance phases of venom immunotherapy ranged from 0% to 38.1% (8/21). In the two studies in which the difference between the arms was calculated, no statistical significant difference was found. Large local reactions to venom immunotherapy were reported in four studies, with a frequency of 6.7%–60% for people receiving subcutaneous therapy. No large local reactions were reported in the one study in which people received venom immunotherapy sublingually.

The Assessment Group also presented comparative studies of non-Pharmalgen venom immunotherapy. The searches for this review identified one meta-analysis and two systematic reviews of non-Pharmalgen venom immunotherapy in the population of interest. One of the reviews is an ongoing Cochrane review. The Assessment Group noted that the other systematic review and the meta-analysis indicate that venom immunotherapy is effective in preventing future systemic reactions to venom in people with venom allergies. Further details can be found on pages 52–55 of the assessment report.

3.1.3 Health-related quality of life

None of the studies identified in the systematic review reported data on health-related quality of life. However, two studies that included health-related quality of life data published in four papers were identified from an ongoing Cochrane review. The studies compared venom immunotherapy (Pharmalgen or Alutard) with the provision of an adrenaline autoinjector, and assessed quality of life using the Vespid Allergy Quality of Life Questionnaire (VQLQ). A meta-analysis of the two studies by the Cochrane group concluded that over time venom immunotherapy was associated with significant improvements in quality of life compared with an adrenaline autoinjector. Further details can be found on page 55–59 of the assessment report.

3.2 Cost effectiveness

The manufacturer of Pharmalgen, ALK-Abello did not provide a systematic review of economic analyses or its own economic analysis. The Assessment Group undertook a systematic review of existing cost-effectiveness evidence and developed an economic analysis of Pharmalgen for the treatment of bee and wasp venom allergy.

The systematic review identified three studies; of which two were full papers and one was in abstract form. No studies were found that compared venom immunotherapy with adrenaline autoinjectors, high-dose antihistamine or avoidance advice. The studies were US based with costs expressed in US dollars.

One study by Bernstein et al. (1994) was a 10-year observational study that reported the safety of rapid venom immunotherapy compared with modified rush venom immunotherapy for people with bee or wasp venom-induced anaphylaxis. A cost analysis was also undertaken and found that rapid venom immunotherapy is less costly than modified rush venom immunotherapy because of lower inpatient costs.

One study by Shaker (2007) evaluated prophylactic self-injectable adrenaline in children with mild venom anaphylaxis. Prophylactic self-injectable

adrenaline was estimated to cost $469, 459 per year of life saved. Sensitivity analyses reported that the cost was reduced to $97,146 per year of life saved when the fatality rate was 2.2 per 100,000 persons at risk.

A study by Brown et al. (2006) was published in abstract form and evaluated venom immunotherapy in children with severe venom anaphylaxis. The paper reported that venom immunotherapy was associated with a cost of $7786 per life year saved when used for reducing the risk of anaphylaxis, and $2278 per life year saved when used to cure venom allergy, in people with a history of severe venom anaphylaxis who have a greater than average risk of severe reactions.

3.2.1 Economic model produced by the Assessment Group

The Assessment Group developed a de novo economic model to evaluate the cost effectiveness of Pharmalgen. The model is constructed as a 1-year decision tree that is extrapolated to a 10-year time horizon, with changes to the size of the cohort at the end of each year because of sting-related deaths or death from other causes. The average age and mortality rate of people in the model increases each year. The key parameters in the model, such as likelihood of sting, resulting systemic reaction and the likelihood of death following systemic reaction, were not given probability distributions because the Assessment Group deemed the evidence for this to be insufficient. Instead a deterministic model was produced with sensitivity and scenario analyses used to test the impact of changing the parameters within plausible ranges. The analyses were conducted from a UK NHS and PSS perspective, with costs and benefits discounted at a rate of 3.5%.

The comparator, as set out in the scope, was a package of care without venom immunotherapy, including: the ruling out of comorbitities, advice on avoidance of insect venom, and high-dose antihistamines and/or adrenaline autoinjectors (with training before use) to be used if stung. The Assessment Group conducted a survey of 32 immunology clinicians in UK allergy centres to determine the appropriate comparators to use in the economic model. Responses to the survey indicated that 97% of people receive venom

immunotherapy with avoidance advice and an emergency kit that includes an adrenaline autoinjector and sometimes high-dose antihistamine. The survey indicated that the appropriate comparators for treatment with venom immunotherapy were: avoidance advice plus an emergency kit containing an adrenaline autoinjector and high-dose antihistamine; or avoidance advice alone.

The Assessment Group used the results from its survey, the clinical effectiveness evidence, the results from a published audit of UK allergy clinics, and published guidelines to inform the treatment pathway in its economic model. The economic model starts with a person receiving either one of the three therapies:

- venom immunotherapy with an emergency kit containing an adrenaline autoinjector and high-dose antihistamine plus avoidance advice; or
- an emergency kit containing an adrenaline autoinjector and high-dose antihistamine plus avoidance advice, or
- avoidance advice only.

In all three treatment arms in the model it is assumed that each person experiences an average of 0.095 stings per year. A proportion of these stings results in systemic reactions classified by Mueller grade (grade 1 to 4). It was assumed that 1.25% of Mueller grade 4 reactions result in death (based on a UK survey by Pumphrey in 2004). The likelihood of a systemic reaction after a sting differs between treatment arms. The model also includes the age-adjusted probability of death from unrelated causes. No adverse reaction associated with treatment with adrenaline autoinjector or high-dose antihistamine is assumed.

For the group treated with Pharmalgen, there are two additional phases: an initial phase with stepwise dose increases (in the first year) and a subsequent maintenance phase (in the first 3 years). In accordance with the summaries of product characteristics (SPCs), there are two forms of dosing in the initial

phase: conventional dosing which lasts 12 weeks with 1 injection per week, and modified rush dosing with 16 injections over a 7-week period. The model assumes that 92% of people receive conventional dosing and 8% receive modified rush dosing (based on results from a published allergy clinic survey). During venom immunotherapy a person may experience an adverse reaction to each treatment injection. The likelihood of a treatment-related adverse reaction is assumed to be 2.0% per injection (based on a pooled estimate of data from the studies of Golden et al. 1980b and Cadario et al. 2004) in the initial phase and 0.26% per injection (based on a non-comparative study by Haye and Dosen 2005) in the maintenance phase. Systemic reactions are classified by Mueller grade (grade 1 to 4), with each grade associated with a particular cost. The proportion of people experiencing adverse reactions by Mueller grade were taken from the studies of Thurnheer et al. (1983) and from Roesch et al. (2008), and were 37.5% for grade 1, 37.5% for grade 2, 12.5% for grade 3, and 12.5% for grade 4. There were assumed to be no deaths as a result of venom immunotherapy.

As noted above, the severity and risk of systemic reaction after a sting differs according the treatment. For the group given avoidance advice only, the likelihood of a systemic reaction after a sting is 56.4% (based on the study of Reismann 1992). The severity of systemic reactions after a sting in people receiving venom immunotherapy and those without venom immunotherapy were taken from a survey by Roesch et al. (2008) (table 5).

Table 5 Grade of systemic reaction after a sting in people receiving venom immunotherapy and those without venom immunotherapy

Mueller grade of systemic reaction	Proportion of people with systemic reaction after a sting without venom immunotherapy (%)	Proportion of people with systemic reaction after a sting receiving venom immunotherapy (%)
1	6.5	38.5
2	80.3	54
3	12.1	7.5
4	1.1	0

For the group given an emergency kit containing an adrenaline autoinjector and high-dose antihistamine, plus avoidance advice, the likelihood of a systemic reaction after a sting was assumed to be 43.9% (based on the assumption that high-dose antihistamine treatment is 25% as effective as venom immunotherapy). Adrenaline auto-injectors are assumed to reduce the number of Grade 3 and Grade 4 systemic reactions by half of the reduction with venom immunotherapy.

The rate of systemic reactions from a sting after treatment with Pharmalgen was estimated to be 6.5% per sting. The severity of systemic reactions was taken from the Roesch et al. (2008) as presented in table 5. The model assumed that bee and wasp venom immunotherapy are equally effective in reducing the likelihood of a systemic reaction. However, because the cost of bee and wasp venom immunotherapy differs, it was considered necessary to differentiate between the two venom types. It was assumed that 23% of people are allergic to bee venom, 70% of people are allergic to wasp venom and 7% are allergic to both (based on the results of a survey by the Assessment Group).

The average age of people in the model is assumed to be 37, and was estimated from responses to the Assessment Group survey. The Assessment Group noted that this age is comparable to the average age reported in the trials. The model assumed that 80% of people in the base case were men (based on responses to the Assessment Group survey). Because differences in gender were only associated with marginal differences in age-related quality of life and no differences in costs, the assumption was not anticipated to have a significant bearing on the results.

The Assessment Group noted that the clinical effectiveness data suggest that there is anxiety about future allergic reactions in people not receiving venom immunotherapy and that this is partly negated by anxiety associated with venom immunotherapy. However, the Assessment Group also noted that there is no evidence to support this using a validated utility measure such as EQ–5D. Therefore it is assumed that there is no change in quality of life

associated with anxiety in the base case. Furthermore, the Assessment Group noted that it is feasible that having a systemic reaction impacts on quality of life, but that there is no evidence to support this. The model therefore assumes there to be no change in quality of life associated with the event of a systemic reaction. The model also assumes that quality of life does not differ according to severity of the systemic reaction. Therefore it is assumed in the base case that all health benefits from treatments are entirely a result of reducing the number of anaphylaxis-related deaths.

A separate analysis was undertaken for a subgroup of people who are assumed to experience reduced anxiety related to future allergic reactions after receiving venom immunotherapy. The analysis used results of a survey of EQ–5D norms undertaken by the University of York to estimate that treatment with venom immunotherapy increases utility by 0.01 per person per year. The Assessment Group noted that this is probably a conservative estimate. A second subgroup analysis assumed that people would be stung five times per year.

The resource used and costs associated with venom immunotherapy are shown in table 6. No published information was available on actual resource use of individual elements so values were based on discussions with a clinical specialist (a consultant in an allergy clinic).

Table 6 Resources use and cost of treatment

Resource	Unit	Usage	Cost (£)	Source
Prophylactic high-dose antihistamine	Per visit	1 dose	0.14	BNF 61
Pre-injection health check (nurse specialist time)	Per visit	15 minutes	16	PSSRU 2010
Venom injection preparation (nurse specialist time)	Per dose	5 minutes	5.33	PSSRU 2010
Post venom injection observation (nurse specialist time)	Per dose	3 minutes	3.20	PSSRU 2010
Pharmalgen cost	Initial phase	1 kit	68.19	BNF 61

initial phase dosing				
Pharmalgen cost maintenance	Per injection	Quarter of a kit	20.57	BNF 61
Avoidance advice (nurse specialist time)	Per consultation	60 minutes	64	PSSRU 2010
Adrenaline autoinjector	Per injector	-	28.77	BNF 61
Ampoule of adrenaline	Per 1 ml ampoule	-	0.57	BNF 61

The emergency kit is assumed to contain an EpiPen adrenaline autoinjector, which is replaced every 18 months, and a high-dose antihistamine, which is replaced annually. The model also included costs for accident and emergency attendance and inpatient stays (see table 20 of the assessment report).

For each adverse reaction to a venom immunotherapy injection, the cost was estimated to be £32.81 for a Mueller grade 1, 2 or 3 reaction and £239.81 for a Mueller grade 4 reaction. For all treatment arms, each systemic reaction to a sting was associated with costs of accident and emergency attendance, inpatient stays, antihistamine and an adrenaline autoinjector (the avoidance advice only arm included the cost of adrenaline instead of an adrenaline autoinjector). Costs differed according to severity of the systemic reaction and for treatments. For costs associated with systemic reactions to a sting see tables 23 and 24 of the assessment report.

In the analyses, the interventions are compared with the previous best option, that is, a treatment that is more clinically effective and cost effective compared with a preceding one (that is, not dominated or extendedly dominated).

The base-case results (table 7) show that pharmalgen plus an emergency kit of adrenaline autoinjector plus high-dose antihistamine and avoidance advice has an incremental cost-effectiveness ratio (ICER) of £2,028,808 per QALY gained when compared with adrenaline autoinjector plus high-dose antihistamine and avoidance advice.

Table 7 Incremental deterministic base case analysis (based on a cohort of 1000 people)

	Total costs (£)	**Total life years**	**Total QALYs**	**Incre-mental costs (£)**	**Incre-mental QALYs**	**ICER (£)**
Avoidance advice only	141,285	9907.6	7626.3	-	-	
Adrenaline autoinjector plus high-dose antihistamine plus avoidance advice	297,921	9907.8	7626.5	156,636	0.2	783,180
Pharmalgen plus adrenaline autoinjector plus high-dose antihistamine plus avoidance advice	2,326,729	9908.0	7626.6	2,028,808	0.1	2,028,808

For the subgroup assumed to have five stings per year, the reduction in costs associated with reductions in systemic reactions to stings over 10 years coupled with the additional QALYs generated, resulted in Pharmalgen dominating the alternatives (being more effective and less costly) (table 8).

Table 8 Incremental deterministic analysis assuming a high rate of stings (five per year) (based on a cohort of 1000 people)

	Total costs (£)	**Total life years**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£)**
Pharmalgen plus adrenaline autoinjector plus high-dose antihistamine plus avoidance advice	2,830,778	9908.0	7626.6	-	-	
Adrenaline autoinjector plus high-dose antihistamine plus avoidance advice	3,888,461	9899.8	7620.7	1,057,683	–5.9	Dominated by venom immunotherapy
Avoidance advice only	4,124,750	9887.1	7611.5	236,289	–9.2	Dominated by venom immunotherapy

For the subgroup assumed to gain quality of life as a result of reduced anxiety about future stings, Pharmalgen plus the emergency kit of adrenaline autoinjector and high-dose antihistamine plus avoidance advice extendedly dominates the emergency kit plus avoidance advice (the ICER for the latter is higher than the next most cost effective regimen) (table 9). The ICER for Pharmalgen plus an emergency kit plus avoidance advice compared with avoidance advice only was £23,868 per QALY gained.

Table 9 Incremental deterministic analysis assuming a gain in quality of life as a result of reduced anxiety about future stings (based on a cohort of 1000 people)

	Total costs (£)	Total life years	Total QALYs	Incre-mental costs (£)	Incre-mental QALYs	ICER (£)
Avoidance advice only	141,285	9907.6	7286.7	-	-	
Adrenaline autoinjector plus high-dose antihistamine plus avoidance advice	297,921	9907.8	7286.9	156,636	0.2	Extendedly dominated by venom immune-therapy
Pharmalgen plus adrenaline autoinjector plus high-dose antihistamine plus avoidance advice	2,326,729	9908.0	7371.9	2,185,444	85.2	23,868

3.2.2 Sensitivity analyses

The Assessment Group conducted a number of different sensitivity analyses (see pages 87–92 of the assessment report). For the base-case, the ICERs for Pharmalgen plus an emergency kit and avoidance advice, compared with an emergency kit and avoidance advice, were never less than £1 million per QALY gained irrespective of the scenario or plausible values for parameters within the model. When compared with avoidance advice alone the ICERs for Pharmalgen plus an emergency kit and avoidance advice still exceeded £700,000 per QALY gained. The Assessment Group noted that although Pharmalgen can lead to reduced systemic reactions, the likelihood of being stung and then dying from that sting is very low.

For the subgroup with a high rate of stings (five per year), for most changes to parameters in the model, treatment with Pharmalgen dominated the alternatives (being more effective and less costly). The exceptions were if a

time horizon of 5 years was assumed, if treatment costs for systemic reaction were 50% lower than the base case, or the most pessimistic plausible values for all parameters in the model were chosen. The Assessment Group noted that at 3.3 stings per year, treatment with Pharmalgen plus an emergency kit and avoidance advice would no longer dominate alternatives. At 3.1 stings per year the ICER for Pharmalgen plus an emergency kit plus avoidance advice was over £300,000 per QALY gained when compared with an emergency kit and avoidance advice. At 2.8 stings per year, the ICER for Pharmalgen plus an emergency kit and avoidance advice was over £30,000 per QALY gained when compared with avoidance advice alone.

For the subgroup assumed to gain in quality of life as a result of reduced anxiety about future stings, for most parameters Pharmalgen compared with the alternatives was associated with an ICER of £20,000 to £30,000 per QALY gained, even when Pharmalgen was assumed to be no more clinically effective than an emergency kit at preventing and reducing the severity of systemic reactions to bee and/or wasp venom. The ICER was above £40,000 per QALY gained when the time horizon was 5 years and below £20,000 per QALY gained when the time horizon was 15 years or longer.

4 Equalities issues

No potential equality issues were identified in the scoping stage, or in the assessment report.

5 Issues for consideration

The main issues for this appraisal are summarised below.

Studies identified in systemic review

No studies comparing Pharmalgen with non-venom immunotherapy interventions were identified in the systemic review. Of the nine studies identified and deemed relevant to the appraisal by the Assessment Group, five compared Pharmalgen with different doses or administration protocols of Pharmalgen, and four compared Pharmalgen with other venom

immunotherapy. Furthermore, all included studies had a small number of participants and were non-UK based. There was heterogeneity between studies in the outcomes reported, the timing of re-stings, the type and length of treatment and in the proportion of people being re-stung.

Quality of life:

Improvement in quality of life as a result of reduced anxiety about future stings, or quality of life reductions as a result of adverse reaction with venom immunotherapy, are not assumed in the base case. The subgroup analysis that assumed a gain in quality of life estimated that Pharmalgen plus an emergency kit and avoidance advice extendedly dominated an emergency kit plus avoidance advice. However given that no analysis was undertaken that incorporated quality of life reductions associated with adverse reactions to Pharmalgen, it is unclear what the total quality of life effect would be on the base case.

Cost effectiveness:

The ICERs depend strongly on the assumptions made on any quality of life improvement derived from Pharmalgen and on the likelihood of future stings.

6 Ongoing research

The following Cochrane review is relevant to this appraisal:

Elremeli M, Bulsara MK, Daniels M et al. Venom immunotherapy for preventing allergic reactions to insect stings**.** Cochrane Database of Systematic Reviews.

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August 2011

Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG)

- Hockenhull JC, Elremeli M, Cherry MG et al. The clinical and cost effectiveness of pharmalgen for the treatment of bee and wasp venom allergy. July 2011.

B Submissions or statements were received from the following organisations:

I Professional/specialist, patient/carer and other groups:

- Royal College of Paediatrics and Child Health