Photodynamic therapy with verteporfin for macular degeneration

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The Secretary
Medical Services Advisory Committee
Department of Health and Ageing
Mail Drop Point 107
GPO Box 9848
Canberra ACT 2601

Inquiries about the content of the report should be directed to the above address.

The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee (MSAC) with assistance from Dr Bruce Hollingsworth and Mr Anthony Harris (Health Economics Unit, Centre for Health Program Evaluation) and Dr Renea Johnston, Ms Elizabeth Burrows, Ms Alexandra Raulli and
Dr Elmer V Villanueva (Centre for Clinical Effectiveness, Monash Institute of Health Services Research) of Monash University.

The report was endorsed by the Commonwealth Minister for Health and Aged Care on 17 September 2001.

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MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Medical Services Advisory Committee — role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. The MSAC advises the Commonwealth Minister for Health and Ageing on the evidence for the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from Monash University was engaged to conduct a systematic review of literature on photodynamic therapy with verteporfin for macular degeneration. A supporting committee with expertise in this area then evaluated the evidence and provided advice to the MSAC.

MSAC's assessment of photodynamic therapy with verteporfin

Clinical need

MD is a progressive disease with clinical and pathological features that can be classified into two groups: non-exudative or atrophic (dry) MD and exudative or neovascular (wet) MD. MD is rare before the age of 55 years, but its prevalence increases rapidly after 65 years and it is present in almost 20 per cent of people older than 85 years. Exudative MD is its more severe form and it is estimated, from community based studies, that between 63 and 67 per cent of Australians with late-stage maculopathy (the precursor to MD) have the exudative form of the disorder. Choroidal neovascularisation, a feature of exudative MD, is the ingrowth of new blood vessels into the retina and resultant lesions. These are classified into two types, occult and classic, based on their appearance with fluorescein angiography. The prevalence of exudative MD with predominantly classic lesions in the Australian general population is not known. By extrapolating from several data sources it is estimated that the prevalence in the year 2000 would have varied widely between 595 and 20,000 cases.

Safety

Safety of verteporfin in PDT was evaluated from randomised controlled trials and post-surveillance studies. Adverse events assessed by the treating ophthalmologist as being directly related to treatment were approximately 40 per cent more likely in patients administered verteporfin than placebo: 192 patients (47.8%) in the verteporfin group compared with 70 (33.8%) in the placebo group, relative risk (RR) = 1.4, 95%, confidence interval (CI) = 1.1-1.8. The number of adverse events related to treatment is relatively high and precise since seven patients need to be treated with verteporfin before one patient suffers an adverse event (95% CI = 5-17). This computation of number of patients needed to harm (NNH) is an underestimate since actual patients would not be suffering adverse events from placebo treatments with saline injections and PDT. Thus the actual NNH from verteporfin therapy versus no treatment (not placebo) would be 2 (95% CI = 2-3).

One hundred and eighty five clinically relevant adverse events occurred in the group treated with verteporfin. These included visual disturbance (22.1%), injection site events (15.9%), infusion-related back pain (2.5%), allergic reactions (2.0%) and photosensitivity reactions (3.5%). The difference in risk of any adverse event between treatment with verteporfin and placebo is 23.3 per cent (95% CI = 15.8-30.8%).

Safety of fluorescein angiography, performed to assess patient eligibility for verteporfin treatment, was also evaluated. However, details of adverse events were found only in case series and surveys, literature of relatively poor methodological quality. It has been reported that the frequency of adverse events are one per 63 angiograms for moderate events and one per 1900 angiograms for severe events. The incidence of adverse events has been reported at 4.8 per cent, but the likelihood of an adverse event increases dramatically if a patient has a history of adverse reactions to the procedure.

This is important in the context of verteporfin therapy as there is a need for multiple fluorescein angiograms in determining whether the treatment has been effective and to determine if re-treatments are required.

Effectiveness

Evidence of clinical effectiveness came from a randomised controlled trial that compared verteporfin with placebo in PDT for patients with neovascular MD. In patients with predominantly classic (≥ 50%) CNV, PDT with verteporfin was more effective than placebo in reducing the loss of fewer than 15 letters in a standard visual acuity, chart-reading test. An average of 5.6 (range 1-8) verteporfin treatments were administered over 24 months to achieve this reduction in visual acuity loss. The NNT was 4 (95% CI = 2-7) in patients with at least 50 per cent classic CNV and 2 (95% CI = 2-4) in patients with no evidence of occult CNV. It did not reverse visual loss.

Verteporfin therapy was no more effective than placebo in patients with CNV lesions that were <50 per cent classic, in patients with evidence of occult CNV and in patients who were current smokers.

In the trial of 609 patients, a minority had visual characteristics that were likely to benefit from treatment with verteporfin: 242 had lesion areas that were ≥ 50 per cent classic and 143 patients had no evidence of occult CNV.

Six systematic reviews also reported results from the same randomised controlled trial. In essence, the reviews concluded that PDT with verteporfin is effective in retarding the loss of visual acuity in patients with predominantly classic subfoveal CNV secondary to MD.

The key issues identified from the evaluation of the randomised controlled trial and the reviews included:

- the conclusion from the randomised controlled trial that verteporfin is effective is based on the outcomes in a subgroup of the total study population;
- the difficulty in diagnosing patients with predominantly classic lesions;
- the effect of treatment on patients' quality of life have not been reported;
- the lack of evidence of effectiveness beyond two years - repeat treatments are required but the number and frequency beyond two years is unknown;
- the number of patients initially screened was not reported, hence the proportion of patients eligible for treatment is not known.

Cost-effectiveness

Verteporfin may lead to a gain in vision years compared with placebo, however there are reservations about some aspects of the trial evidence.

Verteporfin appears to cost substantially more than a watchful waiting/placebo program. The modelling in the submission suggests a cost per

year of vision gained of between $6,120 and $35,456. This is based on an assumed clinical advantage and a considerable series of cost offsets which may not be achieved in practice.

It is estimated that costs will range from $10-30 million in the first year, $16-36 million in the second year and $13.6 million per annum in subsequent years, once only new cases are being treated. These estimates are based on accurate selection of eligible patients, but in reality the difficulty of diagnosing patients with predominantly classic lesions has implications for increased costs.

There is some concern that the group included in the trial may not represent the whole patient group who would receive treatment in clinical practice. No details of the numbers screened in the trial were available. If the actual patient population treated is wider than that selected for the trial the cost per extra year of vision gained could be considerably higher than the estimates provided in the submission.

Recommendations

The MSAC has reviewed the evidence relating to photodynamic therapy for macular degeneration (MD) in terms of clinical need, safety, effectiveness and cost-effectiveness. The MSAC recommends that public funding for this therapy should only be supported for patients with predominantly classic (>50% classic) subfoveal choroidal neovascularisation secondary to MD, a small minority of MD cases. For this sub-group of MD patients, there is some evidence that the therapy may retard the rate of visual loss in the short term.

As there is insufficient evidence of the effectiveness or cost-effectiveness of photodynamic therapy to support funding for this treatment outside the indications outlined above, the Committee also recommends that public funding should only be supported where arrangements are in place to ensure, as far as possible, that the indications in the previous paragraph are met.

The Minister for Health and Aged Care accepted these recommendations on 17 September 2001.

Introduction

The MSAC has reviewed the use of photodynamic therapy (PDT) with verteporfin, which is a treatment for choroidal neovascularisation (CNV) caused by macular degeneration. The MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC's terms of reference and membership are at Appendix A. The MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for photodynamic therapy with verteporfin.

Background

Macular degeneration

Despite the lack of an accepted definition of macular degeneration (MD), it is commonly understood to be a disorder of unknown causality of the macular area of the retina and is most common in older people (50 years and older). Maculopathy is a precursor to MD and is characterised by discrete whitish-yellow spots called drusen. The progressive accumulation of these spots under the retina predisposes to late-stage maculopathy (Royal College of Ophthalmologists 2000).

MD is progressive and usually bilateral, leading to severe and irreversible central vision loss. Central vision loss can lead to impaired visual acuity and legal blindness although individuals often maintain enough peripheral vision to move independently (Tunis et al. 2000). The disease includes a wide range of clinical and pathological features that can be classified into two groups: nonexudative or atrophic (dry) MD and exudative or neovascular (wet) MD (figure 1). Recent Australian community-based studies suggest that nonexudative MD accounts for about one-third of all cases of MD (Mitchell et al. 1995, VanNewkirk et al. 2000). It usually progresses more slowly than the exudative type (Kanski 1999). The two clinical classifications are not divergent and individuals who develop nonexudative MD can also develop the exudative type.

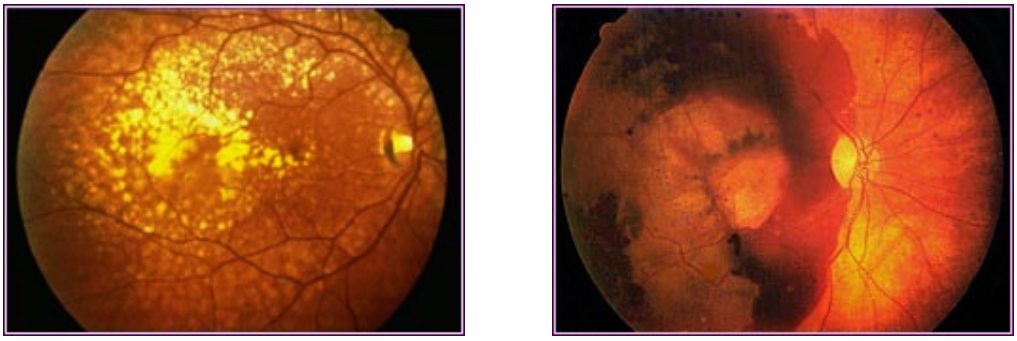

Figure 1 **Fundus photograph showing a retina with nonexudative (left) and exudative macular degeneration.**

Nonexudative MD is characterised by large drusen and abnormalities of the layer of the retina called the retinal pigment epithelium (RPE). These abnormalities include atrophy, hypopigmentation or hyperpigmentation (Soubrane & Bressler 2001). As drusen continue to accumulate the RPE and photoreceptor layers of the retina are lifted away from the choriocapillaris, resulting in a disruption of blood flow to the macula (Aaberg 1980). The level of associated visual impairment is variable and may be minimal (Hardy 1995).

Exudative MD is the more severe type with much of the legal blindness attributable to MD resulting from this variant (Kanski 1999). Two notable features of the exudative form are that the RPE detaches and choroidal neovascularisation (CNV) develops. Focal detachment of the RPE is caused by serous fluid leaking from the choroid and accumulating in the collagenous lamina (Bruch's membrane) underlying the RPE. CNV represents the ingrowth of new vessels extending from the choroid into the subretinal space. Leakage from these abnormal vessels causes lesions to form (Vaughan et al. 1995), and may precede or follow RPE detachment. As neovascularisation precedes fibrous tissue develops and causes an elevated subretinal mass called a disciform scar. This fibrovascular mass is usually centrally located and results in permanent loss of central vision (Vaughan et al. 1995).

CNV lesions can be classified according to their location and appearance. Their location is defined by their relationship with the fovea (a depression in the macula adapted for acute vision) as localised using fluorescein angiography: subfoveal lesions lie directly beneath the foveal avascular zone, juxtafoveal lesions approximately 100-200 μm from the centre of the foveal avascular zone, and extrafoveal lesions more than 200 μm from the centre of the foveal avascular zone (Kanski 1999).

CNV are classified into two types from their appearance during fluorescein angiography. Classical CNV is characterised by a well-defined membrane that fills with dye in a uniformly defined pattern during the early phase of dye infusion, then leaks into the subretinal space and around the CNV within one to two minutes (Kanski 1999). Occult CNV is characterised by a poorly defined membrane with less precise features and gives rise to late non-uniform leakage (Kanski 1999). While lesions can have both classic and occult components, approximately 22 per cent (95% CI = 14.3-31.4%) are classified as subfoveal and predominantly classic (Moisseiev et al. 1995).

The procedure

Photodynamic therapy with verteporfin is a new therapy in the treatment of exudative MD of the predominantly classic type. Verteporfin is a photosensitive agent that is infused intravenously and accumulates preferentially in neovascular endothelium. It is activated by red light (689 nm) from a non-thermal laser. After it is exposed to the light, reactive oxygen intermediates are produced locally and specifically disrupt the endothelial cells of the new abnormal blood vessels in the lesion. This generally causes thrombosis and closes the abnormal, leaking vessels without significantly affecting the retina. These effects appear to reduce vascular leakage and stabilise visual acuity. This procedure is usually performed as an outpatient procedure by an ophthalmologist.

Fluorescein angiography

Information on retinal and choroidal vasculature is provided by fluorescein angiography. This procedure is routinely used in examining MD (Donaldson 1980). It was developed in the late 1950s as an investigative procedure (Novotny & Alvis 1961), but its role has since evolved into an adjunctive diagnostic tool for assessing pathophysiologic mechanisms affecting the ocular fundus and a therapeutic guide for treating retinal and choroidal diseases (Bloome 1980).

An odourless, orange-red aqueous fluorescent dye (sodium fluorescein) is injected intravenously into the antecubital vein. As much as 80 per cent of the dye is bound to serum protein, reducing the amount of visible fluorescence during angiography (Bloome 1980). Within minutes of administration, the dye is rapidly distributed throughout the body, giving patients a yellowish discolouration of the skin which persists for a few hours. The dye is eliminated from circulation through hepatic and renal means within 24-36 hours (Donaldson 1980).

The dye is visible in the eye about 10–18 seconds after it is injected with the period depending on the rapidity of injection, dye concentration in solution, and cardiovascular factors (Bloome 1980). The dye diffuses from the choroidal vasculature into the surrounding choroidal tissue. Tight intercellular junctions normally prevent its spread into the retina. The retention of dye in the choroidal layer gives angiograms a ground-glass appearance. The lack of fluorescein dye in the retinal capillaries enables the visualisation of the entire retinal vasculature (Bloome 1980).

When sodium fluorescein is illuminated by blue light (465-490 nm) it emits green light peaking at 520-530 nm. During angiography, a blue exciting filter is placed in the pathway of a viewing light and a green–yellow barrier is placed in the path of the emitted light. Photos are taken with a high-intensity electronic flash.

Intended purpose

The proposed indication for PDT with verteporfin is for the treatment of sub-foveal CNV secondary to MD where the CNV is composed, predominantly ($\geq$ 50%), of classic lesions as defined by fluorescein angiography.

Clinical need/burden of disease

The prevalence of MD increases with age. Two Australian community-based studies showed that between 0.68 per cent and 1.9 per cent of people older than 40 had MD (Mitchell et al. 1995, VanNewkirk et al. 2000). The condition is rare before the age of 55, but prevalence increases rapidly after 65 so that in those older than 85 years there is a prevalence of nearly 20 per cent (VanNewkirk et al. 2000). Recent studies using similar criteria in the USA and the Netherlands have shown a similar prevalence (Klein et al. 1992, Klaver et al. 1998). In about 60 per cent of patients, both eyes are affected. In the Australian studies between 63 per cent and 67 per cent of patients with late-stage maculopathy (the precursor to MD) had the 'exudative' type.

In the atrophic type, visual impairment is slow and progressive over a decade or two with some patients maintaining fairly good central vision but having substantial limitations including fluctuating vision and difficulty reading because of limited central and night vision and under conditions of reduced illumination (Kanski 1999).

Neovascular MD causes severe damage to the macula and severe loss of central vision relatively quickly, usually over 3–24 months. Vision loss is slower in patients with <50 per cent classic lesions or no classic lesions than in those with ≥ 50 per cent classic lesions. The loss of vision associated with exudative MD can substantially affect quality of life (Weih et al. 2000). People may find it difficult to read, write, drive, get out of the house, shop and manage money. Those with bilateral disease are more likely to have falls than normally sighted people of a similar age (Ivers et al. 1998). They rely more on community services such as home nursing and on regular help from family and friends (Wang et al. 1999). It is difficult to determine the precise role of visual impairment in causing admission to supported accommodation such as hostels and nursing homes because decreased vision is likely to act synergistically with other disabilities (Klein et al. 1996).

In Australia, it has been estimated that the years lived with disability from age-related vision disorders (of which MD is the major one) are 21,056 in 1996 (Mathers et al. 1999). Women account for almost 80 per cent of this disease burden, presumably because of their longer life expectancy.

Estimated prevalence and incidence of exudative MD

The age-specific and total prevalence of MD in the general Australian population have been estimated using data from the Australian Bureau of Statistics (2000), Mitchell et al. (1995), VanNewkirk et al. (2000) and Moisseiev et al. (1995). The results are presented in Table 1. The wide range of estimates implies considerable uncertainty in the prevalence of the condition. It is anticipated that the aging of the general population will increase the overall prevalence.

Table 1 Estimated prevalence of exudative macular degeneration with predominantly classical features in the Australian general population.

Age	Estimated resident population*	Prevalence of MD	Estimated prevalence of MD cases	Estimated prevalence of exudative MD	Estimated prevalence of exudative MD with predominantly classic features	Range of estimates of the prevalence of exudative MD with predominantly classic features
Mitchell et al.						
49–54	1,507,539	0	0	0	0	0
55–64	1,738,870	0.002	3,477.74	1,714.38	377.16	185.48–670.70
65–74	1,299,301	0.007	9,095.11	4,483.50	986.37	485.06–1,754.04
75–84	808,705	0.054	43,670.07	21,527.50	4,736.05	2,329.03–8,421.99
>85	252,228	0.185	46,662.18	22,982.76	5,056.21	2,488.60–8,999.04
Total	5,606,643	-	102,905.10	50,708.14	11,155.79	5,488.17–19,845.75
VanNewkirk et al.						
40–49	2,787,893	0	0	0	0	0
50–59	2,203,532	0	0	0	0	0
60–69	1,461,362	0.005	7,306.81	4,014.64	883.22	0–3,140.48
70–79	1,129,389	0.018	20,329.00	14,016.06	3,083.53	595.03–8,150.64
Total	7,582,176	-	27,635.81	18,030.70	3,966.75	595.03–11,291.13

* As of June 2000 (Australian Bureau of Statistics 2000)

While there are no Australian figures for the incidence of MD, a figure of 10 per cent of the prevalence has been suggested as a reasonable estimate by clinical experts. This would indicate between 400 and 1,100 new patients a year with predominantly classic 'wet' MD based on the average figures derived from the studies of Mitchell et al. (1995) and VanNewkirk et al. (2000).

Existing procedures

Laser photocoagulation treatment is the only widely studied treatment available for exudative MD. However, there are some caveats associated with its use. It appears to be most beneficial for patients with small, classic lesions, particularly extrafoveal and juxtafoveal ones. (Tunis et al. 2000). However CNV lesions often recur subfoveally and the partially selective thermal effect of the laser also damages viable photoreceptors surrounding the lesion (Tunis et al. 2000). In addition, most patients who present with subfoveal CNV secondary to MD have large lesions with an occult component unsuitable for laser photocoagulation (Macular Photocoagulation Study Group 1991).

Experimental treatments

The photodynamic therapy with tin ethyl etiopurpurin ($SnET_2$) study is a randomised controlled trial on the safety and potential efficacy of PDT $SnET_2$ in the treatment of subfoveal CNV associated with MD (Pharmacia Ophthalmology 2001). Further details of this trial are in Appendix F.

Other potential treatments for CNV include radiation therapy, interferon α-2a, transpupillary thermotherapy, advanced retinal surgery, angiogenic agents, antioxidant vitamin and mineral supplements (Norwegian Centre for Health Technology Assessment 2000, National Horizon Scanning Centre 2000).

Comparator

It is unclear whether laser photocoagulation therapy is a viable treatment option for subfoveal CNV secondary to MD. A randomised controlled trial that was not assessed for this report (Macular Photocoagulation Study Group 1993) examined the effectiveness of laser photocoagulation therapy for small subfoveal CNV lesions secondary to MD. It concluded that, although there is immediate vision loss after initial treatment, visual acuity is stabilised about 18 months later. However, because of the initial sharp irreversible reduction in vision, the Royal College of Ophthalmologists suggests laser photocoagulation therapy may not justified for this patient group (Royal College of Ophthalmologists 2000). Thus, 'watchful waiting' or placebo may be the most appropriate comparator for these patients.

Marketing status of the device/technology

The following two products on the Australian Register for Therapeutic Goods (ARTG) relate to this therapy.

- Surgical procedure pack for administration of verteporfin - AUST L 74563 (listed as a therapeutic device on 29 May 2000).

- Verteporfin 15mg powder for injection vial - AUST R 74902 (registered as a prescription only medicine on 2 August 2000).

The Therapeutic Goods Administration approves all listings and registrations on the ARTG. They have approved verteporfin for 'the treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularisation'.

Current reimbursement arrangement

There is currently no listing on the Medicare Benefits Schedule (MBS) for photodynamic therapy with verteporfin for MD. The fluorescein angiography required for patient selection and to assess treatment outcomes (required before and after each treatment session) are covered under the following MBS items:

- 11215 - Retinal photography, multiple exposures, of one eye with intravenous dye injection (Medicare reimbursement of $95.70).

- 11218 - Retinal photography, multiple exposures of both eyes with intravenous dye injection (Medicare reimbursement of $118.25).

Source: Medicare Benefits Schedule, 1 November 2000, Commonwealth Department of Health and Aged Care.

Approach to assessment

Review of literature

Search strategy

The medical literature was searched to identify relevant studies and reviews for the period 1966-2001. The following electronic databases (Table 2) were used to provide a list of citations.

Table 2 Electronic databases used in this review

Database	Period covered
Medline–OVID	1966 to February, 2001
PreMedline–OVID	April 2, 2001
Current Contents	Week 26, 1993 to Week 15, 2001
Cochrane Library	Issue 1, 2001

Health technology assessment databases were also searched on the Internet. The Internet sites are listed in Appendix E. Health technology assessments identified for evaluation are cited in Appendix C.

Table 3 lists the search terms used to identify the citations. The search statements were combined using the Boolean operator 'and'. All articles identified by this strategy were retrieved.

Table 3 Search terms

Visudyne or verteporfin or photodynam$ or PDT or photochemotherapy [MeSH]
Macular degeneration [MeSH] or macular degen$ or macul$ or choroidal neovascularis$

* Terms were searched as text words. A medical subject heading (MeSH) term was conducted if allowed by the database.
$ Represents truncation.

Entry criteria

The following criteria were developed *a priori* to determine eligibility of relevant studies for the critical appraisal of effectiveness.

Characteristics of study population

- Inclusion: patients with a diagnosis of MD
- Exclusion: animal studies, in vitro studies

Characteristics of the intervention

- Inclusion: PDT with verteporfin
- Exclusion: none

Characteristics of the outcome

- Inclusion: all outcomes that address clinical and physiological factors attributable to PDT with verteporfin.
- Exclusion: none

Characteristics of the study design

- Inclusion: individual, randomised, comparative studies and systematic reviews of studies that compare the outcomes of patients who have undergone PDT with verteporfin and the outcomes of control patients not treated with PDT using verteporfin.
- Exclusion: phase I and II studies, case series and case reports, narrative reviews, editorials, and data that is not part of the peer-reviewed, published literature.

Review profile

The search strategy identified 94 articles. Eleven were included for further assessment. Of these, eight studies, two randomised controlled trials published together (TAP Study Group 1999, 2001) and six systematic reviews (Norwegian Centre for Health Technology Assessment 2000, National Horizon Scanning Centre 2000, Fong 2000, Alberta Heritage Foundation for Medical Research 2000, Tunis et al. 2000, Wormald et al. 2000) met the selection criteria for critical appraisal. Eighty six articles did not meet the criteria. Of these, two were phase I/II studies, one a case series, 37 narrative reviews or editorials, 24 animal, two in vitro studies and 20 non-English reports.

Included citations are listed in Appendix C, and excluded citations are listed in Appendix D.

Data extraction

Data were extracted from the included articles using standardised methods. Two independent reviewers examined each article. Discrepancies in evaluation were discussed and resolved through consensus.

Dimensions of evidence

The evidence presented in the selected studies was assessed and classified according to the National Health and Medical Research Council revised hierarchy of evidence that is shown in Table 4 (NHMRC 2000).

Table 4 Evidence dimensions (NHMRC 2000)

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

The strength of the evidence is composed of three sub-domains. Previous assessments concentrated only on the first of these, the level of the evidence. Table 5 lists the designations recommended by the NHMRC (NHMRC 2000).

Table 5 Designation of levels of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test/post-test.

Critical appraisal of published randomised controlled trials

The assessment of validity of randomised controlled trials (RCTs), another important sub-domain, was based on characteristics that reflect important aspects of study design (Schulz et al. 1995, Jadad et al. 1996). Table 6 summarises these characteristics and the ordinal scale used in the assessment.

Table 6 Study design characteristics used to assess the methodological quality of RCTs

Randomisation	
Adequate	Method of allocation is random, such as computer-generated number sequences and tables of random numbers.
Unclear	Trials in which the authors failed to describe the method of randomisation with enough detail to determine its validity.
Inadequate	Method of allocation is non-random, such as alternation methods or the use of case numbers.
Concealment of allocation	
Adequate	Adequate measures to conceal allocations such as central randomisation; serially numbered, opaque, sealed envelopes; or other descriptions that contain convincing elements of concealment.
Unclear	Unclearly concealed trials in which the author failed to describe the method of concealment with enough detail to determine its validity.
Inadequate	Method of allocation is not concealed.
Masking	Masking strategy applied (single, double, etc.).
Participant inclusion	Intention to treat analysis was performed.
Losses to follow-up	Losses specified.

In addition to assessing validity, study results are analysed to determine importance, that is the size of potential benefits (or harm) to patients of the treatment being investigated. Measures that were used to assess the importance of study results are the absolute risk reduction (ARR), relative risk (RR), the number of patients needed to treat (NNT) and the number of patients needed to harm (NNH).

Absolute risk reduction (ARR) is the absolute difference in rates of events (treatment outcome) between the experimental and control groups in a trial. The formula for calculating ARR is:

$$ARR = CER - EER$$

where CER is the event rate in the control group and EER is the event rate in the experimental group. The event rate is the number of events divided by the number of observations.

Relative risk (RR) is the number of times more likely (RR >1) or less likely (RR < 1) the event is to happen in one group compared with another.

$$RR = \frac{EER}{CER}$$

Number needed to treat (NNT) is the number of patients that need to be treated with the experimental intervention to see one patient experience the outcome of interest.

$$NNT = \frac{1}{ARR}$$

Number needed to harm (NNH) is the number of patients that need to be treated with the experimental intervention to see one patient experience an adverse outcome of interest:

$$NNH = \frac{1}{ARI}$$

where ARI is the absolute risk increase (same calculation as ARR).

Critical appraisal of published systematic reviews

Systematic reviews were critically appraised against both a modified checklist recommended by the Quality of Reporting of Meta-Analyses (QUOROM) group (Moher et al. 1999; Table 7) and recognised qualitative criteria (Chalmers & Altman 1995, Greenhalgh 1997, Sackett et al. 2000). Qualitative criteria are designed to assess whether the systematic review was performed in the best way to minimise bias. Criteria assess whether the systematic review contains an explicit statement of the objectives and methods and whether the methods are reproducible. Specific criteria assessed whether the review asked a focused question, if the eligibility criteria for included trials are explicit, what search strategy was used, how the validity of included trials was assessed and whether results of included trials were similar.

Six systematic reviews were identified (Appendix C), a Cochrane systematic review (Wormald et al. 2000) and five health technology assessments (Norwegian Centre for Health Technology Assessment 2000, National Horizon Scanning Centre 2000, Fong 2000, Alberta Heritage Foundation for Medical Research 2000, Tunis et al. 2000).

Table 7 Quality of reporting of published systematic reviews

Heading	Descriptor
Title	Identify the report as a systematic review
Abstract	Use of a structured format
	Explicit description of clinical question
	Description of databases and other information sources
	Description of selection criteria
	Description of methods for validity assessment
	Description of methods for data abstraction
	Description of study characteristics
	Description of quantitative data synthesis
	Description of characteristics of included and excluded studies
	Description of quantitative findings
	Description of qualitative findings
	Description of results of subgroup analysis
Introduction	Explicit description of clinical problem
	Explicit description of biological rationale for intervention
	Explicit description of rationale for review
Methods	Detailed description of information sources
	Detailed description of restrictions on searching
	Description of inclusion and exclusion criteria
	Description of criteria and process used for validity assessment
	Description of processes used for data abstraction
	Description of study characteristics included
	Description of methods of assessment of clinical heterogeneity
	Description of principal measures of effect
	Description of methods of combining results
	Description of methods used to handle missing data
	Description of methods of assessment of statistical heterogeneity
	Description of rationale for *a priori* sensitivity testing and subgroup analysis
	Description of methods to assess publication bias
Results	Description of profile of trial flow
	Presentation of descriptive data for each trial
	Report of agreement on the selection of studies
	Report of agreement on validity assessment
	Presentation of simple summary results
	Presentation of data needed to calculate effect sizes and confidence intervals
Discussion	Summarisation of key findings
	Discussion of clinical inferences based on internal and external validity
	Interpretation of the results in the light of the totality of available evidence
	Description of potential biases in the review process
	Suggestions for future research agenda

Expert advice

A supporting committee with expertise in ophthalmology was established to evaluate the evidence and provide advice to the MSAC from a clinical perspective. In selecting members for supporting committees, the MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations for nominees. Membership of the supporting committee is provided in Appendix B.

Results of assessment

Is it safe?

Safety of verteporfin

The safety of verteporfin in PDT for patients with MD was assessed in the TAP study (TAP Study Group 1999, 2001). Adverse events reported during pre-clinical phases (Schmidt-Erfurth et al. 1998, Miller et al. 1999) and clinical phases were recorded but only for those reported in the randomised controlled trials and post surveillance studies.

An adverse event associated with therapy was based on the assessment by the patient's ophthalmologist. Adverse events were approximately 40 per cent more likely in patients administered verteporfin than placebo: 192 patients (47.8%) in the verteporfin group compared with 70 (33.8%) in the placebo group, RR = 1.4, 95%, CI = 1.1-1.8. The NNH is an estimate of the number of patients who would need to be given verteporfin for harm to be caused to one patient, based on the adverse event rate observed in the trial. As can be seen in Table 8, the number of adverse events related to treatment is relatively high and precise, since seven patients need to be treated with verteporfin before one patient suffers an adverse event (95% CI = 5-17). This calculation underestimates NNH since actual patients would not be suffering adverse events from placebo treatments with saline injections and PDT. Thus the actual NNH from verteporfin therapy versus no treatment (not placebo) would be 2 (95% CI = 2-3).

Adverse events during the 24 month follow-up, reported as clinically relevant irrespective of relationship to treatment are also listed in Table 8. One hundred and eighty five clinically relevant adverse events occurred in the group treated with verteporfin. These included visual disturbance (22.1%), injection-site events (15.9%), infusion-related back pain (2.5%), allergic reactions (2.0%) and photosensitivity reactions (3.5%). The difference in risk of any adverse event between treatment with verteporfin and placebo is 23.3 per cent (95% CI = 15.8-30.8%).

Since some patients would have experienced multiple adverse events, the number needed to be given verteporfin for an adverse event to occur (number needed to harm event rate; NNHER) has been calculated. Only four patients need to be treated with verteporfin before an adverse event occurs (95% CI = 3-6).

Table 8 Comparison of clinically relevant adverse events related to and irrespective of relationship to treatment from baseline to 24 months: verteporfin compared with placebo

Adverse event	Verteporfin (n=402) Frequency (%)	Placebo (n=207) Frequency (%)	Difference (95% CI)	NNH* (95% CI)
Events related to treatment	192 (47.8)	70 (33.8)	13.9 (5.9–22.0)	7 (5–17)
Events irrespective of relation to treatment:				
Visual disturbance†	89 (22.1)	32 (15.5)	6.7% (0.3–13.1)	15 (8–335)
Injection-site adverse events‡	64 (15.9)	12 (5.8)	10.1% (5.3–14.9)	10 (7–19)
Infusion-related back pain	10 (2.5)	0 (0.0)	2.5% (1.0–4.0)	40 (25–104)
Allergic reactions	8 (2.0)	8 (3.9)	0.5% (-1.6–2.7)	n/a§
Photosensitivity reactions	14 (3.5)	0 (0.0)	3.5% (1.7–5.3)	29 (19–59)
Any of above events	185 (46.0)	47 (22.7)	23.3 (15.8–30.8)	NNHER = 4 (3–6)

* NNH = number needed to harm, NNHER = number needed to harm event rate
† Includes reports of abnormal vision, decreased vision, and visual field defect irrespective of judgement of relationship to study treatment.
‡ Includes pain, oedema, extravasation, inflammation, haemorrhage, hypersensitivity, discolouration and fibrosis
§n/a not applicable since not statistically significant

Seven patients (1.7%) withdrew from the study because of adverse events possibly related to treatment. All were from the verteporfin group. Such events included one occurrence each of allergy to fluorescein dye, subretinal haemorrhage, gastrointestinal bleeding, possible allergic reaction to treatment, severe back pain possibly related to the infusion, suprachoroidal haemorrhage with retinal detachment and vitreous haemorrhage, and injection site (drug extravasation) reaction.

The study also reported deaths that were considered unrelated to treatment. Eight deaths (2.0%) in the verteporfin group and four (1.9%) in the placebo group were reported in the first year and five deaths in the verteporfin group and four in the placebo group in the second year of the study.

The size of the lesion and any surrounding atrophy was not significantly different from the size of the lesion without the inclusion of surrounding atrophy for both groups, suggesting that eyes treated with verteporfin did not develop additional surrounding atrophy when compared with eyes treated with placebo.

Noffke et al. (2001) described a patient who experienced a grand mal seizure then subsequent cardio-respiratory arrest following infusion with verteporfin. The patient was an otherwise healthy 43 year old woman who had previously undergone focal laser treatment without incident. Cardiopulmonary resuscitation was administered and her pulse returned and she began to breathe spontaneously. After transfer to a hospital she remained haemodynamically stable and was discharged from hospital fully recovered. The ophthalmologists present regarded it as an episode of cardiopulmonary arrest associated with the infusion of verteporfin; however there is the likelihood that the reaction was a vasovagal response to the procedure.

Safety of fluorescein angiography

Quantitative details of the incidence and prevalence of adverse events after administration of fluorescein as indicated by angiography are unavailable. Frequently cited details are based on descriptive studies (e.g. case reports, case series and surveys) with major flaws in design. Yannuzzi et al. (1986) described three broad classifications of adverse events (Table 9). In a survey of 14,864 ophthalmologists in the United States and Puerto Rico, the frequency of reported moderate adverse events was one per 63 angiograms. Severe adverse events were reported at a ratio of one per 1,900 procedures. One death was reported in 222,000 procedures. The major shortcoming of the study was the poor response rate. Only 16 per cent of the target population returned completed survey forms, raising questions about the generalisability of these quantitative findings.

Table 9 Classification of adverse reactions after administration of fluorescein dye during angiography.

	Mild	Moderate	Severe
Definition*	Transient effect not requiring treatment; reaction with a rapid and complete resolution with no sequelae.	Transient effect requiring medical treatment; reaction has complete but gradual resolution with no sequelae nor threat to the patient's safety.	Reaction exhibiting prolonged effects requiring intense treatment, poses a threat to the patient's safety, and results in variable recovery.
Examples	Nausea, vomiting, itching/hives, sneezing, sphincter relaxation, extravasation, inadvertent intra-arterial injection, paresthesia of the tongue and lips.	Syncope, urticaria, skin necrosis.	Pulmonary oedema, myocardial infarction, cardiac arrest, tonic-clonic seizures, angioneurotic oedema.

* Based on Yannuzzi et al. (1986)

A more rigorous effort at estimating the incidence of these adverse events was reported by Kwiterovich et al. (1991). The prospective study enrolled 2,025 patients who underwent 2,789 consecutive fluorescein angiograms between mid-1988 and mid-1999. Data collection was standardised over the period of the study, as were all angiographic procedures. Overall, the incidence of adverse events was 4.8 per cent. The most commonly reported reactions were nausea (2.9%), vomiting (1.2%), and itching, flushing or hives (0.5%). Dyspnoea and syncope each occurred in two instances and there was one report of sneezing. No severe reactions were noted.

Kwiterovich et al. (1991) also report that the incidence of adverse events was related to the occurrence of reactions during previous fluorescein angiograms. Patients who had not had angiograms previously had an incidence of 5.1 per cent and those who had not reacted adversely to previous angiograms had 1.8 per cent. However almost 50 per cent of patients who had reacted adversely after previous angiograms did so again. The results are significant given the need for multiple fluorescein angiograms to assess the effectiveness of therapy and to determine if further intervention is needed.

Is it effective?

This report assessed the effectiveness of PDT after critically appraising the combined results of two randomised controlled trials and the systematic reviews (including health technology assessments).

Critical appraisal of randomised controlled trials

Two randomised controlled trials (TAP Study Group 1999, 2001), which compared the efficacy of treating MD patients with PDT/verteporfin or placebo, were identified (Table 10). The combined results of these trials were published in two articles reporting results at one (TAP Study Group 1999) and two years (TAP Study Group 2001). Although preliminary results to three years were provided by the applicant, they were excluded from the critical appraisal as they did not meet inclusion criteria (no comparative group, not available in peer-reviewed literature). The two multicentre trials were conducted in 22 ophthalmology practices with 609 patients over about 11 months. Patients were randomly allocated in a 2:1 ratio: 402 patients received verteporfin and 207 received placebo. The average age of participants was 75 years and 44 per cent were men. Although average age was similar for both treatments, more women than men participated in the trial, particularly in the placebo group of which only 37 per cent were men.

Table 10 Descriptive characteristics of TAP study (TAP Study Group 1999, 2001)*

NHMRC level and study design	Location	Enrolment period	Maximum length of follow-up	Study population		
				N	Male n (%)	Age in years mean
Level II RCT	Multicentre trial in countries of North America and Europe	December 1996 through October 1997	24 months	All: 609 V: 402 P: 207	All: 265 (44) V:188 (47) P:77 (37)	All: 75.3 V: 74.9 P: 76.0

*Abbreviations: RCT = randomised controlled trial, V = verteporfin; P = placebo; CNV = choroidal neovascularisation; MD = macular degeneration; RPE = retinal pigment epithelium

Patient selection criteria for randomised controlled trials

Patients were enrolled in the TAP study if they met eligibility criteria determined by an ophthalmologist certified to enrol and treat study patients. Patients were eligible if they were aged 50 or more, had a best-corrected visual acuity of approximately 20/40 to 20/200, had subfoveal choroidal neovascularisation lesions caused by MD with evidence of classic CNV, and a greatest linear dimension of the entire lesion on the retina measuring not more than 5400 μm. The complete inclusion and exclusion criteria are presented in Table 11. It is important to note that no details were provided on the number of patients screened for eligibility.

Table 11 Patient selection criteria for the TAP study* (TAP Study Group 1999, 2001)

Inclusion	Exclusion
• CNV secondary to MD • CNV under geometric centre of foveal avascular zone; • Evidence of classic CNV on fluorescein angiography; • CNV area ≥50% of total neovascular lesion area; • Greatest linear dimension of lesion ≤5400 μm (not including any area of prior laser photocoagulation); • Best-corrected TAP protocol visual acuity of 73 through 34 letters (Snellen equivalent, approximately 20/40 through 20/200); • age ≥50 years; *and* • willing and able to provide written informed consent	• RPE tear (rip); any significant ocular disease (other than CNV) that has/could compromise vision in study eye; • inability to obtain photographs to document CNV, including difficulty with venous access; • history of treatment of CNV in study eye other than nonfoveal confluent laser photocoagulation; • participation in another ophthalmic clinical trial or use of any other investigational new drugs within 12 weeks prior to start of study; • active hepatitis or clinically significant liver disease; • porphyria or other porphyrin sensitivity; • prior photodynamic therapy for CNV; *or* • intraocular surgery within previous 2 months or capsulotomy within previous month in study eye.

* CNV=choroidal neovascularisation, MD = macular degeneration, RPE = retinal pigment epithelium

Validity of randomised controlled trials

The two trials met the validity criteria and thus the potential for bias in results would be expected to be minimised. The result of the validity assessment is summarised in Table 12.

Table 12 Quality assessment of the TAP study (TAP Study Group 1999, 2001)*

Validity					Outcome measures
Method of randomisation	**Concealment of allocation**	**Inclusion of randomised participants**	**Masking**	**Loss to follow-up**	
Centralised, stratified randomisation in a ratio of 2:1 (V:P).	Adequate	Yes	Double blind (patient and outcome assessor)	At 12 months: 5.9% (V: 5.7%; P: 6.3%) At 24 months: 13.1% (V=12.7%; P=14.0%)	Primary outcome: loss of visual acuity measured as loss of fewer than 15 letters or <3 lines Secondary outcomes: loss of visual acuity (loss of fewer than 30 letters or <6 lines); mean changes in visual acuity from baseline, mean change in visual acuity, mean change in contrast threshold, angiographic outcomes (progression of CNV, size of lesion)

* V= verteporfin; P = placebo; CNV = choroidal neovascularisation

Randomisation and allocation concealment

The procedure for randomisation and allocation concealment was considered adequate since this was conducted from a central independent location. Each patient had only one eye randomised; if both eyes were eligible the patient together with ophthalmologist decided which eye would be in the study. Randomisation was stratified by clinical centre and by baseline visual acuity (two levels) using separate groups of colour-coded sealed envelopes.

The randomisation process resulted in similar patient groups for most vision performance and disease-related characteristics (visual acuity and lesion measurements). However more women than men, more patients with a history of smoking and more patients with lesions with blood were allocated to the placebo group. The possible confounding effects of the imbalances taken together were not adjusted for in the analyses although subgroup analyses were conducted and interaction between/among baseline variables was measured using *p* values.

Masking

Attempts were made to maintain masking of the patient, ophthalmologist, and outcome assessors - vision examiner and reading centre personnel. Since verteporfin and placebo differed in colour, the tubing delivering the solutions was covered to mask patients and the treating ophthalmologist during infusion. No information that could identify group status was provided to assessors who graded patients' vision and reading materials. Importantly, masking success was assessed and six cases of unmasking were known to have occurred: two patients and four ophthalmologists in separate situations. No known cases of unmasking of vision examiners or reading graders were observed.

Follow-up and intention-to-treat

Complete follow-up was achieved on a high proportion of patients. Ninety four per cent of patients were followed to 12 months and 87 per cent to 24 months. Intention-to-treat analysis was conducted with missing values imputed using the method of last observation carried forward. No sensitivity analyses were conducted to determine the effect of this method or alternate methods for imputing missing values. However, the relatively high follow-up rate should diminish the impact of the missing values on the accuracy of results.

Sample size and power

Six hundred and nine patients were enrolled in the trial in a ratio of 2:1 with 402 being allocated to verteporfin and 207 to placebo. Based on the primary outcome measure, that is loss of 15 letters or three lines from baseline, this sample size had 80 per cent power to detect an effect size of 20 per cent between verteporfin and placebo, given that 50 per cent of patients receiving placebo would lose fewer than 15 letters or three lines at one year, with a two-sided significance level of five per cent.

A standardised protocol was established for administering study treatments (Table 13). Repeated treatments were allowed for in the protocol with retreatments administered if CNV leakage was detected at the follow-up visit. No details were reported on the extent of deviations from the standardised study protocol.

Table 13 Protocol for administering study treatments (TAP Study Group 1999, 2001)

Intervention	Comparison
Verteporfin: 6mg/m^2 body surface area infused intravenously over 10 minutes. Irradiation with diode laser at 689nm with slitlamp delivery system designed to deliver light dose of 50J/cm^2 at an intensity of 600MW/cm^2 was applied through a fundus contact lens for 83 seconds using a spot size with a diameter of 1000μm larger than the greatest linear dimension of the CNV lesion.	Placebo: 30mL of 5% dextrose in water with identical infusion and irradiation as for verteporfin

Results of randomised controlled trials

Patients in the TAP trials (TAP Study Group 1999, 2001) were given an average of 5.6 (standard deviation 2.2, range 1–8) verteporfin treatments over 24 months of the trial. Over the two years of the trial, approximately 70 per cent of patients in the verteporfin group needed five or more treatments and almost one third needed eight treatments. Only five per cent of patients received one verteporfin treatment.

The evaluation of results from the study was limited to the effects on visual outcomes, as these would be more important to patients than fluorescein angiographic outcomes.

Verteporfin was found to be more effective than placebo in reducing the loss of visual acuity in patients with MD. At three months follow-up, 81.8 per cent in the verteporfin group compared with 71.0 per cent in the placebo group had lost fewer than 15 letters or fewer than three lines, a difference of 10.8 per cent. At 12 months follow-up, 61.2 per cent of patients given verteporfin had experienced a loss of visual acuity of fewer than 15 letters compared with 46.4 per cent of patients given placebo (ARR = 14.8%, 95% CI = 6.5–23.5%). Significantly more patients in the verteporfin group experienced no change or an increase in visual acuity (verteporfin versus placebo: 38.1% versus 23.7%, ARR = 14.4%, 95 % CI = 6.9–21.9%). The number of patients who would need to be treated with verteporfin to have one with this outcome is seven (95% = 4–15). At 24 months similar results were observed (see Table 14).

Table 14 Eyes with a loss of fewer than 15 letters after 3, 12 and 24 months: verteporfin compared with placebo - all patients (TAP Study Group 1999, 2001)

Follow-up period	Verteporfin Frequency (%)	Placebo Frequency (%)	ARR % (95% CI)	NNT (95% CI)
3 months	329 (81.8)	147 (71.0)	10.8% (3.6–18.1%)	9 (6–28)
12 months	246 (61.2)	96 (46.4)	14.8% (6.5–23.1%)	7 (4–15)
24 months	213 (53.0)	78 (37.7)	15.3% (7.1–23.5%)	7 (4–14)

Table 14 also illustrates that visual acuity declined in both groups over the years of the trial but declined faster in the placebo group, however the incremental benefits of verteporfin were maintained.

Other measures of visual outcome and the proportion of randomised patients available for follow-up at 3, 12 and 24 months are presented in Table 15. When different visual acuity cut-offs (<30 letters lost or six lines; no change or improvement in number of letters) were analysed, the benefits of verteporfin over placebo were not as great as that observed for <15 letters. A greater proportion of patients given verteporfin than those given placebo lost fewer than 30 letters, nine per cent more at 12 months and 12 per cent more by 24 months. In addition 14 per cent more verteporfin than placebo patients experienced no change or an improvement in vision at 12 months, although by 24 months this advantage was reduced by half to seven per cent. At 12 and 24 months patients administered verteporfin were less likely to have a visual acuity worse than 20/200 (33 letters or fewer). At 12 months the risk was 27 per cent of the risk in the placebo group (RR = 0.73; 95% CI = 0.60–0.89). The reduced risk was maintained through 24 months (RR = 0.75; 95% CI = 0.63–0.89).

Table 15 Loss of visual acuity from baseline after 3, 12 and 24 months of follow-up: verteporfin compared with placebo (TAP Study Group 1999, 2001)

Outcome	At 3 months	At 12 months	At 24 months
Patient follow-up rate			
Verteporfin, n = 402	99.0%	94.3%	86.3%
Placebo, n = 207	98.1%	93.7%	85.5%
Loss of <30 letters (<6 lines)			
Verteporfin	95.5%	85.3%	81.8%
Placebo	88.9%	76.3%	70.0%
Difference, 95% CI	6.6%, 1.9 to 11.4%	9.0%, 2.2 to 15.7%	11.8%, 4.5 to 19.1%
Loss of no letters lost or increase in letters			
Verteporfin	50.5%	38.1%	30.1%
Placebo	44.4%	23.7%	22.7%
Difference, 95% CI	6.1%, -2.3 to 14.4%	14.4%, 6.9 to 21.9%	7.4%, 0.1 to 14.7%
Percentage of patients with visual acuity <20/200			
Verteporfin	20.9%	34.8%	41.0%
Placebo	29.5%	47.8%	55.1%
Difference, 95% CI	-8.6%, -15.9 to -1.1%	-13.0, -21.2 to -4.8%	-14.0, -22.3 to -5.7%

Subgroup analyses

Subgroup analyses of patients' baseline characteristics were conducted to identify the subgroups of patients given verteporfin or placebo who were more likely to either benefit or experience no improvement, in visual acuity. Patients' baseline characteristics analysed were: lesion area composed of classic CNV (≥50%, <50% but greater than zero, no classic lesions), evidence of occult CNV (evidence, no evidence), initial letters read score (73–54, 53–44), lesion included blood (yes, no), age (<75, ≥75), smoking history (never, past, current) and gender. Treatment outcome for the subanalyses was the loss of <15 letters from baseline (Table 16).

The benefits of verteporfin therapy in reducing the rate of visual acuity loss, measured as a loss of fewer than 15 letters, were most obvious in patients whose classic CNV was at least 50 per cent of the area of the lesion and showed no evidence of occult CNV. At 12 months follow-up patients receiving verteporfin were 1.7 times more likely than the placebo-treated patients to have experienced a visual acuity loss of fewer than 15 letters (RR = 1.7, 95% CI = 1.3–2.3) and at 24 months were almost twice as likely to have lost fewer than 15 letters (RR = 1.9, 95% CI = 1.4–2.7).

Patients were considered to have erratic benefits (because of the wide 95% confidence intervals for NNT and/or inconsistent results between 12 and 24 months follow-up) if the baseline letters read score was 73–54 (Snellen 20/40–20/80), if the lesion included blood, their age was 75 or older or if they had smoked in the past. Gender was not a factor as men and women were observed to benefit equally from verteporfin compared with placebo treatment.

Patients who did not receive any increased benefit at 12 or 24 months follow-up from verteporfin compared with placebo had lesions in which the area of classic CNV was less than 50 per cent, had evidence of occult membranes or were current smokers.

Table 16 Summary of measures of effectiveness of PDT with verteporfin compared with placebo based on loss of <15 letters after 12 and 24 months of follow-up according to patients' baseline characteristics: absolute risk reduction, relative risk and number needed to treat, (TAP Study Group 1999, 2001)

Characteristic at baseline	ARR, % (95% CI), %		RR (95% CI)		NNT (95% CI)	
	12 months	24 months	12 months	24 months	12 months	24 months
Area of classic CNV						
≥50%	28.0 (15.3–40.7)	27.8 (15.2–40.4)	1.7 (1.3–2.3)	1.9 (1.4–2.7)	4 (2–7)	4 (2–7)
0–<50%	0.6 (-11.2–12.4)	3.3 (-8.5–15.1)	1.0 (0.8–1.3)	1.1 (0.8–1.4)	n/a†	n/a
0	6.2 (0.6–57.0)	26.1 (0.9–51.3)	2.0 (1.1–4.2)	1.9 (1.0–4)	3 (2–16)	4 (2–109)
Evidence of occult CNV						
Yes	4.8 (-4.8–14.4)	7.1 (-2.4–16.6)	1.1 (0.9–1.3)	1.2 (0.9–1.5)	n/a†	n/a
No	46.0 (30.5–61.5)	41.3 (25.6–57.0)	2.5 (1.7–4.0)	2.4 (1.6–4.0)	2 (2–3)	2 (2–4)
Initial number of letters read						
73-54	12.1 (0.3–23.9)	9.2 (-2.3–20.7)	1.2 (1.0–1.4)	1.1 (1.0–1.3)	8 (4–360)	n/a
53-34	17.8 (6.3–29.4)	21.7 (10.2–33.3)	1.2 (1.1–1.6)	1.4 (1.2–1.6)	6 (3–16)	5 (3–10)
Lesion included blood*						
Yes	21.4 (8.2–34.6)	18.9 (5.8–32.0)	1.5 (1.2–2.0)	1.5 (1.1–2.1)	5 (3–12)	5 (3–17)
No	10.6 (-0.1–21.3)	12.8 (2.1–23.4)	1.2 (1.0–1.5)	1.3 (1.0–1.7)	n/a	8 (4–47)
Age						
<75	22.0 (9.6–34.4)	17.9 (5.5–30.3)	1.5 (1.2–1.9)	1.4 (1.1–1.9)	5 (3–10)	6 (3–18)
≥75	8.1 (-3.1–19.3)	12.1 (1.2–23.0)	1.2 (0.9–1.5)	1.3 (1.0–1.8)	n/a	8 (4–82)
Gender*						
Men	19.5 (6.5–32.5)	16.8 (4.0–29.5)	1.5 (1.1–2.1)	1.5 (1.1–2.1)	5 (3–15)	6 (3–25)
Women	12.8(2.1–23.5)	15.1 (4.4–25.9)	1.3 (1.0–1.5)	1.4 (1.1.–1.8)	8 (4–49)	7 (4–23)
Smoking*						
Never	13.3 (0.1–26.5)	21.5 (8.5–34.4)	1.3 (1.0–1.7)	1.6 (1.2–2.3)	8 (4–796)	5 (3–12)
Past	18.0 (6.0–30.0)	11.4 (-0.6–23.4)	1.4 (1.1–1.9)	1.3 (1.0–1.7)	6 (3–17)	n/a
Current	8.0 (-15.5–31.5)	11.6 (-11.7–34.9)	1.1 (0.8–1.8)	1.3 (0.8–2.3)	n/a	n/a

* Differed significantly at baseline between patients given verteporfin compared with placebo

Half of the patients in the study (306 patients) had lesions in which classic CNV was below 50 per cent but above zero. Verteporfin was not found to be better than placebo in reducing the rate of visual acuity loss in this group. A further 59 patients with no classic CNV were enrolled in the study despite their not meeting the inclusion requirement for evidence of classic CNV. The lack of precision in results (because of the small sample size), together with their inconsistent inclusion in the study leads to the conclusion that benefits of verteporfin over placebo remain to be confirmed in a larger study that would consistently include this group.

The majority of patients (462 patients) showed evidence of occult CNV and verteporfin was not more effective than placebo in this group. The degree of overlap in patients with these two factors (area of classic and evidence of occult) was not reported.

These analyses indicated that the estimates of beneficial outcome are based on the active treatment of 159 eyes.

Discussion of results of randomised controlled trials

The TAP study (TAP Study Group 1999, 2001), composed of two combined randomised controlled trials, was the only study identified that compared verteporfin with placebo in PDT for patients with neovascular MD and since it met the validity criteria, the potential for bias in results is reduced.

The TAP study found that after an average of 5.6 verteporfin treatments administered according to a standardised protocol (see Table 13) over 24 months, PDT with verteporfin was more effective than placebo in reducing the loss of visual acuity in MD patients whose CNV was composed of at least 50 per cent classic or who showed no evidence of occult CNV. To obtain the incremental benefit, a 28 per cent reduction in the loss of fewer than 15 letters after 24 months of treatment and follow-up, the NNT was 4 (95% CI = 2–7) in patients with at least 50 per cent classic CNV and 2 (95% CI = 2–4) in patients with no evidence of occult CNV.

The TAP study also showed that verteporfin therapy was no more effective than placebo in preventing vision loss in patients with CNV lesions that were <50 per cent classic, in patients with evidence of occult CNV and in patients who were current smokers.

In this trial of 609 patients, only a minority had visual characteristics that were likely to benefit from treatment with verteporfin: 242 had lesion areas that were ≥50 per cent classic and 143 showed no evidence of occult CNV, based on data at 24 months.

Outcomes of patients were assessed for 24 months so effectiveness over longer periods is unknown.

Other issues arising from the evaluation of trial evidence include:

- failure to state the number of patients presenting for the trial and the percentage selected;
- dependence of the findings of beneficial outcomes on the results of active treatment in a subgroup of 159 eyes; and
- the lack of patient-oriented outcomes such as quality of life.

Critical appraisal of systematic reviews

Six systematic reviews were identified (Appendix C). One was a Cochrane systematic review (Wormald et al. 2000) and the remaining five were health technology assessments (Norwegian Centre for Health Technology Assessment 2000, National Horizon Scanning Centre 2000, Fong 2000, Alberta Heritage Foundation for Medical Research 2000, Tunis et al. 2000).

Validity of systematic reviews

Assessment of validity of each review against the modified QUOROM group (Moher et al. 1999) checklist is summarised in Table 17.

Table 17 Quality of reporting of published systematic reviews*

Heading	Descriptor	NHSC 2000	AHFMR 2000	HCFA 2000	SMM 2000	AAO 2000	Cochrane 2001
Title	Identify the report as a systematic review	×	×	×	×	×	×
Abstract	Use of a structured format	No Abstract	No Abstract	No Abstract	×	✓	✓
					×		✓
					×		✓
					×		✓
					×		×
					×		✓
					×		✓
					×		✓
					×		×
					✓		✓
					×		✓
					✓		✓
	Explicit description of clinical question					✓	
	Description of databases and other information sources					×	
	Description of selection criteria					✓	
	Description of methods for validity assessment					✓	
	Description of methods for data abstraction					×	
	Description of study characteristics					✓	
	Description of quantitative data synthesis					✓	
	Description of characteristics of included and excluded studies					×	
	Description of quantitative findings					✓	
	Description of qualitative findings					✓	
	Description of results of subgroup analysis					✓	
Introduction	Explicit description of clinical problem	✓	✓	✓	✓	✓	✓
	Explicit description of biological rationale for intervention	✓	✓	✓	✓	✓	✓
	Explicit description of rationale for review	×	✓	✓	×	✓	✓
Methods	Detailed description of information sources	×	✓	✓	×	✓	✓
	Detailed description of restrictions on searching	×	×	✓	×	✓	✓
	Description of inclusion and exclusion criteria	×	×	✓	×	✓	✓
	Description of criteria and process used for validity assessment	×	×	×	×	×	✓
	Description of processes used for data abstraction	×	×	×	×	✓	✓
	Description of study characteristics included	✓	✓	✓	✓	✓	✓
	Description of methods of assessment of clinical heterogeneity	×	×	×	×	×	×
	Description of principal measures of effect	✓	✓	✓	✓	✓	✓
	Description of methods of combining results	N/A	N/A	N/A	N/A	N/A	N/A
	Description of methods used to handle missing data	×	×	×	×	×	×
	Description of methods of assessment of statistical heterogeneity	N/A	N/A	N/A	N/A	N/A	N/A
	Description of rationale for *a priori* sensitivity testing and subgroup analysis	×	×	×	×	×	×
	Description of methods to assess publication bias	×	×	×	×	×	×
Results	Description of profile of trial flow	×	×	×	×	×	×
	Presentation of descriptive data for each trial	✓	×	✓	×	✓	✓
	Report of agreement on the selection of studies	×	×	×	×	×	×
	Report of agreement on validity assessment	×	×	×	×	×	×
	Presentation of simple summary results	✓	✓	✓	✓	✓	✓
	Presentation of data needed to calculate effect sizes and confidence intervals	✓	×	✓	×	✓	✓
Discussion	Summarisation of key findings	✓	✓	✓	✓	✓	✓
	Discussion of clinical inferences based on internal and external validity	✓	✓	✓	✓	✓	✓
	Interpretation of the results in the light of the totality of available evidence	✓	✓	✓	✓	✓	✓
	Description of potential biases in the review process	×	×	×	×	×	×
	Suggestions for future research agenda	×	×	✓	×	✓	✓

* NHSC — National Horizon Scanning Centre 2000; AHFMR — Alberta Heritage Foundation for Medical Research 2000; HCFA — Health Care Financing Administration — Tunis et al. 2000; SMM — Norwegian Centre for Health Technology Assessment 2000; AAO — American Academy of Ophthalmology — Fong 2000; Cochrane — Wormald et al. 2001

Overall, the reviews rated poorly against the QUOROM checklist (Table 15). The Cochrane systematic review (Wormald et al. 2000) met the most criteria in the QUOROM checklist followed by the American Academy of Ophthalmology review (Fong 2000). Three reviews (National Horizon Scanning Centre 2000, Alberta Heritage Foundation for Medical Research 2000, Tunis et al. 2000) did not include an abstract and this contributed to their relative poor ratings against the QUOROM checklist. As a one dimensional instrument, QUOROM has some limitations as an assessment tool and in some cases may mislead. For example, the Cochrane systematic review (Wormald et al. 2000) does not identify itself as a systematic review in the title although, by virtue of the fact that it is a Cochrane review, is systematic and this is not reflected in the QUOROM checklist.

As the QUOROM checklist is a nominal scale simply reflecting the reporting of systematic reviews, an assessment of the reviews against qualitative criteria (Chalmers & Altman 1995, Greenhalgh 1997, Sackett et al. 2000) was also used to add another dimension to the assessment of the validity of systematic reviews. The Cochrane systematic review (Wormald et al. 2000) was the only one to thoroughly fulfil all the criteria. Although the remaining reviews varied in their validity, all reported on the TAP study group randomised controlled trials. A synopsis of the assessment of the reviews against relevant qualitative criteria follows.

Focused question

The Cochrane review (Wormald et al. 2000) provided a focused review, giving an explicit statement of the patient group (neovascular MD), intervention (PDT) and outcomes (prevention of visual loss, new vessel growth, quality of life, adverse events) that were the focus of the review. The National Horizon Scanning Centre (2000) and the Health Care Financing Administration (Tunis et al. 2000) reviews provided statements of the patient group and intervention that were the focus of the review. The National Horizon Scanning Centre (2000) specifically limited their review to patients with classic or partially classic choroidal neovascularisation in MD, and the intervention was PDT with verteporfin or tin ethyl etiopurpurin ($SnET_2$). Tunis et al. (2000) focused their review on the treatment of patients with neovascular MD using PDT with verteporfin. Fong (2000) and the Alberta Heritage Foundation for Medical Research (2000) also explicitly stated their questions of interest while the Norwegian Centre for Health Technology Assessment (2000) did not specify a question.

Inclusion and exclusion criteria

This criterion addresses whether the review provided explicit *a priori* details of the studies that were to be included in and excluded from the review. The Cochrane review (Wormald et al. 2000) was the only one that fulfilled this criterion, stating that only randomised controlled trials examining the effectiveness of PDT in patients with neovascular MD would be included in the review. Any other study designs, patient groups or interventions were to be excluded.

Explicit comprehensive search strategy

This criterion addresses whether the review incorporated a search strategy comprehensive enough that it was unlikely to have missed studies. The Cochrane review provided the most thorough and explicit search strategy of all the reviews. The authors searched several databases without any language restrictions as well as a specialised register of the Cochrane Collaboration ensuring substantial effort was made to retrieve unpublished, 'grey' literature. Thus it is likely that publication bias was minimised as much as possible in this review. Fong (2000), Alberta Heritage Foundation for Medical Research (2000) and Tunis et al. (2000) described limited search strategies. Fong (2000) searched Medline from 1999 to 2000, but also attempted to uncover unpublished literature by contacting ophthalmology organisations and industry. Contracts were not explicitly stated. Tunis et al. (2000) also searched Medline/Pubmed and contacted unspecified 'experts' while the Alberta Heritage Foundation for Medical Research (2000) contacted the United States Food and Drug Administration to attempt to uncover other literature.

A search strategy was not described in the reviews by the Norwegian Centre for Health Technology Assessment (2000), and the National Horizon Scanning Centre (2000).

Assessed validity of included trials

The Cochrane review (Wormald et al. 2000) and the Health Care Financing Administration review (Tunis et al. 2000) thoroughly and explicitly assessed the validity of their included trials. The American Academy of Ophthalmology review (Fong 2000) and the Alberta Heritage Foundation for Medical Research (2000) stated that included trials were of high quality but did not explicitly describe how they assessed them. The remaining reviews did not state if they assessed the validity of included trials.

Results of systematic reviews

The systematic reviews all reported results from the TAP studies. The National Horizon Scanning Centre (2000) and Cochrane (Wormald et al. 2000) reviews were completed before the publication of the two year TAP trial outcomes (TAP Study Group 2001) and thus they reported only the one year outcomes from the TAP study. The reviews from the American Academy of Ophthalmology (Fong 2000) and the Health Care Financing Administration (Tunis et al. 2000) were published after both the TAP 1 and TAP 2 reports and included a summary of both the first year and second year outcomes. The reviews from the Alberta Heritage Foundation for Medical Research (2000) and the Norwegian Centre for Health Technology Assessment (2000) reported first year results from the TAP study and preliminary results of the second year outcomes that were available in abstract form. Results of the TAP trials have already been discussed in detail and will not be repeated here.

Discussion of systematic reviews

The systematic review and health technology assessments conclude from the TAP trials that PDT with verteporfin is effective in retarding the loss of visual acuity in patients with predominantly classic subfoveal CNV secondary to macular degeneration. Some important issues discussed in the systematic review and health technology assessments include the following:

- There is no long-term evidence (beyond two years) of the effectiveness and cost-effectiveness of PDT with verteporfin.
- The effect of treatment on patient-oriented outcomes such as quality of life have not been reported in peer-reviewed literature.
- Repeat treatments are required. However, the number and frequency of repeat treatments beyond two years is unknown and the safety implications are also unclear.
- Diagnosis of subfoveal classic type CNV lesions is reliant on fluorescein angiography. Even trained readers find it difficult to interpret the results of this procedure, particularly in lesions that are approximately 50 per cent classic. This may lead to the use of PDT with verteporfin for patients unlikely to benefit.
- The number of patients who presented for treatment in the TAP study was not stated. Thus the proportion of patients who were deemed eligible for treatment after fluorescein angiography is not clear. Verbal estimates of 5–7 per cent from one TAP member and 25 per cent from another have been reported (Wormald et al. 2000).

Selection of patients for therapy

A key issue identified in the systematic reviews was identifying eligible patients for this treatment. The Alberta Heritage Foundation for Medical Research (2000) has proposed the following criteria for patients to be treated with photodynamic therapy with verteporfin:

- The patient must have classic CNV secondary to macular degeneration (documented on fluorescein angiogram).
- The area of classic CNV must cover at least 50 per cent of the total area of the CNV.
- The CNV must extend below the geometric centre of the foveal avascular zone.
- The greatest linear dimension of the lesion must be less than or equal to 5400 μm, not including any area of previous laser photocoagulation treatment.
- The patient must have best-corrected visual acuity equal to or better than 20/200, but no better than 20/40 Snellen acuity.
- The patient must be 50 years or older.

This group also stated that for the most effective use of this treatment, the MD type (wet versus dry, classic versus occult) must be correctly identified (per fluorescein angiography) and documented by specially trained physicians before treatment.

Under its Medicare program, The United States Health Care Financing Administration (HCFA, Tunis et al. 2000) has determined that it will fund verteporfin therapy for patients:

- with predominantly classic subfoveal CNV lesions where the area of classic CNV occupies $\geq$ 50 per cent of the area of the entire lesion as determined by fluorescein angiogram.

It will not cover patients:

- with minimally classic CNV lesions (where the area of classic CNV is <50 per cent of the area of the entire lesion);
- with juxtafoveal or extrafoveal CNV lesions (lesions outside the fovea);
- who are unable to obtain a fluorescein angiogram; or
- with atrophic MD.

HCFA (Tunis et al. 2000) also noted the importance of the therapy being given by trained physicians and of recognising that fluorescein angiography is not entirely objective. It proposed a medical review of those administering PDT with verteporfin to ensure treatment was being applied to the appropriate sub-population.

What are the economic considerations?

The submission from the sponsor presented a cost-effectiveness analysis comparing the proposed therapy with placebo only. Results are presented as cost per vision-year gained. The incremental cost per vision year gained from PDT with verteporfin was calculated to be $35,456 (incremental cost $14,038.93, incremental benefit 0.396).

A modelled evaluation was also presented. This showed changes in resource use of individuals after progressive loss of vision with community nursing, meals on wheels, home help, permanent nursing home residency, and probability and costs of accidental falls. These items are in addition to those included in the trial-based evaluation. The model structure seems plausible and the calculations appear to be correct.

The following four scenarios were modelled (Table 18).

1. 24 month outcomes with costs including those for PDT with verteporfin, community care, permanent nursing home residency and accidental falls.

2. 60 month extrapolation of outcomes using exponential growth function for PDT with verteporfin patients and no additional deterioration for placebo; same costs as scenario one, but extended to 60 months.

3. 60 month extrapolation of outcomes using exponential growth function for both groups; same costs as scenario one, but extended to 60 months.

4. 60 month extrapolation of outcomes using exponential growth function for placebo group, rate of decline applied to PDT with verteporfin patients; same costs as scenario one, but extended to 60 months.

Sensitivity analysis was also applied to the modelled evaluation, with cost, outcome and time parameters being varied (Table 18).

Table 18 Cost-effectiveness of PDT with verteporfin

Scenario	Cost- effectiveness as incremental cost per vision year gained	Costs estimated by sensitivity analysis
1	$30,161	$26,850–$35,453
2	$16,356	$13,529–$20,935
3	$9,158	$6,120–$17,880
4	$13,799	$11,823–$18,491

Comparative costs

In the initial trial-based evaluation the costs included are those for therapy, concomitant medications relevant to ophthalmic treatment, and visits to the ophthalmologist and any laboratory tests, over two years. Modelled costs also included community nursing, meals on wheels, home help, probability of permanent nursing home residency and costs of accidental falls.

Key areas of economic uncertainty

Four main areas of uncertainty are listed below.

- The interpretation of the differences in trial outcome measures for verteporfin and placebo as vision years gained is not well justified, and may overstate the gain from treatment to the advantage of verteporfin. The trial-based evidence only extends to 24 months and there is considerable uncertainty as to the long-term course of the disease after treatment. There is no basis to assume that a differential effect will be maintained at five years.

- Patients require angiograms with associated costs and potential risks. This was not included in the submission. For example, if there are on average 10 angiograms (see Table 19 for unit costs) with a range of 5–15 (representing a cost range of $712.10 – $2003.10), the incremental cost per extra year with vision would change to $38,877.85 (range $37,247.73–$40,510.17), based on angiography of one eye.

- While the trial evidence suggests that there is a group of patients who are likely to benefit from treatment, at least in the short term, it may be difficult to identify this population in practice. The treatment may be offered to patients for whom there is no evidence of a clinical advantage. If the numbers of patients actually treated is greater than those selected in the trial, costs will be higher.

- There may be constraints on the availability of trained staff in the short term if the service were to be introduced. An increase in screening and angiograms would use up ophthalmologists' time, with the potential implication that the true opportunity cost of their time may be understated in the cost-effectiveness calculations above.

Table 19 Costs associated with fluorescein angiography

Procedure	Cost
Angiogram	
One eye	$95.70 (MBS item 11215)
Two eyes	$118.25 (MBS item 11218)
Consultation	
Initial	$66.60 (MBS item 104)
Subsequent	$33.40 (MBS item 105)

Source: Medicare Benefits Schedule, 1 November 2000, Commonwealth Department of Health and Aged Care.

Cost per patient per two years

The cost of treating one patient was estimated by the applicant to be $16,250.09 for verteporfin and $2,211.16 for placebo. It is unclear whether the costs of additional fluorescein angiograms in patients being treated have been included.

Likely number of patients per year

The applicant estimated a prevalence of MD of 91,788 in Australia and an associated prevalence of predominantly classic CNV of 12,116. The applicant suggested the annual incidence of MD, is likely to be10 per cent of the prevalence. This is presumably because of the age group and life expectancy of its members although no details of how this was estimated were provided.

This suggests that in the first few years after the introduction of PDT with verteporfin, up to 12,116 patients might be treated in addition to new cases that might develop. However the sponsors claim that more than 80 per cent of prevalent cases are not treatable because they have had lesions for more than two years. If this is accepted, the upper limit on the number of cases eligible for treatment in the first year is 2,424. If all prevalent cases were treated in the first year, only new cases would be treated in subsequent years.

If the incidence of MD is 10 per cent of the prevalence, as suggested by the applicants, then there may be up to 1,212 new cases per year eligible for treatment with PDT with verteporfin. It is more likely that not all eligible cases would be treated in the first year and we might expect that the introduction of PDT with verteporfin would lead to treatment of existing CNV over a few years. It is also possible that treatment extends beyond the trial-eligible population in the first and subsequent years.

Total financial cost

The applicant suggests a range of 1212–3635 patients treated in the first year, and 840 patients per annum subsequently. At a cost of $16,250.09 per patient for two years this suggests a range of costs of up to $10–30 million in the first year, $16–36 million in the second year and $13.6 million per annum in subsequent years, once only new cases are being treated. The Australian community surveys discussed in the current review (Mitchell et al. 1995, VanNewkirk et al. 2000) suggests a wide range for the estimate of the prevalence of eligible cases. Mitchell et al. (1995) suggests an upper range prevalence of 19,846 for exudative MD with classic features, rather than the 12,116 for 'predominantly classic CNV' suggested as a best estimate of the eligible population by the applicant. Using the former figure would increase the first year costs to up to $48.3 million and second year costs to $59.7 million. Subsequent annual costs will depend on the diagnosis rate and the uptake of treatment. It is possible that the rate of diagnosis and treatment among the eligible population will be higher than the 70 per cent assumed by the applicant, and that treatment might extend outside that population in subsequent years. If all 1,985 new patients were diagnosed and treated each year the continuing cost would be up to $32.2 million per year.

These estimates are based on accurate selection of eligible patients, but in reality the difficulty of diagnosing patients with predominantly classic lesions suggests that these may underestimate the total cost to the community of offering PDT with verteporfin.

Summary

The evidence presented in the economic evaluation sections of the submission lead to the following conclusions:

- Verteporfin may lead to a gain in vision years by retarding the rate of visual loss compared with placebo, however there is some uncertainty surrounding the trial evidence.

- Verteporfin costs substantially more than placebo. While the modelling in the submission suggests a cost per year of vision gained of between $6,120 and $35,456 this is based on an assumed clinical advantage and considerable cost offset that may not be reasonable. In addition the notion of a 'year of vision gained' does not clearly relate to the trial evidence. Since we have no data on patient preferences for the trial outcomes it is difficult to establish if the intervention is cost-effective.

- There is some concern that the group included in the trial may not represent the whole patient group that would receive treatment in clinical practice. No details of the numbers screened in the trial are available. If the actual patient population treated is wider than those selected for the trial, the cost per extra year of vision gained could be considerably higher than the estimates provided in the submission.

- The total financial cost of treatment is likely to exceed $10 million per annum. Depending on the true incidence of exudative MD with classic features in the Australian population it may be greater than $30 million per annum, especially if the patient population treated is wider than that selected for the trial.

Conclusions

Safety

Safety of verteporfin in PDT for patients with MD was assessed in the TAP study (TAP Study Group 1999, 2001). Adverse events assessed by the treating ophthalmologist as being directly related to treatment were 40 per cent more likely in patients administered verteporfin than placebo: 192 patients (47.8%) in the verteporfin group compared with 70 (33.8%) in the placebo group (RR = 1.4, 95% CI = 1.1–1.8). The number of adverse events from treatment is relatively high and precise since seven patients need to be treated with verteporfin before one patient suffers an adverse event (95% CI = 5–17). This computation of NNH is an underestimate since actual patients would not be suffering adverse events from placebo treatments with saline injections and PDT. Thus the actual NNH from verteporfin therapy versus no treatment (not placebo) would be 2 (95% CI = 2–3).

One hundred and eighty five clinically relevant adverse events occurred in the group treated with verteporfin. These included visual disturbance (22.1%), injection site events (15.9%), infusion-related back pain (2.5%), allergic reactions (2.0%) and photosensitivity reactions (3.5%). The difference in risk of any adverse event between treatment with verteporfin and placebo is 23.3 per cent (95% CI = 15.8–30.8%).

Effectiveness

Evidence of clinical effectiveness came from the TAP study (TAP study Group 1999, 2001), composed of two combined randomised controlled trials, the only study identified that compared verteporfin with placebo in PDT for patients with neovascular MD. This study met the criteria for validity and would be expected to have reduced potential for bias in its results. However, the study was limited by the lack of data on the number of patients screened for eligibility. Estimates of beneficial outcomes were based on treatment of 143 eyes only and effects on patients' quality of life were not assessed.

After two years, 53 per cent of all patients in the verteporfin group had a visual loss of fewer than 15 letters as against 38 per cent of placebo-treated patients. In patients with predominantly classic (≥ 50%) CNV, PDT with verteporfin was more effective than placebo in reducing the loss of fewer than 15 letters. For patients with at least 50 per cent of the lesion of classic type, the visual acuity loss of fewer than 15 letters was twice that of placebo-treated patients at two years. An average of 5.6 (range 1–8) verteporfin treatments were administered over 24 months to achieve this reduction in visual acuity loss. The NNT was four (95% CI = 2–7) in patients with at least 50 per cent classic CNV and 2 (95% CI = 2–4) in patients with no evidence of occult CNV.

The TAP study also showed that verteporfin therapy was not more effective than placebo in patients with CNV lesions that were <50 per cent classic, in patients with evidence of occult CNV and in patients who were current

In this trial of 609 patients, a minority had visual characteristics that were likely to benefit from treatment with verteporfin: 242 had lesion areas that were ≥50 per cent classic and 143 patients showed no evidence of occult CNV.

Six systematic reviews also reported results from the TAP study. Essentially the reviews concluded that PDT with verteporfin is effective in reducing the loss of visual acuity in patients with predominantly classic subfoveal CNV secondary to MD.

The key issues identified from the evaluation of the randomised controlled trial and the reviews included:

- the conclusion from the randomised controlled trial that verteporfin is effective was based on outcomes for a subgroup of the total study population;
- the difficulty in diagnosing patients with predominantly classic lesions;
- the effect of treatment on patients' quality of life have not been reported;
- the lack of evidence of effectiveness beyond two years – it is known that repeat treatments are required but the number and frequency beyond two years is unknown; and
- the fact that the number of patients initially screened was not reported and hence the proportion of patients eligible for treatment is not known.

Cost-effectiveness

While Verteporfin may lead to a gain in vision years compared with placebo, however there is some uncertainty surrounding the trial evidence.

Verteporfin appears to cost substantially more than placebo. While the modelling in the submission suggests a cost per year of vision gained of between $6,120 and $35,456 this is based on an assumed clinical advantage and considerable cost offset that may not be reasonable. In addition the notion of a 'year of vision gained' does not clearly relate to the trial evidence. The absence of data on patient preferences for the trial outcomes also makes it difficult to establish if the intervention is cost-effective.

If PDT with Verteporfin were to be offered in Australia it is estimated that costs could range from $10-30 million in the first year, $16-36 million in the second year and $13.6 million per annum in subsequent years, once only new cases were being treated. These estimates are based on accurate selection of eligible patients, but in reality the difficulty of diagnosing patients with predominantly classic lesions may increase costs.

There is some concern that the group included in the trial did not represent all of the patients who would receive treatment in clinical practice. No details of the numbers screened in the trial were available. If the actual patient population treated is wider than that selected for the trial the cost per extra year of vision gained could be considerably higher than the estimates provided in the submission.

Recommendations

The MSAC has reviewed the evidence relating to photodynamic therapy with Verteporfin for macular degeneration (MD) in terms of clinical need, safety, effectiveness and cost-effectiveness. The MSAC recommends that public funding for this therapy should only be supported for patients with predominantly classic (>50% classic) subfoveal choroidal neovascularisation secondary to MD, a small minority of MD cases. For this sub-group of MD patients, there is some evidence that the therapy may retard the rate of visual loss in the short term.

As there is insufficient evidence of the effectiveness or cost-effectiveness of photodynamic therapy to support funding for this treatment outside the indications outlined above, the Committee also recommends that public funding should only be supported where arrangements are in place to ensure, as far as possible, that the indications in the previous paragraph are met.

The Minister for Health and Aged Care accepted these recommendations on 17 September 2001.

Appendix A MSAC terms of reference and membership

The MSAC's terms of reference are to:

- advise the Commonwealth Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Commonwealth Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Commonwealth Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise**
Professor David Weedon (Chair)	pathology
Ms Hilda Bastian	consumer health issues
Dr Ross Blair	vascular surgery (New Zealand)
Mr Stephen Blamey	general surgery
Dr Paul Hemming	general practice
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Associate Professor Richard King	internal medicine
Dr Michael Kitchener	nuclear medicine
Professor Peter Phelan	paediatrics
Dr David Robinson	plastic surgery
Professor John Simes	clinical epidemiology and clinical trials
Associate Professor Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council

Appendix B Supporting committee

Supporting committee for MSAC application 1039 — Photodynamic therapy with verteporfin for macular degeneration

Professor Peter Phelan (Chair) BSc, MBBS, MD, FRACP Emeritus Professor of Paediatrics University of Melbourne	member of the MSAC
Dr Terri Jackson MA, PhD Senior Research Fellow Health Economics Unit, Monash University and Manager of the Hospital Services Research Group	member of the MSAC
Associate Professor Ian Favilla DO, FRACS, FRANZCO Ophthalmic Surgeon and Clinical Associate Professor of Surgery Monash University, Melbourne	co-opted Ophthalmic Surgeon
Associate Professor Frank Fisher MEnvSt(Hons), BA(Geog)(Hons), BE(Elec)(Hons), FEIA Associate Professor and Director Graduate School of Environmental Science Monash University, Melbourne	consumer representative nominated by the Consumers' Health Forum of Australia
Dr Alex Harper MBBS, FRACS, FRANZCO Ophthalmologist Victoria Parade Eye Consultants St Vincent's Medical Centre, Fitzroy	co-opted Ophthalmologist
Associate Professor Justin O'Day MBBS, FRACS, FRACP, FRCS, FRANZCO, FRC Ophth Eye Specialist Victoria Parade Eye Consultants St Vincent's Medical Centre, Fitzroy	nominated by the Royal Australian and New Zealand College of Ophthalmologists
Associate Professor Denis Stark MBBS, FRCS (Edinburgh), FRANZCO Clinical Associate Professor Department of Child Health University of Queensland	nominated by the Royal Australian and New Zealand College of Ophthalmologists
Ms Linda Marshall BSc, BA, MBA MSAC Project Manager	Diagnostics and Technology Branch, Department of Health and Ageing

Appendix C Studies included for critical appraisal

Clinical Trials

TAP Study Group (1999). Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin - One-year results of 2 randomized clinical trials - TAP report 1. Archives of Ophthalmology 117: 1329–1345.

TAP Study Group (2001). Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin - Two-year results of 2 randomized clinical trials - TAP report 2. Archives of Ophthalmology 119: 198–207.

Systematic Reviews/Health Technology Assessments

Alberta Heritage Foundation for Medical Research (2000). Visudyne therapy for the treatment of age-related macular degeneration. AHFMR, Alberta.

Fong DS (2000). Photodynamic therapy with verteporfin for age-related macular degeneration. Ophthalmology 107: 2314–2317.

National Horizon Scanning Centre (2000). Photodynamic therapy for treatment of age-related macular degeneration - horizon scanning review (project) [Online]. Available: www.hsrc.org.uk/horizon [Accessed on: April 3 2001].

Norwegian Centre for Health Technology Assessment (2000). Photodynamic therapy for age-related macular degeneration. [Online]. Available: http://www.olso.sintef.no/smm/Publications/FramesetPublications.htm [Accessed on: April 3 2001].

Tunis SR, Patel SB, Rotter PS and Londner M (2000). Ocular Photodynamic Therapy with Verteporfin [Online]. Available: www.hcfa.gov/coverage/8b3-ee5.htm [Accessed on: April 3 2001].

Wormald R, Evans J and Smeeth L (2001). Photodynamic therapy for neovascular age-related macular degeneration (Cochrane Review). In: The Cochrane Library, Issue 1. Oxford: Update Software.

Appendix D Studies excluded from critical appraisal

Phase I/II studies

Miller JW, Schmidt-Erfurth U, Sickenberg M, Pournaras CJ, Laqua H, Barbazetto I, Zografos L, Piguet B, Donati G, Lane AM, Birngruber R, van den Berg H, Strong A, Manjuris U, Gray T, Fsadni M, Bressler NM and Gragoudas ES (1999). Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of a single treatment in a phase 1 and 2 study Archives of Ophthalmology 117**:** 1161-1173. [published erratum appears in Archives of Ophthalmology 2000; 118(4):488].

Schmidt-Erfurth U, Miller JW, Sickenberg M et al. (1999). Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of retreatments in a phase 1 and 2 study [comment] [see comments] [published erratum appears in Archives Ophthalmology 2000; 118(4):488]. Archives of Ophthalmology 117**:** 1177-1187

Case series

Schmidt-Erfurth U, Miller J, Sickenberg M et al. (1998). Photodynamic therapy of subfoveal choroidal neovascularization: clinical and angiographic examples. Graefes Archive for Clinical & Experimental Ophthalmology 236: 365-374.

Narrative reviews, editorials

Anonymous (1999). Photodynamic therapy for ARMD. British Journal of Ophthalmology 83: 260.

Anonymous (2000). Photodynamic therapy with verteporfin (Visudyne) for macular degeneration. Medical Letter on Drugs & Therapeutics 42: 81-82.

Arnold JJ and Sarks SH (2000). Extracts from 'clinical evidence': age related macular degeneration. British Medical Journal 321: 741-744.

Bressler NM (2000). Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: One-year results of 2 randomized clinical trials - TAP report 1 (vol 117, pg 1329, 1999). Archives of Ophthalmology 118: 488 [erratum]

Bressler NM and Bressler SB (2000). Photodynamic therapy with verteporfin (Visudyne): impact on ophthalmology and visual sciences. Investigative Ophthalmology & Visual Science 41: 624-628.

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Appendix E Internet sites

Agencia de Evaluación de Tecnologías Sanitarias AETS
http://www.isciii.es/aets/caet.html
accessed 10/4/2001

Agencia de Evaluación de Tecnologías Sanitarias de Andalucía. AETSA
http://www.csalud.junta-andalucia.es/orgdep/AETSA/default.htm
accessed 10/4/2001

Alberta Heritage Foundation for Medical Research (AHFMR)
http://www.ahfmr.ab.ca/index.html
accessed 10/4/2001

Agency for Health Care Policy and Research (AHCPR)
http://www.ahrq.gov/
accessed 10/4/2001

Agence Nationale d'Accréditation et d'Evaluation en Santé
http://www.anaes.fr/ANAES/anaesparametrage.nsf/HomePage?ReadForm
accessed 10/4/2001

L'Agence Nationale pour le Development de l'Evaluation Medicale (ANDEM)
http://www.upml.fr/andem/andem.htm
accessed 10/4/2001

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S)
http://www.racs.edu.au/open/asernip-s.htm
accessed 10/4/2001

The Centre for Health Services and Policy Research (CHSPR)
http://www.chspr.ubc.ca/
accessed 10/4/2001

Catalan Agency for Health Technology Assessment and Research (CAHTA)
http://www.aatm.es/ang/ang.html
accessed 10/4/2001

Canadian Coordinating Office for Health Technology Assessment (CCOHTA).
http://www.ccohta.ca/
accessed 10/4/2001

Center for Medical Technology Assessment (CMT)
http://www.imt.liu.se/cmt/
accessed 10/4/2001

College voor zorgverzekeringen
http://www.cvz.nl/
accessed 10/4/2001
Agence d'évaluation des technologies et des modes d'intervention en santé (AÉTMIS)

http://www.cets.gouv.qc.ca/en/index.htm
accessed 10/4/2001

German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DAHTA@DIMDI
Informationssystem Gesundheitsökonomische Evaluation/ Health Technology Assessment
http://www.dahta.dimdi.de/
accessed 10/4/2001

Danish Institute for Health Technology Assessment (DIHTA)
http://www.dihta.dk/
accessed 10/4/2001

Danish Institute for Health Services Research (DSI)
http://www.dsi.dk/
accessed 10/4/2001

ECRI
http://www.healthcare.ecri.org/
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Finnish Office for Health Technology Assessment (FinOHTA).
http://www.stakes.fi/finohta/e/
accessed 10/4/2001

The Health Council of the Netherlands (GR)
http://www.gr.nl/engels/welcome/frameset.htm
accessed 10/4/2001

Minnesota Health Technology Advisory Committee
http://www.health.state.mn.us/htac/
accessed 10/4/2001

Institute of Technology Assessment of the Austrian Academy of Science (ITA)
http://www.oeaw.ac.at/ita/hta/
accessed 10/4/2001

International Network of Agencies for Health Technology Assessment (INAHTA)
http://www.inahta.org/
accessed 10/4/2001

Medicare Services Advisory Committee
http://www.health.gov.au/haf/msac/
accessed 10/4/2001

Medical Technology Assessment Group (M-TAG)
http://www.m-tag.net/
accessed 10/4/2001
Medical Technology & Practice Patterns Institute (MTPP)
http://www.mtppi.org/frameset.asp?Pg=/&MI=1
accessed 10/4/2001

National Co-ordinating Centre for Health Technology Assessment
http://www.hta.nhsweb.nhs.uk/
accessed 10/4/2001

National Horizon Scanning Centre
http://www.bham.ac.uk/PublicHealth/horizon/
accessed 10/4/2001

National Institute for Clinical Excellence
http://www.nice.org.uk/
accessed 10/4/2001

New Zealand Health Technology Assessment (NZHTA)
http://nzhta.chmeds.ac.nz/
accessed 10/4/2001

Netherlands Organization for Scientific Research (NWO)
http://www.nwo.nl/english/nwo/
accessed 10/4/2001

Basque office for Health Technology Assesment (OSTEBA)
http://www.euskadi.net/sanidad/
accessed 10/4/2001

The Swedish Council on Technology Assessment in Health Care (SBU)
http://www.sbu.se/sbu-site/index.html
accessed 10/4/2001

The Norwegian Centre for Health Technology Assessment, SINTEF Unimed,
http://www.oslo.sintef.no/smm/News/FramesetNews.htm
accessed 10/4/2001

Swiss Science Council Technology Assessment
http://www.ta-swiss.ch/
accessed 10/4/2001

TNO Prevention and Health (TNO)
http://www.health.tno.nl/homepage_pg_en.html
accessed 10/4/2001

Veterans Affairs Technology Assessment Program (VATAP)
http://www.va.gov/resdev/ps/pshsrd/mdrc.htm#HealthCareTechnologyAssessment
accessed 10/4/2001

WHO Health Technology Assessment Programme (Collaborating Centres)

http://www.who.int/pht/technology_assessment/index.html
accessed 10/4/2001

Appendix F Ongoing primary studies

Photodynamic Therapy with Tin Ethyl Etiopurpurin ($SnET_2$ Study)

The $SnET_2$ study is a randomised controlled trial currently being conducted with the objective of determining the safety and potential efficacy of PDT with tin ethyl etiopurpurin ($SnET_2$) in the treatment of subfoveal CNV associated with MD (Pharmacia Ophthalmology 2001).

Patient enrolment closed in December 1999. A total of 934 patients were enrolled and treated at 59 U.S. ophthalmology centres. Patients receive an initial single treatment of $SnET_2$ or placebo, and are followed up for 12 months with retreatments if required (Pharmacia Ophthalmology 2001). Results are unavailable at the time of writing.

Abbreviations

ARR	absolute risk reduction
CI	confidence interval
CNV	choroidal neovascularisation
FAZ	foveal avascular zone
MD	macular degeneration
NNT	number needed to treat
PDT	photodynamic therapy
QUOROM	Quality of Reporting of Meta-Analyses
RCT	randomised controlled trial
RPE	retinal pigment epithelium
RR	relative risk
TAP	Treatment of Age related macular degeneration with Photodynamic therapy

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