Comments on:
NICE Pharmalgen for the treatment of venom allergy. Assessment Report

The clinical and cost effectiveness of Pharmalgen® for the treatment of bee and wasp venom allergy

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Order number	Section number	Page number	Comment
	General		The main areas of concern are in accuracies in - some of the clinical assumptions - some of the assumptions in the economic model It would be helpful for the non expert in economic analysis and calculation of QALYs and ICERs, to have discussion.
	2.1	9	Fatal anaphylaxis to venom is thought to be under-reported so the figures quoted are likely to be an underestimate
	2.4	11	A logical comparator is venom immunotherapy (VIT) versus no VIT which may include provision of adrenaline auto-injector (AAI). Following the controlled trail demonstrating efficacy (Hunt et al 1987) most studies looked at VIT alone, presumably because of the risks in these patients. The outcome is a. the incidence of further systemic reactions (SR) and b. their severity.
	2.4	11	Advice on avoidance of bee and wasp stings is an extremely minor component of management, unlikely to have significant impact. It seems surprising this was included in the decision process. If it had any effect it would be in both VIT and non VIT groups
		12	High dose antihistamines are not standard treatment in venom allergy for self–treatment of severe systemic reactions. They may be used in mild reactions but these are rarely an indication for VIT.
		12	Questionnaire used. A UK survey of allergy

			clinics offering VIT showed variable clinical practice, variable adherence to good practice and that current international guidelines for the diagnosis and management of hymenoptera venom allergy are not being followed (Diwakar et al Clin Exp Allergy 2008). Indications for VIT were variable. It is therefore questionable whether responses can be used for the economic model. BSACI have updated their guidelines (Krishna et al Clin Exp Allergy Aug 2011). This paper should be considered as the basis of and standard required in UK practice
		12	Economic model. In many patients AAI are not required after successful VIT. AAI appear to be included in all patients post VIT. This will falsely increase cost of VIT
			This treatment (self treatment kit) includes oral drugs which would not be useful for severe SR to venom. Not in ref 23
	3.4.1	16	This is not the UK indication for VIT (ref 26).in the UK this would be based on clinical assessment (severity of SR, and other clinical risk factors) combined with positive tests
	3.4.1	17	The questionnaire includes many small providers and found that guidelines were not followed. Major users of VIT would follow the standard protocol. variations are only when a patient has had an adverse reaction, usually in the updosing phase, and usually temporary. Conventional schedule is the standard regime in UK.
	3.4.3	19	RCUK guidance does not cover diagnosis and management of venom allergy. It focuses on acute treatment of anaphylaxis of any cause; and recommends onward referral to an allergy clinic.
	3.4.1	18	The lack of a standard approach is not because there are not guidelines. VIT is being performed without appropriate training.
	3.4.3	18	There are old BSACI guidelines on venom allergy; and new version to be published August
	4.1	22	Comment on comparators, see above
	4.1	22	Not clear what is meant by ‘Contraindication to adrenaline’ – it is difficult to perceive such a scenario, if the alternative is risk of death.
	5.1.4	24	A local reaction should not be considered as a secondary outcome. Not clear of the logic here. VIT is not indicted for local reactions
	5.1.4	24	Not clear why number of stings would be used

			as a secondary outcome – as not influenced by the treatment choice : VIT v. no VIT ; or VIT v AAI
	Table 4	30	Modified Pharmalgen®: Monomethoxy polyethylene glycol-coupled HBV (17) This is not used
	Table 4	30 +other pages	Important to distinguish bee from wasp as efficacy and side effects vary. This has not does not appear to have been addressed. Most VIT in UK is wasp, with higher efficacy rate and fewer s/es
			Population to be studied. This should not be *any* SR to a sting, according to UK guidelines
		39	Patient chars. What proportion were bee or wasp? Patterns of bee or wasp dominance vary in different countries eg bee allergy more common in Switzerland where much venom research comes from.
		42	Outcomes – given as SR; in addition the severity of the SR should be measured
		43	Outcomes – LLR not relevant
		46	
		general	Most studies on efficacy are older and did not include factors now recognised to be important eg raised baseline tryptase. This factor will increase incidence of further reactions, but VIT has still been effective in reducing one of 2 pathways into the reaction.
	Table 9	43	Outcomes. Thurmeer study – this 36% rate of further SRs is one of the highest in the range. However data shows only 1/11 pts (9%) had same severity SR. all others improved. 7/24 =29% had further SR (conv + rush combined) 6 were markedly decreased in severity, and 1 was the same ie 1/24 (4%) had same reaction after VIT. Thus in 4% disease was not modified by VIT.
	Table 9	43	Outcomes. Monomethoxy polyethylene glycol-coupled HBV This preparation is not used
	Table 11	44 46	Adverse reactions. These should be considered separately for bee and wasp as rates differ. This should be discussed . Also usually higher in rush which is now little used. This should be taken into account.
	Table 12	47	LR would not usually be considered as an outcome.
		62	Sting challenge is not longer used as an assessment tool, although it was in earlier studies
		62-63	Efficacy. The paper comparing pure venom IT

			with placebo, and whole body extract is important, and might be highlighted.
		62	Re difficulty comparing studies due to difft venom extracts and concentrations, it would seem reasonable to compare extracts of pure venom to 100 mcg top dose
	6	66-	Cost effectiveness Economic model – incorrect assumptions made - points as above. For example, most patients after VIT do not require AAI.
		67	Econ model. The adverse reactions to VIT should not affect cost as they would be factored into the normal appt process and cost, ie these do not incur extra cost
	general		As noted the choice of parameters for the economic model is difficult and some of the assumptions might be reconsidered. See earlier comments
	6.3.2	69	Assumptions in economic model are not correct. Emergency kit would not be prescribed for a lifetime, except in defined patients
		69	Avoidance advice will have minimal impact. It therefore seems inappropriate to consider this
	6.3.2	69	Bee and wasp may have to be considered separately – as different efficacies (and % of population affected)
	6.3.2	69	Number of subsequent stings varies in bee to wasp allergy as most bee allergics are beekeepers.
	6.3.4	70	Subgroup analysis ‘high risk of sting’ group. Not many will have 5 stings pa. although further stings clearly affect risk of a SR and this is a high risk group. However whether the patient had a further anaphylaxis in year 1,2,3 etc is not the main issue; it is protecting the patient from this whenever it would occur. The major risk is thought to be severity of previous reaction, but there are other factors eg raised baseline tryptase. Some of these other factors were not known at the time of most of the efficacy studies
	6.3.4	73	It is not correct to assume AHs will be 25% as effective as VIT in reducing SRs. VIT should prevent severe SRs occurring (and in a minority will reduce severity of a subsequent SR). Antihistamines aim to control established symptoms once a SR has occurred and will not deal with the more severe reaction.
	6.3.4	76	It is assumed that bee and wasp VIT are equally effective. This is not correct.

	Tables 23 and 24	79	VIT group will have many fewer SRs v. non VIT group. How has this been factored in? a. The VIT gp do not seem to have fewer SRs. b. The VIT group also all seem to carry AAI
		80	Incorrect model assumption Efficacy of bee and wasp VIT is not the same.
	Table 25	82	Model assumptions – see earlier comments
	Table 28	86	Giving 'Advice only' is not a recognised treatment option