Pharmalgen for the treatment of bee and wasp venom allergy

Technology appraisal guidance
Published: 22 February 2012
nice.org.uk/guidance/ta246
Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
Contents

1 Guidance ........................................................................................................................................................................ 4
2 Clinical need and practice ........................................................................................................................................ 5
3 The technologies ........................................................................................................................................................... 7
4 Evidence and interpretation .................................................................................................................................... 9
  4.1 Clinical effectiveness ............................................................................................................................................................ 9
  4.2 Cost effectiveness ........................................................................................................................................................... 11
  4.3 Consideration of the evidence ........................................................................................................................................ 15
  Summary of Appraisal Committee’s key conclusions ...................................................................................................... 22
5 Implementation ............................................................................................................................................................ 28
6 Related NICE guidance ............................................................................................................................................... 29
7 Review of guidance ........................................................................................................................................................ 30
Appendix A: Appraisal Committee members and NICE project team ........................................................................ 31
  A Appraisal Committee members ........................................................................................................................................ 31
  B NICE project team .......................................................................................................................................................... 33
Appendix B: Sources of evidence considered by the Committee .................................................................................... 34
Changes after publication .................................................................................................................................................. 36
About this guidance .......................................................................................................................................................... 37
1 Guidance

1.1 Pharmalgen is recommended as an option for the treatment of IgE-mediated bee and wasp venom allergy in people who have had:

- a severe systemic reaction to bee or wasp venom, or

- a moderate systemic reaction to bee or wasp venom and who have one or more of the following: a raised baseline serum tryptase, a high risk of future stings or anxiety about future stings.

1.2 Treatment with Pharmalgen should be initiated and monitored in a specialist centre experienced in venom immunotherapy.
2 Clinical need and practice

2.1 Bees and wasps inject venom when they sting. When a person is stung by a bee or wasp they typically have an intense, burning pain followed by erythema (redness) and oedema (swelling) at the site of the sting. This usually subsides within a few hours. After an initial sting, some people have an immune response and produce IgE antibodies. In these people, subsequent stings can trigger a rapid inflammatory response referred to as a ‘type I’ hypersensitivity reaction.

2.2 Hypersensitivity reactions to bee or wasp venom can be local or systemic, can vary in severity, and are typically of rapid onset. Large local reactions are characterised by oedema, erythema and pruritus, cover more than 10 cm in diameter and peak at between 24 and 48 hours after the sting. Systemic reactions can be measured using the Mueller grading system. Severity ranges from grade I to grade IV. A grade I systemic reaction is characterised by generalised urticaria or erythema, itching, malaise or anxiety. Grade II reactions may include symptoms associated with grade I reactions as well as generalised oedema, tightness in the chest, wheezing, abdominal pain, nausea and vomiting, and dizziness. Grade III reactions may include symptoms associated with grade I or II reactions as well as symptoms of dyspnoea, dysarthria, hoarseness, weakness, confusion, and a feeling of impending doom. Grade IV reactions may include symptoms associated with grade I, II or III reactions as well as loss of consciousness, incontinence of urine or faeces, or cyanosis.

2.3 Recently published guidelines for the treatment of bee and wasp venom allergy issued by the British Society for Allergy and Clinical Immunology classify systemic reactions as mild, moderate or severe. A mild systemic reaction is characterised by pruritus, urticaria, erythema, mild angio-oedema, rhinitis and conjunctivitis. Moderate systemic reactions may include mild asthma, moderate angio-oedema, abdominal pain, vomiting, diarrhoea and minor or transient hypotensive symptoms such as light-headedness and dizziness. Severe systemic reactions may include respiratory difficulty such as asthma or laryngeal oedema, hypotension, collapse or loss of consciousness, as well as double incontinence, seizures, or loss of colour vision. Anaphylaxis is defined by the European Resuscitation Council as a severe, life-threatening, generalised or systemic hypersensitivity reaction.
2.4 Data from the USA suggest that the prevalence of allergy to bee and wasp venom is between 0.4% and 3.3%. In the UK, insect stings are the second most frequent cause of anaphylaxis outside medical settings. It is estimated that of all deaths from anaphylaxis between 1992 and 2001 in the UK, approximately 62% were a result of reactions to wasp venom and approximately 9% were caused by reactions to bee venom. Some people who have a systemic reaction after being stung do not have another reaction when re-stung. It is estimated that after a large local reaction 51–55% of people go on to develop a systemic reaction when next stung. Approximately 14–20% of those who have a mild systemic reaction have another systemic reaction when next stung. For people who have experienced an anaphylactic reaction, the risk of having a recurrent episode is estimated to be between 60% and 70%.

2.5 The main method for diagnosing an allergy to bee and/or wasp venom is skin testing with venom. Another less sensitive method is measurement of allergen-specific IgE antibodies in serum. Clinicians may also measure serum tryptase at baseline (after a reaction to a sting has subsided) because this may predict the severity of a response to a subsequent sting.

2.6 Clinicians typically give an emergency kit to people with a venom allergy who are considered at risk of systemic reactions. The kit includes adrenaline (epinephrine; intramuscular injection) and can also include other emergency treatments such as a high-dose antihistamine (oral), a corticosteroid (inhaled), and/or a bronchodilator (inhaled). Preventive measures include advice on how to avoid bee and/or wasp stings.

2.7 In the UK, clinicians consider offering venom immunotherapy to people with a history of systemic allergic reactions to bee venom and/or wasp venom. Venom immunotherapy aims to reduce the risk of future systemic reactions and the severity of a systemic reaction when one occurs. People considered for venom immunotherapy are usually those who have had severe systemic reactions, or those who have experienced moderate systemic reactions and have additional risk factors, such as a high baseline serum tryptase or a high risk of future stings, or whose quality of life is significantly affected by venom allergy.
3 The technologies

3.1 Pharmalgen bee venom extract (ALK-Abelló) has a marketing authorisation for the treatment of IgE-mediated allergy to bee venom. Pharmalgen wasp venom extract (ALK-Abelló) has a marketing authorisation for the treatment of IgE-mediated allergy to wasp venom. Pharmalgen bee venom extract and Pharmalgen wasp venom extract (from now on referred to as Pharmalgen) also have marketing authorisations for the diagnosis of IgE-mediated allergy to bee or wasp venom, but this indication is outside the scope of this appraisal.

3.2 Treatment with Pharmalgen is in two phases: an initial phase and a maintenance phase. Before people receive Pharmalgen treatment, IgE-mediated allergy to bee or wasp venom must be confirmed by case history and by in vivo and/or in vitro diagnosis. Pharmalgen is given by subcutaneous injection.

3.3 During the initial phase, an increasing dose of Pharmalgen is given until the maximum tolerated dose is reached. The following types of dosing schedules can be used during the initial phase: conventional (one injection every 3–7 days), modified rush (clustered; two to four injections weekly given at intervals of 30 minutes) or rush (injections at 2-hour intervals with a maximum of four injections per day). During the maintenance phase, Pharmalgen is administered at a dose of 100 micrograms every 4–6 weeks for at least 3 years. The dosage may be adjusted depending on the person's history of allergic reactions and sensitivity to the specific allergen used.

3.4 The summary of product characteristics (SPC) as provided by the manufacturer states that Pharmalgen is contraindicated in people with malignancies, severe chronic or seasonal asthma, and immunological conditions. It is also contraindicated in people with diseases or conditions that prevent the treatment of possible anaphylactic reactions, such as chronic heart and lung disease, severe arterial hypertension and treatment with beta-blockers. Pharmalgen is also contraindicated in people taking tricyclic antidepressants, monoamine oxidase inhibitors, and angiotensin-converting enzyme inhibitors, and should not be initiated during pregnancy. Pharmalgen treatment may be associated with local or systemic immunological reactions, which can include anaphylaxis. The SPC recommends that people be observed for at least 60 minutes after an injection of Pharmalgen. For full details of adverse effects and contraindications see the SPC.
3.5 Pharmalgen bee venom costs £54.81 for an initial treatment set and £63.76 for a maintenance treatment set (excluding VAT; 'British national formulary' [BNF] edition 61). The maintenance treatment set includes four vials; therefore, the cost per injection in the maintenance phase is £15.94. Pharmalgen wasp venom costs £67.20 for an initial treatment set and £82.03 for a maintenance treatment set (excluding VAT; BNF edition 61). The maintenance treatment set also includes four vials; therefore, the cost per injection in the maintenance phase is £20.51. Costs may vary in different settings because of negotiated procurement discounts.
4  Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B). The manufacturer of Pharmalgen, ALK-Abelló, 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.

4.1  Clinical effectiveness

4.1.1  The Assessment Group conducted a systematic review of the evidence on the clinical effectiveness of Pharmalgen 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. All nine of the studies compared Pharmalgen with an active treatment: five compared different doses or dosing schedules of Pharmalgen with each other, one compared Pharmalgen with a modified form of Pharmalgen, and three compared Pharmalgen with other venom immunotherapy. Therefore, none of the studies identified compared Pharmalgen with a non-venom immunotherapy intervention. Of the nine studies identified, four were randomised controlled trials (RCTs), two compared an intervention group with historical controls, and three were quasi-experimental studies. The Assessment Group explored the possibility of conducting a mixed treatment comparison or an indirect comparison, but did not consider either appropriate because of the limitations in the data.

4.1.2  The type of allergy and the severity of systemic reactions to stings were specified as inclusion criteria 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. Seven studies included adults only, one study included people aged 15–68 years, and one study included people aged 6–70 years. The average age of participants was similar across studies and ranged between 35 and 49 years. All studies recruited people with allergies to bee or wasp venom confirmed by skin tests, and seven studies also confirmed this with IgE testing. The protocols for the initial phase of treatment differed between studies and varied between 6 and 35 doses, over a period of 3 hours to 16 weeks. Most studies used a maintenance dose of 100 micrograms every 4 weeks. The studies measured outcomes at different time points from 4 days to more than 3 years.
4.1.3 The outcome from eight studies in people allergic to bee or wasp venom included the proportion of stings that resulted in systemic reactions. This ranged from 0 to 36.4% depending on the dose of immunotherapy or dosing schedule. Three studies reported proportions of stings that resulted in systemic reactions after approximately 3 years of maintenance therapy; these ranged between 0 and 36.4%. In the study with a rate of 36.4%, three of the four participants with a systemic reaction had a diminished response with mild symptoms. The proportions of stings that resulted in large local reactions was reported in two studies, and ranged from 35.7% to 88.9% across the treatment groups.

4.1.4 The Assessment Group presented data on systemic reactions to stings from observational non-comparative studies of Pharmalgen. The Assessment Group found 17 studies that reported the proportion of stings that resulted in systemic reactions before, during or after venom immunotherapy. The reported proportion of stings that resulted in systemic reactions ranged from 0 to 32.7%. For the studies that reported systemic reactions after Pharmalgen treatment, the proportion of stings that resulted in systemic reaction ranged from 0 to 12.5%.

4.1.5 People receiving venom immunotherapy may develop an allergic systemic reaction (adverse reaction) to the treatment. 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. The proportion of people developing adverse reactions during the initial and maintenance phases of venom immunotherapy ranged from 0 to 38.1%.

4.1.6 The Assessment Group also presented evidence from comparative studies of venom immunotherapy other than Pharmalgen. Searches identified one meta-analysis and two systematic reviews of venom immunotherapy (specific brands not specified) in the population of interest. One of the reviews is an ongoing unpublished Cochrane review. The Assessment Group noted that the systematic reviews and the meta-analysis concluded that venom immunotherapy is effective in lowering the risk of future systemic reactions to venom in people with venom allergies.

4.1.7 None of the studies identified in the systematic review by the Assessment Group reported data on health-related quality of life. However, the ongoing
4.2 Cost effectiveness

4.2.1 The Assessment Group undertook a systematic review of existing cost-effectiveness evidence and developed an economic model 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 an abstract. The studies were US based with costs expressed in US dollars. The Assessment Group did not find any health economic studies that compared venom immunotherapy with adrenaline auto-injectors, high-dose antihistamine or advice on how to avoid bee and wasp stings (avoidance advice).

4.2.2 The Assessment Group developed a de novo economic model to evaluate the cost effectiveness of Pharmalgen. The model is deterministic and 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 Assessment Group chose a 10-year horizon because it identified evidence to support the maintenance of effect over 10 years, and it did not identify any studies that considered a longer follow-up. The analyses were conducted from a UK NHS and personal social services perspective, with costs and benefits discounted at a rate of 3.5%.

4.2.3 The Assessment Group used the clinical effectiveness evidence and the results from its own survey of 32 immunology clinicians in allergy centres in the UK, 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 one of three therapies:

- venom immunotherapy with Pharmalgen, an emergency kit containing an adrenaline auto-injector and high-dose antihistamine, plus advice on how to avoid being stung, or
- an emergency kit containing an adrenaline auto-injector and high-dose antihistamine, plus advice on how to avoid being stung, or
- advice on how to avoid being stung.

4.2.4 For people treated with Pharmalgen, there is an initial phase with stepwise increases in dosage and a subsequent 3-year maintenance phase. The model includes two forms of dosing in the initial phase: conventional dosing, which lasts 12 weeks with 1 injection per week, and modified rush (clustered) 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.

4.2.5 The model assumes that a person experiences an average of 0.095 stings per year irrespective of their treatment, based on a weighted average from six studies. A separate analysis explored a scenario in which a person experiences five stings a year. In the model, the probability of a systemic reaction after a sting is 56.4% for people given advice on avoidance only. For people given an emergency kit plus advice on avoidance, the probability of a systemic reaction after a sting is 43.9%. The probability of a systemic reaction after a sting for people receiving Pharmalgen is 6.5%. If a systemic reaction occurs, the likelihood of a Mueller grade I reaction is 6.5%, 9.8% and 38.5% for the advice only, emergency kit and Pharmalgen groups respectively; the likelihood of a Mueller grade II reaction is 80.3%, 83.6% and 54.0%; the likelihood of a Mueller grade III reaction is 12.1%, 6.05% and 7.5%; and the likelihood of a Mueller grade IV reaction is 1.1%, 0.55% and 0%. The model assumes that 1.25% of Mueller grade IV reactions result in death regardless of previous treatment.

4.2.6 During venom immunotherapy with Pharmalgen a person may experience an adverse reaction to treatment. The model assumes that the probability of a treatment-related adverse reaction is 2.0% per injection in the initial phase and 0.26% per injection in the maintenance phase. Systemic adverse reactions are classified by Mueller grade; each grade is associated with a particular cost. Of people who experience systemic adverse reactions to treatment, 37.5% experience (by Mueller grade) grade I, 37.5% experience grade II, 12.5% experience grade III, and 12.5% experience grade IV. The model assumes that no deaths result from adverse reactions to venom immunotherapy. The model assumes that treatment with adrenaline auto-injector or high-dose antihistamine is not associated with adverse reactions.
4.2.7 The model assumes that bee and wasp venom immunotherapy reduces the risk of a systemic reaction following a sting to the same extent. However, because the cost of bee and wasp venom immunotherapy is different, it was necessary to differentiate between the two venom types. The model assumes that 23% of those with a bee and/or wasp allergy are allergic to bee venom, 70% are allergic to wasp venom and 7% are allergic to both (based on the results of the Assessment Group's survey of immunology clinicians in the UK). The average age of the modelled population is 37 years, and 80% are men.

4.2.8 Because no data on health-related quality of life were available, in the base case the model assumes that there are no changes in quality of life associated with venom allergy or venom immunotherapy. The model also assumes no change in quality of life associated with any grade of systemic reaction, either as a result of Pharmalgen treatment or a sting. Therefore, in the base case the model assumes that all health benefits from treatments result from reducing the number of anaphylaxis-related deaths.

4.2.9 The Assessment Group undertook a separate analysis for a scenario in which people are assumed to be less anxious about future allergic reactions after receiving Pharmalgen than before receiving therapy, and therefore experience an improvement in quality of life. The analysis quantified quality of life using results of a survey of norms of EQ-5D undertaken by the University. This survey estimated a reduction in utility of 0.16 based on a 'health state characterising level 2 anxiety/depression' which lowers utility by 0.07 per year, and a 'health state characterising usual activities level 2' which lowers utility by 0.036. The Assessment Group assumed that anxiety about stings would reduce utility by 25% of 0.16 (that is, a reduction in utility of 0.04 associated with venom allergy), and that treatment with Pharmalgen would increase utility by 0.01 per person per year.

4.2.10 No published information was available on actual resource use so the Assessment Group chose values based on discussions with a clinical specialist. The Assessment Group assumed that the emergency kit contains an adrenaline auto-injector, which is replaced every 18 months, and a high-dose antihistamine, which is replaced annually. The model also included costs for attending accident and emergency and for inpatient stays.
4.2.11 The cost of each adverse reaction to Pharmalgen was estimated as £32.81 for a Mueller grade I, II or III reaction and £239.81 for a Mueller grade IV reaction. For all three groups in the model, each systemic reaction to a sting was associated with the cost of attending accident and emergency, with inpatient stays and with antihistamines. The avoidance advice only group included the cost of adrenaline whereas the other two groups included the cost of an adrenaline auto-injector. Costs differed according to severity of the systemic reaction.

4.2.12 The Assessment Group presented deterministic pairwise results comparing Pharmalgen plus an emergency kit (adrenaline auto-injector and high-dose antihistamine) plus avoidance advice with two comparators: an emergency kit plus advice or advice alone.

4.2.13 The Assessment Group presented base-case results for a simulated 1000 patient cohort. The results showed that treatment with Pharmalgen plus an emergency kit plus avoidance advice provides an additional 0.11 quality-adjusted life years (QALYs) per 1000 patients compared with an emergency kit plus avoidance advice, with additional costs of £2,028,808, and an incremental cost-effectiveness ratio (ICER) of £18,065,527 per QALY gained. Compared with advice only, Pharmalgen plus an emergency kit plus avoidance advice provided an additional 0.29 QALYs per 1000 patients, with additional costs of £2,185,444, leading to an ICER of £7,627,835 per QALY gained.

4.2.14 For the scenario assuming five stings per year, the reduction in costs associated with fewer systemic reactions to stings over 10 years, coupled with the additional QALYs generated from fewer deaths, resulted in Pharmalgen dominating both alternatives (that is, it was more effective and less costly than the alternatives).

4.2.15 For the scenario assuming that Pharmalgen improves quality of life by reducing anxiety about future stings, the ICER for Pharmalgen plus an emergency kit plus avoidance advice compared with an emergency kit plus avoidance advice was £23,868 per QALY gained (based on incremental costs of £2,028,808 and incremental QALYs of 85.00 for a 1000 patient cohort). The ICER for Pharmalgen plus an emergency kit plus avoidance advice compared with advice only was £25,661 per QALY gained (incremental costs of £2,185,444 and incremental QALYs of 85.17 for a 1000 patient cohort).
4.2.16 The Assessment Group conducted sensitivity analyses. In the base case, all ICERs for Pharmalgen plus an emergency kit and avoidance advice, compared with an emergency kit and advice, exceeded £1 million per QALY gained irrespective of the scenario or values for parameters used within the model. When compared with advice alone, the ICERs for Pharmalgen plus an emergency kit and advice still exceeded £700,000 per QALY gained.

4.2.17 In the sensitivity analyses for the scenario assuming 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 included a shortened time horizon (5 years), reduced treatment costs for a systemic reaction (50% of the base case) or using the most pessimistic values for all parameters in the model. Assuming 3.3 stings per year, treatment with Pharmalgen plus an emergency kit and avoidance advice no longer dominated the alternatives. Assuming 3.1 stings per year, the ICER for Pharmalgen plus an emergency kit plus avoidance advice was over £30,000 per QALY gained when compared with an emergency kit and advice. Assuming 2.8 stings per year, the ICER for Pharmalgen plus an emergency kit and advice was over £30,000 per QALY gained when compared with advice alone.

4.2.18 In the sensitivity analyses for the scenario assuming that Pharmalgen improves quality of life by reducing anxiety about future stings, for most parameters Pharmalgen plus emergency kit plus advice was associated with an ICER of £20,000 to £30,000 per QALY gained. 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.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of Pharmalgen, having considered evidence on the nature of bee and wasp venom allergy and the value placed on the benefits of Pharmalgen by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
Clinical effectiveness

4.3.2 The Committee discussed current clinical practice for the diagnosis of bee or wasp venom allergy. The Committee heard from the clinical specialists that people who have had a systemic reaction following a bee or wasp sting should be referred to an allergy specialist for the diagnosis of venom-specific IgE allergy to bee and/or wasp venom by skin or intradermal testing and serum-specific IgE testing. The clinical specialists stated that raised serum tryptase at baseline (after a reaction to a sting has subsided) is associated with an increased probability of severe systemic reactions to future stings. However the Committee also noted the consultation comment that the immunological condition mastocytosis may be associated with a raised baseline serum tryptase, and a diagnosis of mastocytosis may be a contraindication to Pharmalgen. The Committee understood that before treatment with Pharmalgen, a positive test for specific IgE antibodies is required, and that clinicians would also take into account baseline serum tryptase and other comorbid conditions when deciding whether to offer treatment with Pharmalgen.

4.3.3 The Committee discussed the treatment of bee and wasp venom allergy in current clinical practice. The Committee heard from the clinical specialists that people who have had a moderate or severe systemic reaction to bee or wasp venom are normally given an emergency kit containing adrenaline. The kit can also include other emergency treatments such as a high-dose antihistamine. Clinicians also advise people on how to avoid being stung, but they do not consider this advice to be effective on its own. The Committee discussed the use of venom immunotherapy in current clinical practice in the UK. The Committee heard from the clinical specialists that Pharmalgen, the only venom immunotherapy with a UK marketing authorisation, is an established therapy for venom allergy which should be initiated and monitored by healthcare professionals within a specialist centre with experience in venom immunotherapy and treating systemic reactions. The clinical specialists stated that they give Pharmalgen in accordance with the SPCs, most frequently using a conventional dosing schedule in the initial phase, followed by a maintenance period of 3 years. The Committee heard that in children and adults Pharmalgen is considered to provide immunity for at least 15 years. The Committee understood that the regimen of most relevance to the appraisal was an initial phase using a conventional dosing regimen and a maintenance phase lasting 3 years, with the treatment administered within a specialist centre.
4.3.4 The Committee discussed which patients currently receive Pharmalgen in clinical practice. It heard from the clinical specialists that Pharmalgen is offered to people with a history of severe systemic reactions to bee or wasp venom, or to people with moderate systemic reactions to bee or wasp venom if they have other risk factors such as raised baseline serum tryptase, a high risk of future stings, or anxiety about future stings. The Committee noted consultation comments that following publication of British Society for Allergy and Clinical Immunology guidelines, Pharmalgen may also be offered to people with a history of moderate systemic reactions to bee or wasp venom if they live far from emergency medical care, have certain comorbid conditions or request treatment with Pharmalgen. The Committee heard from the clinical specialists that children generally have a less severe reaction to venom than adults and a better prognosis over time. However, it is not possible to identify in advance which children will 'outgrow' their allergy to bee and/or wasp venom, and therefore Pharmalgen is an appropriate treatment for some children. The Committee understood that Pharmalgen is indicated for both adults and children, and that Pharmalgen is offered to people who have had severe systemic reactions or to people who have had moderate systemic reactions, and have additional risk factors for future systemic reactions such as raised baseline serum tryptase, or an increased risk of future stings, or whose quality of life is affected by anxiety about future stings.

4.3.5 The Committee discussed the impact of an allergy to bee and/or wasp venom on quality of life. The clinical specialists and patient experts stressed how frightening it is to be stung when there is an expectation of a possible systemic reaction following a sting, and that anaphylaxis can be accompanied by a sense of impending doom. The Committee heard from the patient experts that many people who have experienced a systemic reaction to bee or wasp venom are anxious about the possibility of systemic reactions following future stings, regardless of the actual risk of a reaction. The Committee heard that this anxiety affects usual daily activities of those affected and their family members. The Committee heard that people willingly tolerate the adverse effects of Pharmalgen treatment and the length and intensity of the administration schedule to reduce the probability of a systemic reaction to future stings. The Committee heard from patient experts that after treatment with Pharmalgen, anxiety levels return to normal for many people, and that carrying and having to administer an adrenaline auto-injector does not reduce anxiety to the same degree as having venom immunotherapy. The Committee heard from the clinical
specialists that published trials have reported an improvement in quality of life in people who received venom immunotherapy compared with those who received an adrenaline auto-injector only. On balance, the Committee was persuaded that although the extent to which people might feel anxious following a systemic reaction would vary, and the risk of a sting might be very low, many people with a history of systemic reactions to bee or wasp venom would be anxious about the possibility of systemic reactions following future stings.

4.3.6 The Committee discussed the relevant comparator in the appraisal. The comparator as set out in the scope is a package of care without venom immunotherapy, including advice on avoidance of insect venom, and high-dose antihistamines and/or adrenaline auto-injectors (with training before use) to be used if stung. The Committee heard from the clinical specialists that the British Society for Allergy and Clinical Immunology recently issued guidelines for the treatment of bee and wasp venom allergy. It heard that clinicians advise people with a history of systemic reactions to bee or wasp venom on ways of minimising their risk of further stings, but do not provide advice alone. Instead clinicians offer people an adrenaline auto-injector (and training in its use) to carry and use following a bee or wasp sting that is accompanied by symptoms of a systemic reaction. The Committee concluded that an adrenaline auto-injector given alongside avoidance advice was the most appropriate comparator for Pharmalgen treatment.

4.3.7 The Committee discussed the clinical effectiveness evidence for Pharmalgen and noted that no RCTs or controlled studies had been identified that compared Pharmalgen with standard care without venom immunotherapy, as defined in the scope. The Committee discussed the available non-comparative data for Pharmalgen and the comparative data for non-Pharmalgen venom immunotherapy. The Committee heard from the clinical specialists that they considered that the results of non-Pharmalgen studies would also apply to Pharmalgen, and that venom immunotherapy is associated with changes in IgE production and a reduced risk of a systemic reaction following a sting. The Committee considered that the available evidence base for Pharmalgen was of poor quality and was limited. On balance, it was persuaded that Pharmalgen had demonstrated some efficacy in reducing the rate and severity of systemic reactions following a bee or wasp sting. However, the Committee considered that the relative efficacy could not be quantified with certainty.
Cost effectiveness

4.3.8 The Committee discussed the economic model developed by the Assessment Group. It noted that in the base-case analysis, Pharmalgen plus an adrenaline auto-injector plus high-dose antihistamine and avoidance advice had an ICER of £18,070,000 per QALY gained compared with an adrenaline auto-injector plus high-dose antihistamine and advice. The Committee heard from the Assessment Group that this estimate was robust to changes in parameters associated with costs and effects. However, the estimate was particularly sensitive to assumptions about utility and about how frequently a person is stung. The Committee considered the importance of the assumption in the base-case analysis that Pharmalgen treatment did not affect health-related quality of life. The Committee noted its earlier conclusions that having a venom allergy increases anxiety and affects daily activities, and that treatment with Pharmalgen may reduce some of this anxiety. The Committee concluded that the assumption in the base-case analysis that Pharmalgen had no effect on health-related quality of life underestimated the cost effectiveness of Pharmalgen compared with alternative treatments.

4.3.9 The Committee discussed comments received during the consultation about the robustness of the Assessment Group's model. The Committee noted the consultation comments that some of the inputs in the economic model relating to costs, efficacy and the likelihood of having a systemic reaction while receiving treatment with Pharmalgen were not plausible. The Committee considered that although there are some uncertainties as to the plausibility of assumptions and inputs, the Assessment Group's sensitivity analyses showed that the estimates of cost effectiveness were not sensitive to changes in these parameters. The Committee understood from the Assessment Group that the key drivers of cost effectiveness were assumptions about utility and about how frequently a person is stung. On this basis the Committee concluded that the Assessment Group's model was an appropriate basis for decision-making despite uncertainties around the plausibility of some parameter estimates.

4.3.10 The Committee considered the Assessment Group's scenario analyses that had assumed that people have five bee or wasp stings per year. The Committee heard from clinical specialists that some people are stung at least five times per year. These may include beekeepers plus their children and neighbours, roofers and gardeners. However, the risk of being stung varies. The Committee noted
that in these scenario analyses, treatment with Pharmalgen dominated the alternatives (that is, it was more effective and less costly), and that this remained the case until the average frequency of stings dropped to approximately three per year. The Committee concluded that Pharmalgen is an appropriate use of NHS resources for people with IgE-mediated allergy to bee and wasp venom, who have a high risk of stings.

4.3.11 The Committee then considered the scenario analyses that included an effect on health-related quality of life related to anxiety about re-stings and Pharmalgen treatment. The Committee noted that in these analyses the ICER for Pharmalgen decreased to less than £30,000 per QALY gained. The Committee was aware that the Assessment Group had been unable to identify any data on anxiety associated with venom allergy or changes in anxiety as a result of venom immunotherapy that could be used in the economic model. Therefore the Assessment Group had used the EQ-5D survey of norms to explore how much disutility was generated when a person went from having no problems with anxiety and daily activities to moderate anxiety with some effect on daily activities (0.16). The Committee considered that the Assessment Group's assumption that fear of being stung would generate a quarter of that value (0.04), and that venom immunotherapy would reduce this anxiety by a quarter (0.01), was plausible and, given the testimony of the patient experts, may even underestimate the gains in utility associated with treatment with Pharmalgen. The Committee concluded that for people who do not have a high risk of future stings the analyses that assume reduced anxiety about re-stings with Pharmalgen treatment are the most appropriate on which to base the most plausible estimate of the ICER.

4.3.12 The Committee considered the 10-year time horizon in the economic model. It was aware that it had not been presented with evidence of the duration of immunity; but it also considered the testimony of the clinical specialists that immunity was likely to be longer than 10 years. The Committee was presented with a scenario analysis with a time horizon of 20 years for people who have a gain in health-related quality of life associated with reduced anxiety about re-stings and treatment with Pharmalgen. In this scenario, the ICER was £13,800 per QALY gained for treatment with Pharmalgen plus an emergency kit plus advice compared with an emergency kit and advice alone. The Committee concluded that it is appropriate to use a time horizon of longer than 10 years, and that with reduced anxiety about re-stings after treatment with Pharmalgen
the most plausible ICER would be less than £20,000 per QALY gained. The Committee concluded that Pharmalgen is an appropriate use of NHS resources for people with IgE-mediated allergy to bee and wasp venom, who are anxious about future stings.

4.3.13 The Committee then discussed its conclusions on the cost-effectiveness modelling and the use of Pharmalgen in current clinical practice (see section 4.3.4). The Committee took into account the evidence from the clinical specialists and patient experts. It concluded that it was appropriate to assume a health-related quality of life benefit from Pharmalgen for people with a history of severe systemic reactions and for people who have a history of moderate systemic reactions to bee and/or wasp venom and who have other risk factors for future systemic reactions such as anxiety about the possibility of systemic reactions following future stings, a higher risk of being stung or raised baseline serum tryptase. The Committee therefore concluded that Pharmalgen could be considered an appropriate use of NHS resources for the treatment of people with IgE-mediated bee and/or wasp venom allergy with the above characteristics. The Committee considered that anxiety about the possibility of systemic reactions following future stings should be such that it affects usual daily activities.

4.3.14 The Committee discussed comments received during consultation, noting that Pharmalgen may also be offered to people with a history of moderate systemic reactions to bee or wasp venom if they live far from emergency medical care, have comorbid conditions or request treatment with Pharmalgen. The Committee discussed the patient expert testimony, and concluded that these people would have heightened awareness of their situation and be anxious about the possible effects of having a systemic reaction from future stings. Therefore the Committee concluded that these groups were covered in its recommendation for people with a history of moderate systemic reactions, who are anxious about future stings.

4.3.15 The Committee discussed whether it should make a separate recommendation for people with raised baseline serum tryptase. The Committee noted that people with raised baseline serum tryptase are at higher risk of more severe reactions to future stings but that a person would only be aware of an increased risk once raised baseline serum tryptase had been diagnosed. The Committee also noted the consultation comment that a raised baseline serum tryptase may
indicate mastocytosis, which is a possible contraindication for Pharmalgen. The Committee concluded that comorbid conditions, including mastocytosis, would be identified by the responsible clinician when considering whether to offer treatment with Pharmalgen. The Committee concluded that it was appropriate to include in its recommendations raised baseline serum tryptase as an additional risk factor for people who have had a moderate systemic reaction.

4.3.16 The Committee supported the statement made by the clinical specialists that treatment with Pharmalgen should be initiated and monitored in a specialist centre experienced in venom immunotherapy. The Committee discussed comments from consultation about the need for specialist centres to have staff appropriately trained in resuscitation or immediate access to age-appropriate resuscitation facilities. It noted that the SPCs specify that Pharmalgen should be provided under supervision of a doctor experienced in specific immunotherapy and that because of the risk of potentially fatal anaphylaxis, treatment with Pharmalgen must be carried out in clinics or hospitals where full facilities for cardiopulmonary resuscitation are immediately available for use by adequately trained personnel. The Committee therefore concluded that Pharmalgen should be provided within a specialist centre and that the details of the provision of resuscitation equipment were sufficiently specified in the SPC.

Summary of Appraisal Committee’s key conclusions

<table>
<thead>
<tr>
<th>TA246</th>
<th>Appraisal title: Pharmalgen for the treatment of bee and wasp venom allergy</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key conclusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmalgen is recommended as an option for the treatment of IgE-mediated bee and wasp venom allergy in people who have had:</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>• a severe systemic reaction to bee or wasp venom, or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• a moderate systemic reaction to bee or wasp venom and who have one or more of the following: a raised baseline serum tryptase, a high risk of future stings or anxiety about future stings.</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Treatment with Pharmalgen should be initiated and monitored in a specialist centre experienced in venom immunotherapy.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Committee considered the available evidence to be of poor quality and limited. It was persuaded that Pharmalgen had demonstrated efficacy in reducing the rate and severity of systemic reactions. However, the relative effect could not be quantified with certainty. The Committee concluded that it is appropriate to use a time horizon of longer than 10 years, and that with reduced anxiety about re-stings after treatment with Pharmalgen the most plausible ICER would be less than £20,000 per QALY gained.

<table>
<thead>
<tr>
<th>Current practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical need of patients, including the availability of alternative treatments</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed benefits of the technology</td>
</tr>
<tr>
<td>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>What is the position of the treatment in the pathway of care for the condition?</td>
</tr>
<tr>
<td>Adverse effects</td>
</tr>
</tbody>
</table>

**Evidence for clinical effectiveness**

| Availability, nature and quality of evidence | No randomised controlled trials or controlled studies were identified that compared Pharmalgen with standard care without venom immunotherapy, as defined in the scope. The Committee heard from the clinical specialists that they considered that the results of non-Pharmalgen venom immunotherapy studies were also relevant to Pharmalgen. | 4.3.7 |
| Relevance to general clinical practice in the NHS | The Committee considered that the available clinical evidence base for Pharmalgen was of poor quality and was limited. | 4.3.7 |
| Uncertainties generated by the evidence | The Committee did not consider that the relative efficacy of Pharmalgen compared with standard care without venom immunotherapy could be quantified with certainty. | 4.3.7 |
| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | The Committee was persuaded that many people with a history of systemic reactions to bee or wasp venom would be anxious about the possibility of future stings. | 4.3.5 |
|  | The clinical specialists stated that elevated serum tryptase at baseline (after a reaction to a sting has subsided) is associated with an increased probability of severe systemic reactions to future stings. | 4.3.2 |
### Estimate of the size of the clinical effectiveness including strength of supporting evidence

The Committee was persuaded that Pharmalgen had demonstrated some efficacy in reducing the rate and severity of systemic reactions following a bee or wasp sting. However, it considered that the relative efficacy could not be quantified with certainty.

### Evidence for cost effectiveness

<table>
<thead>
<tr>
<th>Availability and nature of evidence</th>
<th>The Committee considered that the economic model developed by the Assessment Group was appropriate to form the basis of its decision-making, despite uncertainties around the plausibility of some parameter estimates.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The Assessment Group was unable to identify any data on anxiety associated with venom allergy or changes in anxiety as a result of venom immunotherapy that could be used in the economic model.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncertainties around and plausibility of assumptions and inputs in the economic model</th>
<th>The Committee concluded that the assumption in the base-case analysis that Pharmalgen had no effect on health-related quality of life underestimated the cost effectiveness of Pharmalgen compared with alternative treatments.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The Committee considered the scenario analyses that had assumed that people have five bee or wasp stings per year. It heard from clinical specialists that there are people who are stung at least five times per year and that these may include beekeepers plus their children and neighbours, roofers and gardeners.</td>
</tr>
<tr>
<td></td>
<td>The Committee concluded that it is appropriate to use a time horizon of longer than 10 years.</td>
</tr>
</tbody>
</table>

© NICE 2012. All rights reserved.
<p>| Incorporation of health-related quality-of-life benefits and utility values | In a scenario analysis the Assessment Group assumed that a history of systemic reactions to bee or wasp stings reduced utility by 0.04 per person per year, and that treatment with Pharmalgen increased utility by 0.01 per person per year. The Committee recognised the limitations of the evidence, but accepted on balance that this utility estimate was plausible and, given the testimony of the patient experts, may even underestimate the gains in utility associated with treatment with Pharmalgen. | 4.3.11 |
| Are there specific groups of people for whom the technology is particularly cost effective? | Not applicable. |
| What are the key drivers of cost effectiveness? | Effect on quality of life | 4.3.8, 4.3.11 |
| | Risk of stings | 4.3.10 |
| | Time horizon | 4.3.12 |
| Most likely cost-effectiveness estimate (given as an ICER) | For people with a high risk of stings, treatment with Pharmalgen dominated the alternatives (that is, it was more effective and less costly). For people without a high risk of stings but reduced anxiety about re-stings after treatment with Pharmalgen, the most plausible ICER was less than £20,000 per QALY gained. | 4.3.10, 4.3.12 |
| Additional factors taken into account | Patient access schemes (PPRS) | Not applicable. |</p>
<table>
<thead>
<tr>
<th>End-of-life considerations</th>
<th>Not applicable.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equalities considerations and social value judgements</td>
<td>No equality issues were identified during the scoping process or during the course of the appraisal.</td>
</tr>
</tbody>
</table>
5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has bee and wasp venom allergy and the doctor responsible for their care thinks that pharmalgen is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools to help organisations put this guidance into practice (listed below).

- A costing statement explaining the resource impact of this guidance.
6 Related NICE guidance

Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode. NICE clinical guideline 134 (2011).
7 Review of guidance

7.1 The guidance on this technology will be considered for review in January 2017. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
February 2012
Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital, Cambridge

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, Department of Primary Health Care, University of Oxford

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Dr Michael Boscoe
Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust

Professor John Cairns
Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine
Dr Mark Chakravarty
External Relations Director – Pharmaceuticals and Personal Health, Oral Care Europe

Mrs Eleanor Grey
Lay member

Dr Neil Iosson
General Practitioner

Mr Terence Lewis
Lay member

Professor Ruairidh Milne
Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre, University of Southampton

Professor Stephen Palmer
Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel
Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital, Carshalton

Mr Alun Roebuck
Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Dr Florian Alexander Ruths
Consultant Psychiatrist and Cognitive Therapist, Maudsley Hospital, London

Mr Navin Sewak
Primary Care Pharmacist, NHS Hammersmith and Fulham

Mr Roderick Smith
Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling
Lay member
**Professor Ken Stein (Vice Chair)**
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

**Professor Andrew Stevens**
Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

**Mr Tom Wilson**
Director of Contracting and Performance, NHS Tameside and Glossop

**B NICE project team**

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Scott Goulden**
Technical Lead

**Zoe Garrett**
Technical Adviser

**Jeremy Powell**
Project Manager
Appendix B: Sources of evidence considered by the Committee

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


B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- ALK-Abelló

II Professional/specialist and patient/carer groups:

- Anaphylaxis Campaign
- British Society for Allergy and Clinical Immunology
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Department of Health
- NHS Tower Hamlets
- Welsh Government

IV Commentator organisations (without the right of appeal):

- British National Formulary
C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on Pharmalgen by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Nicola Braithwaite, Consultant Paediatric Allergist, nominated by the Royal College of Paediatrics and Child Health – clinical specialist
- Dr Pamela Ewan, Consultant Allergist, nominated by the British Society for Allergy and Clinical Immunology – clinical specialist
- Dr Thirumala Krishna, Consultant Allergist and Immunologist, nominated by the British Society for Allergy and Clinical Immunology – clinical specialist
- Moira Austin, nominated by the Anaphylaxis Campaign – patient specialist
- David Glaser, nominated by the Anaphylaxis Campaign – patient specialist

D Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy. They were also invited to comment on the ACD.

- A-Abelló
Changes after publication

**February 2014:** implementation section updated to clarify that pharmalgen is recommended as an option for treating bee and wasp venom allergy. Additional minor maintenance update also carried out.

**June 2012:** minor maintenance
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE multiple technology appraisal process.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Copyright

© National Institute for Health and Clinical Excellence 2011. All rights reserved. NICE copyright material can be downloaded for private research and study, and may be reproduced for educational and not-for-profit purposes. No reproduction by or for commercial organisations, or for commercial purposes, is allowed without the written permission of NICE.
Accreditation

NICE accredited

www.nice.org.uk/accreditation