Final Appraisal Determination

Photodynamic therapy for age-related macular degeneration

1  Guidance

1.1  It is recommended that treatment of wet age-related macular degeneration using photodynamic therapy (PDT) should be carried out only in centres specialising in this treatment and as part of an ongoing nationally co-ordinated collection of robust and relevant data on clinical outcome and cost effectiveness, including quality of life as assessed by properly validated instruments, when the following criteria are met:

- the individual has predominantly classic subfoveal CNV
- the individual has relatively good residual visual acuity (6/36 or better) in the eye to be treated
- the better-seeing eye, or only functioning eye is to be treated (that is, patients who develop the condition in the eye that they rely on for most of their visual function).

1.2  Other than under the circumstances outlined in Section 1.1, it is recommended that PDT is used in wet age-related macular degeneration only as part of ongoing or new clinical trials that are designed to generate robust and relevant outcome data, including data on quality of life and costs.

2  Clinical need and practice

2.1  Age-related macular degeneration (ARMD) is characterised by irreversible damage to the central part of the retina (the macula) resulting in progressive loss of central vision. Peripheral vision is not affected and so individuals retain some useful vision. The condition has two forms, dry (non-exudative or non-neovascular) and wet (exudative or neovascular). The wet form is characterised by the development of new blood vessels beneath the retina known as choroidal neovascularisation (CNV). CNV can be subdivided into classic and occult forms according to its appearance on investigation by fluorescein angiography. The classic form is associated with more rapid progression than the occult form. A mixture of classic and occult CNV can occur within the same lesion.
2.2 CNV lesions are also classified according to their location relative to the fovea (the area at the centre of the macula that is associated with colour vision and perception of fine detail and where there are no blood vessels to interfere with vision). CNV lesions that extend under the fovea are described as subfoveal.

2.3 ARMD occurs in people over 50 years of age. On the basis of limited epidemiological data it is estimated that each year in England and Wales there may be approximately 5000 to 7500 new cases of predominantly classic subfoveal CNV associated with wet ARMD. However, there is a high degree of uncertainty about this estimate.

2.4 In people with the wet form of ARMD, the newly formed blood vessels may leak fluid and blood leading to scar formation and permanent damage to the macula. Individuals lose visual acuity (that is, the ability to detect fine details or small distances) and contrast sensitivity (that is, the ability to see less well-defined objects, such as faces, clearly). They may also experience distortion of vision, where the edges of objects and straight lines appear wavy. Wet ARMD usually progresses from a localised lesion to an end stage involving the entire macula, with complete or near complete loss of central vision. It has been estimated that 70% of eyes with CNV will have severe loss of vision within 2 years of diagnosis.

2.5 Central vision loss particularly impairs the perception of fine visual detail and colours. Thus activities such as reading, recognising faces and driving are affected. Significant loss of independence may occur. Rapidly deteriorating vision has an impact on emotional well-being, and individuals are likely to suffer depression and anxiety due to their loss of vision and reduction in independence. However, there is a great deal of individual variation in the ability to cope with visual loss.

2.6 For most patients with ARMD, management consists of 'best supportive care'. Visual rehabilitation, with teaching of skills and the provision of equipment to facilitate reading and other activities of daily living, may help people make the most of their remaining vision. However, the availability of these services is limited, and not everyone has access to high-quality visual rehabilitation.

3 The technology

3.1 The aim of photodynamic therapy (PDT) is to destroy CNV lesions without damaging the overlying retina, thereby slowing the progression of vision loss. The treatment involves infusion of a light-sensitive agent followed by light activation of the drug. At present, only verteporfin (Visudyne), a benzoporphyrin derivative, is available for this indication, but other agents are in
Verteporfin is given by intravenous infusion over 10 minutes at a dose of 6 mg per square metre of body surface area. Fifteen minutes after the start of the infusion, a low-powered laser calibrated to a specific wavelength is applied over a circular area slightly larger than the lesion. The laser is not powerful enough to cause any damage on its own, but the light is absorbed by the drug, which is 'activated' resulting in the formation of cytotoxic free radicals. These free radicals damage the new blood vessels, which may result in their closure.

In ARMD, verteporfin PDT is licensed for patients with subfoveal CNV that is predominantly composed of the 'classic' form (50% or more of the lesion). (Verteporfin is also licensed for PDT in the treatment of CNV associated with pathological myopia, but this indication is outside the scope of this appraisal.)

A 15-mg vial of verteporfin (sufficient for one PDT treatment) costs £850 (British National Formulary 43, March 2002). Patients are re-evaluated every 3 months using fluorescein angiography. If CNV leakage is present, they are retreated.

4 Evidence and interpretation

The Appraisal Committee considered evidence from a number of sources, including the Assessment Report, submissions by consultees, and views put forward at the meeting by clinical experts and representatives of patient/carer organisations (see Appendix B).

4.1 Clinical effectiveness

4.1.1 Two randomised, double-blind, placebo-controlled trials of verteporfin PDT were identified: the 'Treatment of age-related macular degeneration with photodynamic therapy (TAP) study' and the 'Verteporfin in photodynamic therapy (VIP) study'.

4.1.2 The TAP study included patients with ARMD and subfoveal CNV with some evidence of classic CNV, and visual acuity between 6/12 (mild visual impairment) and 6/60 (severely impaired vision). The VIP study was in two parts. One part included patients with CNV related to pathological myopia and was therefore outside the scope of this appraisal. The other part included patients with ARMD, but most of them suffered from the occult form of CNV (only 6% had predominantly classic CNV).
4.1.3 Both studies found less deterioration in visual acuity in the PDT-treated group compared with the placebo-treated group. In the TAP trial at 24 months 47% (95% confidence interval, 42% to 52%) of eyes treated with verteporfin PDT had lost 15 or more letters of visual acuity compared with 62% (95% confidence interval, 56% to 69%) of placebo-treated eyes. For the VIP study in ARMD, the corresponding figures were 54% (95% confidence interval, 47% to 60%) and 67% (95% confidence interval, 58% to 75%). The loss of 15 letters of visual acuity corresponds to being able to read three fewer lines on a standard type of eye-test chart.

4.1.4 A subgroup analysis of the TAP data found that the treatment effect was larger in the 40% of patients (242 of 609) whose lesions were composed of at least 50% classic type CNV. In this subgroup at 2 years 41% (95% confidence interval, 33% to 49%) of eyes treated with verteporfin PDT had lost 15 or more letters of visual acuity compared with 69% (95% confidence interval, 59% to 79%) of placebo-treated eyes. This is the basis of the licensed indication. In patients with between 0 and 50% classic lesion composition, verteporfin PDT appeared to have no benefit.

4.1.5 A further finding from the TAP trial was that PDT with verteporfin reduced the loss of contrast sensitivity. The extent to which this reduction contributes to the effect of verteporfin PDT on quality of life has not been quantified. In addition, improvement in distortion of vision has been reported anecdotally, but this aspect of the condition was not assessed in the clinical trials.

4.1.6 Some patients treated with verteporfin PDT have reported visual disturbances (vision abnormal, vision decreased, visual field defect) after treatment. Some of these disturbances involved severe loss of vision. In most patients who experienced severe loss of vision after verteporfin PDT there was partial or complete recovery of vision to baseline values. Other adverse effects reported in clinical trials of verteporfin PDT included infusion-related pain primarily presenting as back pain, and photosensitivity reactions in the form of sunburn following exposure to sunlight, usually within 24 hours of treatment. For full details of side effects and contraindications, see the Summary of Product Characteristics.

4.1.7 Overall, verteporfin was found to improve the chance of avoiding appreciable loss of vision (loss of three or more lines of visual acuity) over a period of 2 years.

4.2 Cost effectiveness

4.2.1 The Appraisal Committee considered three estimates of the cost effectiveness of verteporfin PDT: one was performed by the Assessment Group, another was
commissioned by the manufacturer and submitted for this appraisal, and a third was found in the published literature. All three evaluations expressed the benefits of treatment in terms of quality-adjusted life years (QALYs), which were related to change in visual acuity alone, and all assumed that patients were receiving treatment in their better-seeing eye. The analyses by the Assessment Group and in the manufacturer's submission included costs to the public sector (NHS and social services). The published study was from North America, and so the costs included in that assessment reflected the healthcare system in the USA.

4.2.2 All three economic evaluations were based on data from the TAP study. The Assessment Group used the whole trial data to estimate effectiveness, whereas the manufacturer's submission and the published evaluation based their estimate on data from the subgroup of patients with predominantly classic subfoveal CNV.

4.2.3 The Assessment Group's economic evaluation estimated that it would cost between £151,000 and £182,000 to gain one additional QALY over 2 years (the duration of the TAP study). The Assessment Group did not extrapolate the estimate of cost effectiveness beyond 2 years, considering that there were insufficient data on longer-term effectiveness or cost.

4.2.4 The manufacturer's submission estimated the cost effectiveness to be approximately £70,500 per additional QALY at 2 years. The model also made an estimate of cost effectiveness beyond 2 years. This required some assumptions about the long-term outcome as the clinical trials were only 2 years in duration, although the model was supported by unpublished follow-up data from a third year for some of the patients in the TAP study. The model was based on effectiveness data in the subgroup with predominantly classic CNV, and included assumptions that a proportion of patients would fail to respond and would receive no more than two treatments, all patients would receive no further treatment after 42 months, and visual acuity would remain relatively stable after treatment. Using the assumptions regarding long-term outcome and continuation of treatment in this model resulted in continually improving cost effectiveness over time. For example, the manufacturer's model suggests that by 5 years, the cost per additional QALY could have fallen to about £33,000, and by 7 years to about £25,000.

4.2.5 The published estimate of cost effectiveness was between £61,000 and £122,000 (US $86,700-US $173,900, converted to pounds sterling at 2000 rates) per additional QALY at 2 years. The estimate was dependent on visual acuity at the start of therapy. The lower cost per QALY was obtained if the patient was assumed to have reasonably good vision in the better-seeing eye at the start of treatment (visual acuity 6/12), while the higher estimate related to a patient with relatively poor vision (visual acuity 6/60 in the better-seeing eye). This analysis also estimated cost effectiveness beyond 2 years. The assumption used in this
model was that the effectiveness of the treatment would decline with time by 10% per year. At 11 years (the estimated average life-expectancy of patients in the TAP trial) the cost per additional QALY had fallen to £30,600 ($43,500) for a patient with good initial visual acuity, and to £61,300 ($87,200) for a patient with poor initial visual acuity.

4.2.6 The cost effectiveness of PDT for ARMD depends on whether the benefits seen at 2 years in the clinical studies persist over time, and whether further treatment is required. As there is no direct evidence on which to base estimates of continued benefit, long-term cost effectiveness depends on assumptions about the future progress of treated patients. However, there is some support for a relatively stable outcome after treatment from studies of patients treated with 'hot' laser photocoagulation. There are also follow-up data for up to 4 years for 58% (93) of the verteporfin-treated patients from the TAP study, which support a relatively stable outcome, after the first 2 years, in patients with predominantly classic CNV. Loss of 3 lines of vision being seen in 36% of patients at 24 months, 41% at 36 months and 43% at 48 months. However, these data must be interpreted with caution because not all patients in the original study entered the extension phase and only those in whom it was judged that continued PDT might reduce the risk of further vision-loss were enrolled, so various biases could be operating.

4.3 Consideration of the evidence

4.3.1 The Committee noted that two of the estimates of cost effectiveness were based on data from the subgroup of the TAP trial (that is, predominantly classic subfoveal CNV). The Committee considered that, in general, subgroup analyses should be interpreted with caution. These analyses may exaggerate the potential treatment benefit and may provide a much less sound basis for an estimate of effectiveness than the results of a whole trial. The Committee accepted, however, that a difference in response according to specific types of lesion, in particular in this case predominantly classic CNV, was a biologically plausible assumption on which to base the predetermined subgroup analysis.

4.3.2 The Committee reviewed the different estimates of cost effectiveness of PDT. These estimates were dependent on a number of different assumptions. In the case of the Assessment Group's economic model, decline in visual acuity was assumed to be linear with time, in both control and treated groups. This does not take into account the facts that the change in visual acuity was greatest in the early part of the TAP study and that the difference between treated and placebo groups was established during the first year. A recalculation, which corrected for this assumption of linearity, produced a cost-effectiveness estimate of approximately half that in the original submission, in the region of £80,000 per additional QALY at 2 years.
4.3.3 The Committee believed that there was likely to be benefit of treatment beyond the 2 years of the clinical trial even though the evidence base for this assumption was limited. Therefore limiting estimates of the cost effectiveness of this technology to the first 2 years led to an unduly pessimistic analysis. The Committee therefore gave particular consideration to the economic evaluations that attempted to evaluate cost effectiveness beyond 2 years.

4.3.4 In the manufacturer's economic evaluation, the trial results were extrapolated using various assumptions about the long-term course of treated ARMD in comparison with the natural history of the condition. The model presented by the manufacturer assumed that vision remained relatively stable after treatment. This is the most optimistic outcome possible, as treatment is not expected to improve baseline visual acuity, but reduces further loss of vision. There is little direct evidence on the long-term outcome after verteporfin PDT has been completed, so this approach might overestimate the benefits of treatment. Uncertainties were such that the Committee considered that the cost effectiveness of this technology beyond 2 years had not been fully substantiated and that the collection of further data on long-term progression after treatment was required.

4.3.5 The Committee noted that all the estimates of cost effectiveness assumed that it was the patient's better-seeing eye that was being treated. Treatment of the poorer-seeing eye is unlikely to provide a similar extent of benefit in terms of improvements in an individual's ability to function and quality of life. PDT is therefore likely to be less cost effective in people with only one affected eye. It should be reserved for people whose better-seeing eye is affected, or who have (for whatever reason) only one functioning eye that has become affected by ARMD.

4.3.6 The Committee considered that the selective treatment of individuals who retained relatively good vision at baseline was likely to improve the overall cost effectiveness of treatment. The published economic evaluation, in which the cost per additional QALY was very much lower in patients with relatively good vision (6/12) at the start of treatment than in patients with severely impaired vision (6/60), supported this view. The Committee concluded, on the basis of the evidence presented and the views of experts, that treatment of individuals with visual acuity lower than 6/36 would provide little or no further utility benefit as assessed by improvement in overall quality of life. They considered therefore that treatment only of patients with a visual acuity of 6/36 or better in the better-seeing or only-seeing eye would provide maximum clinical benefit and be cost effective.

4.3.7 In view of the high cost of each PDT treatment, a key issue in determining cost effectiveness is the number of treatments received by patients. In the TAP study patients received further treatment if there was evidence of CNV leakage on
fluorescein angiography, regardless of whether their visual acuity had deteriorated further. It is also uncertain if it is necessary to continue treatment once vision has stabilised whether or not CNV leakage as defined by fluorescein angiography is still present. Neither is it known whether further treatment is indicated if visual acuity declines significantly despite treatment. The economic analysis submitted by the manufacturer assumed that patients who lost more than 3 lines of visual acuity by the 6-month assessment would be deemed to have not responded and would receive no further treatment. Preliminary data from follow-up for 12 months of 134 patients treated with PDT in the UK have shown that, on average, patients have received 2.7 treatments in the first year. In the first year of the TAP trial patients received an average of 3.4 treatments. Further data are required on the number of treatments required for effective use of this technology in clinical practice.

4.3.8 The Committee heard from experts in the field and carefully discussed the considerable uncertainty as to the most appropriate treatment regimen for verteporfin PDT. They were made aware of the need for further research to clarify whether the clinical effectiveness and/or cost effectiveness can be improved by adjusting the treatment regimen - in particular whether continuation of verteporfin PDT should be related to decline in visual acuity or to the presence of continuing leakage for CNV as defined by fluorescein angiography, or whether a regimen involving more frequent treatment in the early phase might be more effective.

4.3.9 The Committee considered in detail uncertainties surrounding the use of PDT. These uncertainties were such that the Committee was unable to recommend that this technology should be generally available for the treatment of wet ARMD.

5 Recommendations for further research

5.1 There are several randomised controlled trials of PDT ongoing. One uses a different photosensitising agent. There are another two placebo-controlled trials of verteporfin PDT, one in patients with minimally classic CNV using standard or reduced laser settings, and one in patients with occult CNV.

5.2 The Committee recommended that individuals with predominantly classic CNV related to ARMD, whose better-seeing or only-seeing eye is affected, and who retain visual acuity in that eye of 6/36 or better, should be entered into a national surveillance programme of PDT. This should have the primary objective of determining the long-term benefit of PDT, both in terms of visual outcomes and quality of life, as measured by validated instruments. Other objectives should include estimating the number of treatments required for effective use in clinical
practice, and the identification of those individuals who are most likely to achieve a substantial response in terms of improvements in quality of life. The impact of treatment on all aspects of quality of life should be assessed.

5.3 If available, further data from the existing studies (particularly TAP) regarding long-term outcome of treated and untreated patients would provide further evidence on which to base the time horizon for the cost-effectiveness model.

5.4 The Committee considered that the regimen investigated in the clinical studies might not represent optimal use of this therapy. Further research is needed to clarify whether the clinical effectiveness and/or cost effectiveness can be improved by adjusting the treatment regimen.

6 Implications for the NHS

6.1 Our current best estimate suggests that in England and Wales as many as 5000-7500 new cases of predominantly classic CNV associated with wet ARMD may occur each year. It is not known how many of these would fulfil the criteria outlined in section 1.1. As a guide, treatment of 1000 patients per year with the current PDT regimen would cost in the region of £4,000,000 in the first year, rising to £8,300,000 by the third year, and remaining constant thereafter. There may be additional costs associated with a surveillance programme.

6.2 Wet ARMD can progress rapidly. For a PDT service to be as effective as possible, individuals with early wet ARMD and without serious visual loss will need to be fast-tracked through the referral and waiting list processes in order to receive treatment before further loss of vision occurs.

7 Implementation and audit

7.1 Clinicians who provide care for people with wet ARMD should take note of the guidance set out in Section 1.

8 Related guidance

8.1 There is no related guidance for this technology.
9 Review of guidance

The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.

9.1 The guidance on this technology will be reviewed in July 2005.

Andrew Dillon
Chief Executive
May 2002

Appendix A. Appraisal Committee members

NOTE

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members appears below. The Appraisal Committee meets twice a month other than in December, when there are no meetings. The Committee membership is split into two branches, with the Chairman, Vice-chairman and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If 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 declaration of interests, are posted on the NICE website.

Dr Jane Adam
Radiologist, St. George's Hospital, London

Professor R L Akehurst
Dean, School of Health Related Research, Sheffield University

Dr Sunil Angris
General Practitioner, Waterhouses Medical Practice
Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy, St Bartholomew's and Royal London School of Medicine

Dr Sheila Bird
MRC Biostatistics Unit, Cambridge

Professor Carol Black
Consultant Physician, Royal Free Hospital & UCL, London

Professor John Brazier
Health Economist, University of Sheffield

Professor Martin Buxton
Director of Health Economics Research Group, Brunel University

Professor Mike Campbell
Statistician, Institute of General Practice & Primary Care, Sheffield

Dr Karl Claxton
Health Economist, University of York

Professor Sarah Cowley
Professor of Community Practice Development, Kings College, London

Professor Jack Dowie
Health Economist, London School of Hygiene & Tropical Medicine, London

Mr Chris Evennett
Chief Executive, Mid-Hampshire Primary Care Group

Dr Paul Ewings
Statistician, Taunton & Somerset NHS Trust

Professor Terry Feest
Clinical Director and Consultant Nephrologist, Richard Bright Renal Unit, and Chairman of the UK Renal Registry

Professor Gary A Ford
Professor of Pharmacology of Old Age / Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Mrs Sue Gallagher
Chief Executive, Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs
Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline

Sally Gooch
Director of Nursing, Mid-Essex Hospital Services Trust

Mr John Goulston
Director of Finance, The Royal Free Hampstead NHS Trust

Professor Trisha Greenhalgh
Professor of Primary Health Care, University College London

Miss Linda Hands
Consultant Vascular Surgeon, John Radcliffe Hospital, Oxford

Professor Philip Home
Professor of Diabetes Medicine, University of Newcastle

Dr Terry John
General Practitioner, The Firs, London

Dr Diane Ketley
Research into Practice Programme Leader, NHS Modernisation Agency

Dr Mayur Lakhani
General Practitioner, Highgate Surgery, Leicester, and Lecturer, University of Leicester

Ruth Lesirge
Patient Representative; Director, Mental Health Foundation

Dr George Levy
Patient Representative; Chief Executive, Motor Neurone Disease Association

Dr Gill Morgan
CEO, North & East Devon Health Authority
Appendix B. Sources of evidence considered by the Committee

The following documentation and opinion were made available to the Committee:
A. Assessment Report prepared by West Midlands Health Technology Assessment Group, Department of Public Health and Epidemiology, The University of Birmingham:

Clinical effectiveness and cost utility of photodynamic therapy for wet age-related macular degeneration (January 2002)

B. Manufacturer/sponsor submissions from:

- Novartis

C. Professional/specialist group submissions from:

- British Geriatrics Society
- The College of Optometrists
- Royal College of General Practitioners
- Royal College of Ophthalmologists
- Moorfields Eye Hospital NHS Trust
- Department of Health and Welsh Assembly Government
- Health Technology Board for Scotland
- East Riding and Hull Health Authority

D. Patient/carer group submissions from:

- Macular Disease Society
- RNIB
- Wales Council for the Blind

E. Expert perspectives from:

- Dr Bob Thompson, President Elect, The Macular Disease Society
- Mr Jonathan Dowler, Consultant Ophthalmologist, Moorfields Eye Hospital.
- Professor Alan Bird, Professor of Clinical Ophthalmology, UCL