NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Ranibizumab and pegaptanib for the treatment of age-related macular degeneration

Response to consultee and commentator comments on the draft scope

Consultee	Subject in Scope	Comment	Response by the Institute
Macular Degeneration Support (MD Support)	Background	1. Insert underlined words: "...wet (neovascular or exudative) and dry (non-neovascular or atrophic) ARMD."	No change, as original text not incorrect
		2. Ref: "Dry ARMD is more benign and associated with a discrete loss of retinal pigment cells." "Benign" may not be the best term here, and photoreceptors are also lost to dry AMD. I suggest replacing this sentence with something like: "Dry ARMD progresses more slowly than wet ARMD, causing a less dramatic loss of retinal pigment cells and photoreceptor cells."	Wording of scope changed accordingly.
		3. Change "abnormal blood vessels" to "immature blood vessels."	Wording of scope changed accordingly.
		4. "Scarring" is misspelled.	
		5. Ref: "...in occult CNV the vessels are difficult to **locate**." "Locate" suggests that the vessels are hidden from view, while the term "occult AMD" means that the vessels (i.e. the sources of the leaking) are not easily identified. Perhaps a more descriptive word in this sentence would be "define."	Wording of scope changed accordingly.

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		6. Ref: "... their vision may become very poor, with complete or near-complete loss of central vision **leading to significant loss of independence**." This phrase (in bold type) is not true if the patient receives proper low vision rehabilitation and support. Can this sentence be deleted? 7. Ref: "Rapidly deteriorating vision can have a major impact on emotional well being, and **[if proper information, training and support is not made available]** individuals are likely to suffer depression and anxiety." See recommended insert in bold type.	
	Population	Perhaps this should read: "People with choroidal neovascularization from diseases involving degeneration of the macula." Wet age-related macular degeneration is the focus of the trials, but it is only part of the much larger targeted population once these drugs are approved.	The population needs to be defined within the licensed indication of the drugs and the remit
	Comparators	1. Ref under Standard comparators: "For the subgroup of individuals with a confirmed diagnosis of classic with no occult subfoveal wet ARMD, PDT with verteporfin **[with and without steroid injection]** is also a comparator. For extrafoveal lesions, photocoagulation is a comparator. See recommended insert in bold type.	No change, as original text not incorrect
	Outcomes	1. Recommend including "color perception."	No change, as original text not incorrect
The Macular Disease Society	Background	The figures used for the number of new cases per year is probably low and need further exploration. The figure of 16,000 is lower than was used for the original application for Visudyne PDT	Figure amended to 26,000.

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	Population	See comment above. Treatment should not be distinguished between first and second eye. Both eyes ought to be treated individually regardless of pathology of the fellow eye. If one gets a retinal vascular occlusion in the other eye which is not uncommon in the elderly then the patient would be totally blind. There is no moral justification for waiting for the second eye involvement. It is possible to define various sub groups of CNV by location following flourescein angiography or Optical Coherence Tomography	Noted, no to scope change required Noted, no to scope change required
	Other considerations	What is the intensity and duration of treatment? The treatment frequency recommendation for Macugen is intravitreal injection every 6 weeks for 1 to 2 years for Lucentis the recommended frequency is monthly and for Retaane it is 6 monthly. From a patient's view point the fewer the number of injections the better the compliance and fewer the complications. The logistics of getting patients to clinics monthly over a long period will be demanding. However these treatments should not be seen as competing and clinicians should be allowed to use which ever they are getting the best results with also taking into account patient attendance difficulties.	Noted, no to scope change required
	Additional comments	Will the new drugs be used instead of PDT and/or photocoagulation or possibly in combination with PDT ? Our understanding is that they will be used mainly as a monotherapy.	Noted, combination treatment mentioned under 'other considerations'
Novartis Pharmaceutic	Background	Page 1, 1st Paragraph – The second sentence of this paragraph states,	No change, original

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als UK Ltd	information	"Age-related macular degeneration (ARMD) is one of the leading causes of irreversible sight loss..." It should be noted that ARMD is the leading cause of sight loss in people over the age of 50 years.(http://www.rnib.org.uk/xpedio/groups/public/documents/publicwebsite/public_smoking.hcsp, Fine et al, NEJM, 2000;342:483-492) In addition, results from the ranibizumab trials demonstrated improvements in visual acuity ie sight loss can be reversed with ranibizumab treatment. We therefore propose that the above statement is revised as follows, "Age-related macular degeneration (ARMD) is the leading cause of sight loss..."	wording not incorrect
		Page 1, 1st Paragraph – The last sentence of this paragraph suggests that there are around 16,000 new cases of wet ARMD in the UK each year. This is likely to be an underestimate, our estimate of incidence calculated from prevalence figures presented by Owen et al (Br J Ophthalmol 2003;87:312–317) indicates that there are around 26,000 new cases of wet ARMD in the UK each year.	Figure changed to 26,000
		Page 1, 3rd Paragraph – The first two sentences of this paragraph are incorrect and misleading. Contrary to the statements in the draft scope, loss of central vision, whether it involves one or both eyes, is associated with a dramatic loss of quality of life.(Berdeaux et al, Am J Ophthalmol 2005;139:271-279) Furthermore, it is misleading to state that retention of peripheral vision prevents patients from becoming completely blind. We therefore propose that this section is revised as follows, "People with macular degeneration lose central vision but retain their	Wording in draft scope amended.

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		peripheral vision. Loss of central vision is associated with a dramatic loss of quality of life, affecting the ability to read, recognise faces and drive. Their vision may become very poor...." Page 2, 1st Paragraph – The third sentence of this paragraph states, "The aim of therapy for people with wet ARMD is to alter the progression of vision loss." The unprecedented results demonstrated by ranibizumab in improving visual acuity means that the aim of therapy can be upgraded to improving as well as maintaining vision. We therefore propose the following revisions to the above sentence, "The aim of therapy for people with wet ARMD is to maintain or improve vision."	No change, as original wording not incorrect
	Technology	Page 2, 3rd Paragraph – The first sentence of this section states that ranibizumab is an anti-vascular endothelial growth factor (VEGF) antibody. This should say antibody fragment. Page 2, 3rd Paragraph – The second sentence of this section which refers to ranibizumab states, "It is administered as monthly intravitreal injections at a dose of 0.3-0.5mg for as long as the patient benefits." It should be noted that a ranibizumab trial to evaluate a reduction in dose frequency is nearing completion and will report prior to formal assessment by NICE.	Wording in draft scope changed accordingly Noted, no change to scope required
	Licensing Issues	Novartis note that the manufacturers of anecortave (Alcon) have withdrawn the European (and hence UK) application for wet AMD, as communicated by the EMEA in their press release of the 2 March 2006 (Doc. Ref. EMEA/76945/2006)	Anecortave acetate has been removed from the scope

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	Population	Page 3 – It is very important that the correct lesion definitions, as recognised and used by clinicians, are used throughout the appraisal. Comparators can then be defined according to the lesion type. The lesion definitions should be consistent with those used in all of the clinical trials and referred to in the resulting publications. Any changes to these definitions could lead to unnecessary complication, confusion and potential delays in the appraisal process. - Predominantly classic (PC): The area of classic choroidal neovascularisation (CNV) represents over 50% of the entire lesion area (includes 100% classic) - Minimally classic (MC): The area of classic choroidal neovascularisation (CNV) represents less than 50% of the entire lesion area - Occult No Classic (ONC): The lesion does not have a classic component Extra and juxtafoveal lesions are estimated to make up a small proportion (12%) of all forms of wet AMD, and were not evaluated in the clinical trials for ranibizumab and pegaptinib, nor will they be covered by the anticipated product licences. Ranibizumab was tested in subfoveal lesions (which account for 88% of lesions). Therefore references to extrafoveal lesions and photocoagulation are not relevant to this appraisal and should be removed from the "Background" section, page 2, 2nd paragraph and "Standard Comparators" section, page 3, of the scope.	Noted, no change to scope required Wording in scope amended accordingly.

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	Comparators	Standard comparators, Page 3 – Comparators should be defined according to the lesion type as follows; The appropriate comparators are as follows; Minimally classic – best supportive care. Predominantly classic – PDT with verteporfin. Occult no classic - best supportive care.	Current NICE guidance (TA 68) does not recommend PDT for predominantly classic CNV in routine care.
	Outcomes	Page 3 – The outcome measure "Visual acuity" should be sub-defined into maintenance and improvement. – "Number of treatments" per se is not an outcome measure and should be removed from this list. – Patient reported outcomes based on validated patient questionnaires should be added to the list as this adds to the information available for each of the interventions on quality of life	No change, as wording in scope is not incorrect Amended accordingly Already included in QoL
	Additional Comments	Questions for consultation Are the comparators sufficiently clearly defined? As stated above it is important that the lesions are appropriately defined and the comparator assigned according to lesion type as follows; - Minimally classic – best supportive care. - Predominantly classic – PDT with verteporfin. - Occult no classic - best supportive care.	Current NICE guidance (TA 68) does not recommend PDT for predominantly classic CNV in routine care.

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		Can the population (classic, occult, subfoveal, extrafoveal CNV) be sufficiently defined as the licensed indications are not yet known for two of the drugs? Based on the available evidence and anticipated licences the lesion types can be clearly defined as follows; - Predominantly classic (PC): The area of classic choroidal neovascularisation (CNV) represents over 50% of the entire lesion area (includes 100% classic). - Minimally classic (MC): The area of classic choroidal neovascularisation (CNV) represents less than 50% of the entire lesion area. - Occult No Classic (OC): The lesion does not have a classic component. These lesion definitions are consistent with those used in all of the ranibizumab clinical trials and referred to in the resulting publications. Extra and juxtafoveal lesions are estimated to make up a small proportion (12%) of all forms of wet AMD, and were not evaluated in the clinical trials for ranibizumab and pegaptinib, nor will they be covered by the anticipated product licences. Ranibizumab was tested in subfoveal lesions (which account for 88% of lesions). Therefore references to extrafoveal lesions and photocoagulation are not relevant to this appraisal and should be removed from the "Background" section, page 2, 2nd paragraph and "Standard Comparators" section, page 3, of the scope.	Scope amended accordingly
		Will the new drugs be used instead of PDT and/or photocoagulation, or possibly in combination with PDT (as undertaken in one study)? Completed phase I/II trials for ranibizumab (FOCUS) provide	Covered under 'other considerations'

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		preliminary evidence relating to the combination of verteporfin and ranibizumab therapy versus verteporfin alone. Formal phase III registration studies provide evidence of the benefits of ranibizumab as a monotherapy compared to verteporfin in predominantly classic lesions (ANCHOR) or versus placebo in minimally classic and occult lesions (MARINA). Ongoing Phase II studies (PROTECT) will provide additional evidence for efficacy and safety for ranibizumab, including the potential for combination therapy to reduce dosing requirements for either component of the combination and may be available within the timeframe of this appraisal. What is the intensity and duration of treatment? Current phase III studies indicate a dosing frequency of every 4 weeks for ranibizumab. However, a phase IIIb ranibizumab trial (PIER) to evaluate the benefits of ranibizumab with a reduction in dose frequency (compared to the 4-weekly dosing frequency) is due to complete shortly and will report within the timeframe of this appraisal. Additional phase IIIb studies (EXCITE & SUSTAIN) will provide data outside the timeframe of the appraisal that will inform as to other reduced dosing frequency regimens for ranibizumab.	
Pfizer Ltd	Background information	lsen (Ophthalmology 2004;111:250-5) performed a cross sectional study of 200 cases of neovascular AMD and classified 10 (5%) as extrafoveal. This is lower than the quoted 10-15% stated on page 2.	Wording in scope changed accordingly.

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		In addition, according to clinical opinion, Olsen provides the best estimate of the division between classic and occult CNV. 118 out of 157 (75%) patients with subfoveal CNV had occult with no classic.	Noted, no change to scope required
		It is important to emphasise these estimates are uncertain due to the low diagnostic ability of fluorescein angiography to differentiate between CNV sub-types. A number of recent studies confirm that the process of determining the lesion subtype using fluorescein angiography is unreliable. In a systematic review of FAs from patients in three continguous Medicare coverage areas, Schein and colleagues (Arch Ophthalmology 2005;123:58-63) note a 17% to 44% rate of error in subtyping. A study assessing the rate of variability within (intraobserver) and between (interobserver) two groups of ophthalmologists in determining lesion subtypes from fluorescein angiography photographs, found low to moderate levels of agreement between the two groups. The authors note that subtype classification can vary considerably not only between observers but also for repeated evaluations by the same observer (Holz et al. Ophthalmology 2003, 110: 400-405).	Noted, no change to scope required
		As well as depression and anxiety, loss of vision can also have a burden on healthcare through increased incidence of falls and fractures. Falls and associated fractures, such as hip fractures, are important co-morbid conditions in patients with visual impairment in general and are particularly prevalent in older people (National Service Framework for Older People 2001). Individuals with low vision, including patients with AMD, may have incorrect awareness of their physical environment, including obstacles in their environment, and consequently have an elevated risk of slipping or tripping accidentally and falling. Dargent Molina and colleagues (1996) found that visual impairment was an independent risk factor for hip fracture, with the risk inversely related to VA. (Lancet 1996 Jul	Wording in scope amended accordingly

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		20;348:145-9)	
	Technology	Ranibizumab is a pan-VEGF inhibitor that blocks all isoforms of VEGF. Pegaptanib sodium is a selective VEGF inhibitor that targets VEGF165, a major pathogenic isoform of VEGF. Pathologic VEGF is the primary cause of CNV, the single disease process underlying all AMD. Pegaptanib is administered as an intravitreal injection into the eye to be treated every 6 weeks	Noted, no change to scope required
	Licensing	Pegaptanib is licensed in the UK for the treatment of neovascular AMD. No further indications are pending within the timeframe of the appraisal.	Noted, no change to scope required
	Population	Pegaptanib was investigated in patients with subfoveal neovascular AMD	Scope amended accordingly
	Outcomes	Adherence to the frequency of injection should be considered	Scope has been amended accordingly
	Economic analysis	AMD is primarily a disease of the elderly population (mean age 75 years), therefore a 10 year time horizon covers the lifetime of the benefits and costs.	Noted, no change to scope required
	Other considerations	Consideration should be given to the treatment protocol with regards the intensity of treatment	Noted, no change to scope required
	Additional Comments	In response to questions for consultation: The comparators are sufficiently clearly defined. It is extremely difficult to sufficiently define the population using classification as occult or classic due to the low diagnostic accuracy of fluorescein angiography. Regardless of the lesion subtype, CNV is	Noted, no change to scope required

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		the hallmark of neovascular AMD and the single disease process that defines neovascular AMD (Ambiati et al. Survey of Ophthalmology 2003;48(3):257-93). Use of fluorescein angiography to classify lesion subtypes is therefore only required for existing laser treatments and is no longer relevant for pegaptanib therapy. Pegaptanib will be used instead of PDT and photocoagulation to meet unmet need in subfoveal neovascular AMD. There is no evidence to support combination use of pegaptanib and PDT. Pegaptanib is licensed for administration every 6 weeks. Duration of treatment has been demonstrated to be beneficial for two years, with results from a third year follow-up pending.	
Royal College of Nursing	Technology	In this context these drugs do not inhibit the 'formation' of CNV but prevent further growth of CNV as they are only given in the presence of CNV not as a profolactic treatment!	Wording of scope amended accordingly
	Population	What about considerationns for other neovascular maculopathies ie-cvn due to pathological myopia and idiopathic causes of CNV?	The population is limited by licence and remit
	Outcomes	Not all these studies will have QOL data to measure efficacy so this could be a problem. Will the personal social services measure take into account the impact on carer's?	The effect on carers is not usually included in the economic modelling.
	Economic Analysis	Needs to be mapped over a minimum of two years	Noted, no change to scope required
	Other considerations	Cost implications for the NHS on 'clean room' facilites or the use of theatre space for intravitreal injections	Specifics of cost are not included in the scope, but will be considered in detail in the protocol

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	Additional comments	Do we really need to consider 'lesion type' in this context as the forthcoming antivegF's are showing efficacy for all CNV lesion types. It is necessary that with the information now available with the introduction of these new therapies, that sufficient time is given to patients and their relatives to make a fully informed choice as to which therapy regimen would be the most suitable taking into consideration their eye condition and other factors such as general health and subsequent ability to make very frequent hospital visits.	Noted, no change to scope required Noted, no change to scope required
	Comparators	'Extra foveal' photocoagualtion is not a good comparator as the other treaments are for 'subfoveal' CNV's	Wording of scope amended accordingly
The Royal College of Ophthalmologists	Background	We would question the frequency of extrafoveal CNV undergoing photocoagulation being quoted as 10-15% and the figure may even be as low as 1%. There is also a high risk of recurrence following photocoagulation of such lesions. The current NICE guidance on PDT recommends treatment for classic no occult lesions in section 1.1, and predominantly classic lesions with occult in section 1.2 as long as this is part of a clinical trial. PDT treating units participate in the VPDT cohort study so that predominantly classic lesions with occult are being funded for NHS treatment on the basis of this NICE guidance. The description that ARMD is associated with 'gradual painless loss of vision' (line 4) may be true for dry ARMD, but in wet ARMD there is often a rapid onset of symptoms of blurring and distortion of central vision. The description of the fluorescein angiographic features for classic and occult lesions given here is oversimplified and somewhat misleading. It is hard to give a very succinct definition: it may be	Wording of scope amended accordingly Noted, no change to scope required Wording of scope amended accordingly Wording of scope amended accordingly

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		better to either give a full accurate definition or simply comment that there are different sub-classifications of CNV based on the way the lesions behave on fluorescein angiography.	
	Technology	Anecortave acetate is administered via a posterior juxtascleral depot. Studies are underway looking at the possibility of reduced dosage frequencies/duration of treatment, as well their use in combination with other treatment such as PDT.	Anecortave acetate has been removed from the scope Covered under 'other considerations'
	Population	We would agree that all lesion types should be included as per trial inclusions. Lesion subtypes are routinely defined in clinical practice.	Noted, no change to scope required
	Comparators	Extrafoveal lesions were not included in the trials, so it would be difficult to include this group in the analysis. Could PDT be used as a comparitor for predominantly classic lesions with occult as well as classic/no occult lesions? - as per earlier comments about patients currently undergoing treatment with PDT for whom data is being collected in the VPDT cohort study.	Wording in scope amended accordingly. Current NICE guidance (TA 68) does not recommend PDT for predominantly classic CNV in routine care
	Outcomes	Would it be possible to consider data from 1st eye patients independently of second eye patients for health-related quality of life?	No change of scope required
	Economic Analysis	Will NNT also be assessed? The cost of managing possible complications of treatment should be included in the assessment. A two year time horizon is likely to be the most appropriate.	Noted. Specifics of cost are not included in the scope, but will be considered in detail in the protocol.

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	Other considerations	Other types of disease causing subretinal neovascularisation, such as such as angioid streaks, pathologic myopia.	The appraisal is confined by the remit and the licensed indications of the drugs.
Royal National Institute of the Blind	Background	We feel that this is an acccurate description of age-related macular degeneration and its impact on individuals. We particularly welcome the recognition of the severe impact of rapidly deteriorating vision on emotional wellbeing and the fact that individuals are likely to suffer depression and anxiety. This is an often overlooked fact. We would like to point out that slowly progressing vision loss, particularly if it is clear that there are no treatment options can have the same devastating effect. We do recognise, however, that in the context of treatments for wet AMD rapid vision loss is the reality for most patients. Also, we feel that the background information puts too much emphasis on the distinction between different types of CNV. In particular, we do not believe that the distinction between classic and occult is relevant. (see also "other considerations" below RNIB would want to be sure that "The aim of therapy for people with wet ARMD is to alter the progression of vision loss" includes not merely slowing down or halting vision loss but also the improvement in vision.	Noted, no change to scope required Wording in scope amended accordingly No change, original text not incorrect
	Technology	All of our comments relate to Macugen and Lucentis only since Alcon plc has withdrawn its application for the approval of Retaane.	Anecortave acetate has been removed from the scope
	Population	The reference figure for the incidence of AMD used for the NICE appraisal of PDT in 2000 was 21,000 patients. Given the increase in the elderly population we feel that this number is likely to be higher	Figure amended to 26,000.

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		rather than lower and would therefore suggest a figure that is closer to 26,000 but definitely not 16,000.	
	Comparators	Since the licencing application for Macugen and Lucentis is seeking for both treatments to be approved for the treatment of subfoveal CNV we do not believe that a comparison with photocoagulation which can only be used for the treatment of extra-foveal CNV is appropriate. When PDT treatment for subfoveal AMD was assessed the only comparator was best supportive care. It would therefore seem illogical to introduce photocoagulation into this assessment. The only comparators should be PDT treatment and best supportive care.	Wording in scope amended accordingly.
	Economic Analysis	It is important that a wider range of costs are taken into account. To merely consider NHS and Personal Social services expenditure is to ignore some important areas of expenditure associated with sight loss (e.g on Disability Living Allowance and Attendance Allowance, transport and mobility, accessible information. See RNIB "The Costs of Sight Loss, 2004)	Methods guide stipulates NHS and PSS costs.
	Other considerations	The fact that Macugen and Lucentis can treat all types of subfoveal CNV should play a major role in the assessment since it increases the number of patients who are eligible for treatment. When looking at Macugen and Lucentis in isolation no distinction between different types of CNV is necessary. When comparing Macugen and Lucentis to PDT the comparison should be made with the treatment indications for PDT as licensed by the EMEA, not the guidance issued by NICE since this did not cover occult CNV.	The comparator is standard care in the NHS.
	Additional	Given the strong indications of the benefits of combination treatments this aspect should be included in the assessment. The background information mentions that severe sight loss usually sets in when both eyes are affected by AMD. RNIB would argue strongly that sight loss in the first eye is important to the patient and	Covered under ‘other considerations’ Wording in scope amended accordingly

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		impacts on quality of life. Certainly for the new treatments the appraisal should assume that treatment will commence as soon as subfoveal CNV is detected in one eye to increase the chances of avoiding severe sight loss.	
Southampton Health Technology Assessments Centre	Technology	We understood that the license for Ranibizumab was not expected within the timeframe of this appraisal and that it would therefore not be included. Please clarify. In the description of each drug dosing regimen the scope states that treatment occurs "for as long as patient benefits". How is patient benefit defined / measured? Please clarify intensity / duration of treatment for the interventions and comparators.	Ranibizumab will be included in this appraisal if a licence is granted before the Assessment Report is issued for consultation. Treatment duration depends on trial evidence.
	Comparators	It is not clear from the scope whether treatment with each of the interventions should be compared with supportive care (which in this case seems to be visual rehabilitation) and then separately to PDT or photocoagulation for the identified sub-groups (extrafoveal lesions or "classic with no occult subfoveal wet ARMD"). In other words are we expected to treat these as separate sub-group analyses or are they embedded in the reference case? The scope asks whether PDT and/ or photocoagulation might be used in combination with the new drugs. In this case would PDT or photocoagulation on their own be the comparator or would the relevant comparator be best supportive care?	The comparator is best supportive care (including visual rehabilitation), in addition, for the subgroup of individuals with a confirmed diagnosis of classic with no occult subfoveal wet ARMD, PDT with verteporfin is also a comparator. If the evidence and

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			licence allows, combination treatments should be considered.

Statement of 'no comment':

Department of Health

Royal Pharmaceutical Society of Great Britain