

# A systematic review of the clinical effectiveness and cost-effectiveness of Pharmalgen® for the treatment of bee and wasp venom allergy

J Hockenhull,<sup>1\*</sup> M Elremeli,<sup>2</sup> MG Cherry,<sup>1</sup>  
J Mahon,<sup>3</sup> M Lai,<sup>1</sup> J Darroch,<sup>4</sup> J Oyee,<sup>1</sup>  
A Boland,<sup>1</sup> R Dickson,<sup>1</sup> Y Dundar<sup>1</sup> and R Boyle<sup>5</sup>

<sup>1</sup>Liverpool Reviews and Implementation Group, Liverpool, UK

<sup>2</sup>Department of Paediatrics, Paediatric Allergy, Imperial College London, London, UK

<sup>3</sup>Coldingham-Economics Consultancy, Coldingham, UK

<sup>4</sup>Royal Liverpool University Hospital, Liverpool, UK

<sup>5</sup>Department of Paediatrics, Imperial College London/NIHR Comprehensive Biomedical Research Centre, Imperial College Healthcare NHS Trust, London, UK

\*Corresponding author

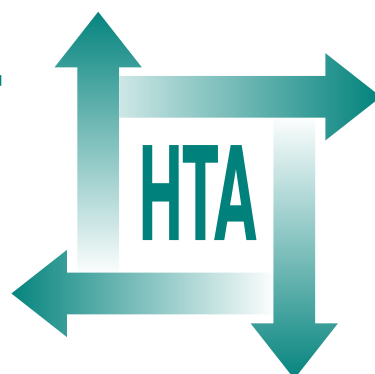


## *Executive summary*

*Health Technology Assessment* 2012; Vol. 16: No. 12

DOI: 10.3310/hta16120

Health Technology Assessment  
NIHR HTA programme  
[www.hta.ac.uk](http://www.hta.ac.uk)



# Executive summary

## Background

Each year in the UK there are between two and nine deaths from anaphylaxis caused by bee and wasp venom. Anaphylactic reactions to bee and wasp venom are a medical emergency, necessitating immediate treatment with drugs, oxygen and fluids to decrease the patient's response to the venom and support breathing and circulation.

In venom-sensitive individuals, allergic reactions to bee and wasp venom can occur rapidly following a sting, and vary in severity. Initially mild symptoms can progress to a life-threatening condition within minutes. The most severe systemic (or generalised) allergic reaction is referred to as anaphylaxis, which is characterised by features such as low blood pressure (with fainting or collapse), bronchospasm (asthma-like response) and laryngeal oedema (with constriction of the upper airway).

To avoid further reactions in people with a history of anaphylaxis to bee and wasp venom, the use of desensitisation, through a process known as venom immunotherapy (VIT), has been investigated and is in use in the UK. VIT consists of subcutaneous injections of increasing amounts of purified bee and/or wasp venom extract. Pharmedgen® products (ALK Abelló) have had UK marketing authorisation for VIT (as well as diagnosis) of allergy to bee venom (using Pharmedgen Bee Venom) and wasp venom (using Pharmedgen Wasp Venom) since March 1995. They are used by 44 centres in England and Wales.

## Objectives

This review assessed the clinical effectiveness and cost-effectiveness of Pharmedgen in providing immunotherapy to individuals with a history of type 1 (immunoglobulin E-mediated) systemic allergic reaction to bee and wasp venom.

## Methods

Three electronic databases were searched for comparative trials and economic evaluations of VIT using Pharmedgen (PhVIT) in the treatment of venom allergy. Outcomes for clinical effectiveness included systemic reactions, local reactions, mortality, anxiety related to the possibility of future allergic reactions, health-related quality of life (QoL) and adverse reactions (ARs) to treatment. Cost-effectiveness outcomes included cost per quality-adjusted life-year (QALY) gained. Two reviewers independently screened all titles and/or abstracts including economic evaluations, applied inclusion criteria to relevant publications and quality assessed the included studies. Where multiple publications of the same study were identified, data were extracted and reported as a single study. The results of the data extraction and quality assessment are summarised in structured tables and as a narrative description. The manufacturer did not provide an evidence submission to the National Institute for Health and Clinical Excellence for this appraisal.

## Results

### Clinical review

A total of 1065 citations were identified, of which 266 full-text papers were obtained. No studies were identified that compared PhVIT with any comparator outlined in the decision problem [adrenaline auto-injector (AAI) prescription and training, high-dose antihistamines (HDAs) or advice on the avoidance of bee and wasp stings]. The decision problem was widened to include different types of PhVIT (such as subcutaneous vs sublingual) or differing protocols of PhVIT administration. Four randomised controlled trials (RCTs) and five quasi-experimental studies were identified for inclusion in the systematic review.

The quality of the included trials was poor. All trials included in the review were small, with none including more than 65 participants (range 6–65), and all of the studies took place outside the UK. The authors did not describe the method of randomisation used, and there were imbalances in the rate of dropout between arms in all but one study. There was heterogeneity between studies in the outcomes reported, the timing of re-stings, the type and length of treatment and the proportion of people being re-stung. As such, it was not possible to conduct a meta-analysis or mixed-treatment comparison with the available data.

Eight studies reported re-sting data and the rate of systemic reactions ranged from 0.0% to 36.4%. ARs to PhVIT were reported in eight studies. Systemic reactions were reported at rates of between 0.0% and 38.1% and none was fatal. Data were supported by non-comparative studies of PhVIT. Seventeen non-comparative studies of PhVIT reported rates of systemic reactions following re-sting, which ranged from 0.0% to 32.7%, with 12 studies reporting re-sting data before the completion of VIT. Post-VIT systemic reaction rates ranged from 2.0% to 12.5%.

Health-related QoL was not reported in any of the included studies; however, details from two RCTs that used a combination of PhVIT and non-PhVIT indicate that the QoL of people receiving VIT improved more than the QoL of those using an EpiPen® (Mylan Inc.) (test for overall effect:  $z = 36.25$ ,  $p < 0.00001$ ).

In general, clinical evidence suggests that there is a decrease in reactions to stings following PhVIT, but there is no direct evidence related to the comparators included in the scope for this project. PhVIT is associated with ARs, but these are treatable and transient. These ARs are also associated with non-PhVIT, and studies have indicated that they may to some extent be balanced by improvements in QoL.

### Economic review

No published economic evidence relevant to the decision problem was identified through the systematic review of cost-effectiveness studies. The manufacturer of PhVIT did not submit any clinical effectiveness or cost-effectiveness evidence to NICE in support of PhVIT. The Assessment Group (AG) developed a de novo economic model designed specifically to compare the cost-effectiveness of PhVIT with currently available NHS treatments. A questionnaire was designed and sent out to the 44 allergy clinics in the UK that provide PhVIT to elicit data for use in the economic model. PhVIT + HDA + AAI were compared with (1) HDA + AAI and (2) avoidance advice only.

In the AG base case, the comparison of PhVIT + HDA + AAI versus AAI + HDA yields an incremental cost-effectiveness ratio (ICER) of £18,065,527 per QALY gained; PhVIT + HDA + AAI versus avoidance advice only yields an ICER of £7,627,835 per QALY gained. The sensitivity analyses and scenario analyses showed that the results of the base-case economic evaluation were robust for every plausible change in parameter made. Under the base-case assumptions, the incremental cost per QALY gained of PhVIT + AAI + HDA compared with an emergency kit of AAI + HDA is never less than £1M per QALY gained under any scenario or any plausible values for parameters within the model. The ICER falls below £1M only when PhVIT + AAI + HDA is compared with avoidance advice and when the most optimistic scenario for PhVIT + AAI + HDA is considered; this ICER still exceeds £700,000 per QALY gained.

The AG's results for the 'High Risk of Sting Patients' subgroup analysis show that PhVIT + HDA + AAI dominates both AAI + HDA and avoidance advice only (i.e. is less expensive and more effective). The AG's 'VIT Anxiety QoL Improvement' subgroup analysis shows that PhVIT + HDA + AAI versus HDA + AAI has an ICER of £23,868 per QALY gained, and PhVIT + HDA + AAI versus avoidance advice only yields an ICER of £25,661 per QALY gained.

Although the findings of the economic model are considered robust, there are some key weaknesses in the data used to inform the economic model. The AG has identified key gaps in the available clinical effectiveness literature and notes specifically that there is a paucity of clinical effectiveness data from RCTs of PhVIT versus any other comparator. The AG is also concerned that the number of stings in people who have had PhVIT in the UK and the number of bee and/or wasp stings in the general population is not known. The AG considers that the likelihood of death following sting for individuals who are allergic to bee and/or wasp venom and the size of the improvement in utility as a result of PhVIT because of a reduction in anxiety because of reduced risk of sting are uncertain.

## Conclusions

The current use of PhVIT in clinical practice in the NHS appears to be based on limited and poor-quality clinical effectiveness research.

The AG did not identify any studies of PhVIT that directly addressed the original decision problem set for this appraisal, that is, a comparison of the use of PhVIT with the alternative treatment options of advice on the avoidance of bee and wasp venom, HDA and/or AAIs.

This lack of evidence and the need to identify data to inform the development of an economic model prompted the AG to broaden the search criteria for the systematic review in order to compare PhVIT with other PhVIT and PhVIT with non-PhVIT, to consider data from non-comparative studies of PhVIT and to examine studies reporting the clinical effectiveness of non-PhVIT.

In general, research in the area is limited to small-scale studies that do not appear to have been carried out using robust methods, and none of the studies reported on the use of PhVIT within the UK. There is also heterogeneity in the published evidence related to the methods of PhVIT administration and length of treatment described in the trials. Therefore, conclusions regarding the clinical effectiveness of PhVIT to reduce the rate of future systemic reactions in patients with a history of bee and/or wasp allergic reaction cannot be drawn with any confidence. Available evidence indicates that sting reactions following the use of PhVIT are low and that the ARs related to treatment are minor and easily treatable.

Anxiety related to the possibility of future stings is an issue for debate and data from studies of VIT indicate a small improvement in QoL as a result of a decrease in sting-related anxiety after VIT.

No published research on the cost-effectiveness of PhVIT or non-PhVIT was identified by the literature searches. The results of the AG's de novo base-case economic evaluation demonstrate that PhVIT + AAI + HDA compared with AAI + HDA and compared with avoidance advice only yields ICERs in the range of £8–20M per QALY gained. The results of extensive sensitivity and scenario analyses demonstrate that the base-case results are robust. Two subgroups were considered in the economic evaluation and the AG concludes that use of PhVIT + AAI + HDA may be cost-effective in both groups. In the subgroup of patients at high risk of future stings (five stings per year), PhVIT + AAI + HDA dominates the alternatives. In the subgroup of patients whose QoL improves from reduced anxiety as a result of PhVIT, when PhVIT + AAI + HDA is compared with the alternatives the ICERs are in the range of £25,767–27,504 per QALY gained.

## Future research

Use of PhVIT in clinical practice in the UK NHS is commonplace; it is therefore highly unlikely that placebo-controlled studies will ever be carried out. The findings of this review indicate, however, that it is necessary to identify more clearly the groups of patients most likely to benefit from treatment and ensure that clinical practice is focused on these groups. Second, given the paucity of UK data in this area, it would be informative if data could be collected routinely when VIT is administered in the NHS (e.g. rates of systemic ARs to VIT, rates of systemic reactions to bee/wasp stings).

## Funding

The National Institute for Health Research Health Technology Assessment programme.

## Publication

Hockenhull J, Elremeli M, Cherry MG, Mahon J, Lai M, Darroch J, *et al.* A systematic review of the clinical effectiveness and cost-effectiveness of Pharmedin<sup>®</sup> for the treatment of bee and wasp venom allergy. *Health Technol Assess* 2012;**16**(12).

# NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

## Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 10/01/01. The protocol was agreed in December 2010. The assessment report began editorial review in November 2011 and was accepted for publication in November 2011. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley CBE  
Series Editors: Dr Martin Ashton-Key, Professor Aileen Clarke, Dr Tom Marshall, Professor John Powell, Dr Rob Riemsma and Professor Ken Stein  
Associate Editor: Dr Peter Davidson  
Editorial Contact: edit@southampton.ac.uk

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

© Queen's Printer and Controller of HMSO 2012. This work was produced by Hockenhill *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (<http://www.publicationethics.org/>).

This journal may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by Prepress Projects Ltd, Perth, Scotland ([www.prepress-projects.co.uk](http://www.prepress-projects.co.uk)), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.