Comments on Appraisal Consultation Document (ACD) – NICE Pharmalgen for the treatment of venom allergy

From clinical experts (representing BSACI and RCP):

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Thank you for giving us the opportunity to review the ACD. The following are our comments:

General

Section number	Page number	Comment
	General	The recommendations are appropriate overall. However, as pointed out in earlier comments (Aug 2011), areas of concern are inaccuracies in a. some of the clinical assumptions and b. some of the assumptions in the economic model. This appears to arise from assumptions made in the Liverpool Review. Some are not consistent with recommended UK practice. Our concern is that if these are included, without qualification – that they are not representative of the expert view – that at a later stage, any body reviewing the evidence will assume they are correct. Some examples follow (boxes below) but this is not comprehensive. Will the Liverpool Assessment Group report appear in full? Would a solution be to add further qualifying statements, with the expert view [this has already been done in some places]?
	General 4.2.3	Example. The logical comparator is venom immunotherapy (VIT) versus no VIT with provision of adrenaline auto-injector (AAI). Avoidance advice alone would not be given (this is a minor component of management with little impact). All treatment groups get the same avoidance advice. Giving 'avoidance advice alone' is not a recommended treatment option. This is covered in 4.3.6
	General 4.2.3	Example. 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
	General	Example. 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
	General	Example. It is important to distinguish bee from wasp as efficacy and side effects vary. This not does not appear to have been addressed. In the paper it is assumed that bee and wasp venom IT are equally effective. Most VIT in UK is wasp, and this has a significantly higher efficacy rate and fewer side effects (SRs) than bee VIT.
	General	Example. 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. Antihistamines will not reduce SRs

A. **Has all the relevant evidence been taken into account ?** – Yes, but see above.

B. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence ?** – No

a. Page 5 and 22-23: Given that recommendations are based on 'moderate' and 'severe' systemic reactions, the classification of mild, moderate and severe systemic reactions should be clearly defined. We suggest the committee refers to recent BSACI guideline (Krishna MT et al. Clin Exp Allergy 2011;41:1201-20; Page-1206 [Table-5]).

b. Page 5 & 6: Diagnosis: Skin testing should be performed in all cases unless there is a reason they cannot be performed (this is rare; eg generalised severe eczema or unable to stop antihistamine therapy). Skin tests should be the primary diagnostic tool. Serum specific IgE can occasionally generate false positive results.

c. Page 6, section 3.4, Contraindications: This section is requires greater clarity.

i. Absolute contraindications include chronic severe/brittle asthma, heart failure or patients with 'poor' lung reserve. In other chronic heart and lung conditions, decision on venom immunotherapy (VIT) is based on a careful 'risk-benefit analysis' by the specialist. Mild/moderate

chronic asthma and seasonal asthma are not absolute contraindications.

ii. Similarly, immunological disorders (immunodeficiency, systemic autoimmunity), malignancy, beta blockers, angiotensin converting enzyme (ACE) inhibitors are not absolute contraindications and decision on venom immunotherapy is based on a careful 'risk-benefit analysis' by the specialist. However, as far as possible beta blockers and ACE inhibitors should be withdrawn prior to commencing VIT.

iii. Pregnancy – VIT should not be initiated in pregnancy but may be continued if the patient has tolerated treatment and is in maintenance phase and there is a significant risk of insect sting/s. VIT does not have teratogenic effects.

d. Page 8, section 4.1.3: Adverse reactions: Systemic reactions (SRs) reported in previous studies are influenced by dosage protocols and patient selection criteria and these data have to be interpreted cautiously. The range of SRs stated in the document are too broad (0-36.4%), and in routine clinical practice, SRs, in particular, grade 3 and 4 are extremely rare, particularly with the conventional (slow) 12 weekly up dosing. SRs are relatively more common with bee VIT and with 'ultra-rush/rush' protocols, the latter rarely employed in UK practice.

e. Page 11, section 4.2.5: Probability of SR to bee/wasp sting/s following Pharmalgen treatment: The figure of 38.5% for grade-1 in the 'Pharmalgen' group is incorrect. VIT reduces both severity and incidence of SRs to bee/wasp stings and this figure is significantly greater than the 2 comparative groups considered i.e., advice only and advice and AAI and this would have significantly affected the calculations for cost effectiveness against the 'Pharmalgen' group. Similarly, the figure of 54% for grade-2 SRs in Pharmalgen group appears relatively high. Wasp VIT is effective in about 95% of patients; bee VIT efficacy is lower 80-85%.

f. Page 12, section 4.2.6: SRs during VIT: SR rates of 12.5% for grade 3 and 4 reactions are unacceptably high, particularly for UK practice, where over 92% centres employ the 12 week up dosing protocol.

g. Page 12, section 4.2.7: Whilst dual sensitisation is common, dual clinical reactivity of 7% is unacceptably high.

h. Page 12, section 4.2.11, Costs to treat SRs during VIT: Patients developing grade 1-3 reactions are treated in the out patients department and the costs involved are covered with the 'standard tariff' for a follow up appointment. Grade-4 reactions are uncommon/rare and such patients are likely to be admitted for observation/treatment for a period of 12-24 hours. Therefore, the costing of £32.81 to treat grade 1-3 SRs would have significantly affected the calculations against the cost effectiveness of Pharmalgen.

i. Page 14, section 4.2.15, QALY/ICERs: There are additional costs for patients in the advice + AAI group which has not been factored into the model. Patients carrying AAI would require annual training (indefinitely, i.e., for life time) in nurse led clinic (£120 approx. per year). This would significantly increase overall costs for the advice + AAI group, i.e., not including these costs would have influenced the cost effectiveness of the Pharmalgen group adversely.

j. Page 17, section 4.3.3 Immunity: There is no data in the literature to support the statement that Pharmalgen induces 'lifelong immunity' in children. Observational studies in children have been up to 20 years only. It is suggested a similar statement (as currently stated for adults) is given for both adults and children.

C. Are the provisional recommendations sound and suitable for guidance to the NHS ? – These are acceptable but we recommend that patients with moderate SRs who live in remote rural areas with no immediate access to emergency medical care are also offered VIT (in addition to the groups already identified).

D. Are there any aspect of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief ? - No

E. Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document ? - No