National Institute for Health and Clinical Excellence

Bevacizumab for the treatment of recurrent glioblastoma

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Society of British Neurological Surgeons	Our understanding is that this appraisal would be to assess bevacizumab as a 'single agent' for use in patients with recurrent Glioblastome Multiforme. Whilst we commend the early examination of new treatments for this group of patients, particularly where there is little to offer, we are concerned that there is little data at present to make a sensible estimation of ICER, and that most data relates to combined use of bevacizumab with other drugs, notably irinotecan. This latter data does suggest survival benefit for this group of patients. As a consequence such a drug combination with bevacisumab might form a more realistic appraisal than this drug used alone. We note that the data for single use (Gonzalez, Norden) together with that from data from use in other cancer sites allows some estimation of incremental toxicity over cytotoxic therapy alone.(Vance, Friedman,Vredenbergh, Friedland,Raval,Al) reviews by Omuro and Delattre, Fiedman. If there is other single use data prefereably RCT available from the manufacturer that addresses these concerns, or the remit would allow appraisal of combinational therapy with this agent, then we would support early consideration of this drug technology for this group of underserved patients.	The technology will be appraised in accordance with its licensed indication. If the marketing authorisation includes both monotherapy and combination therapy both may be considered in the appraisal.
	Roche Products Ltd.	This is appropriate.	Noted.

Section	Consultees	Comments	Action
	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	There is a lot of interest in using avastin in the clinic, and from this perspective STA may be appropriate, but it is early in the development of this agent for use in glioma. Phase III studies are just starting, currently the evidence base is limited to non-comparative studies and there are no quality of life data.	Noted.
Wording	Society of British Neurological Surgeons	No comment at this stage.	Noted.
	Roche Products Ltd.	No comment.	Noted.
	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	Yes.	Noted.

Section	Consultees	Comments	Action
Timing Issues	Society of British Neurological Surgeons	There are a number of difficulties in defining recurrence (eg psudoprogression) in these patients that will need clarification early during scoping. Importantly there is much concern as to what therapy should be offered to this group of patients at recurrence. The effect of the NICE guidance on the use of Gliadel and Temozolomide at diagnosis has made decison making for treatment of patients at recurrence using these and other agents complicated and confusing to patients, doctors and commissioners. It is timely to review this area and important to clarify the postion before patients' expectations regarding secondary therapy with bevacisumab and/or combinational agent develop	The technology will be appraised in accordance with its licensed indication. Recurrence/relapse will be defined as per the licensed indication.
	Roche Products Ltd.	No comment.	Noted.
	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	Not currently urgent.	Noted.
Additional comments on	Society of British Neurological Surgeons	No further comment at this stage.	Noted.

Section	Consultees	Comments	Action
the draft remit	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	Avastin has been used in combination and this will not address which if any agents should be used with it.	The technology will be appraised in accordance with its licensed indication. If the marketing authorisation includes both monotherapy and combination therapy both may be considered in the appraisal, including any combinations of treatments specified.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Department of Health	Rewording suggested: (emphasis added to highlight changes) "The annual incidence in England and Wales of malignant brain tumours in those aged 15 years and over is 8.5 per 100,000, corresponding to approximately 3500 new cases each year. GBM accounts for approximately **70%** of high grade gliomas, representing around **2400** cases per year. The median survival of patients with GBM is 10 to 12 months from initial diagnosis. Approximately 30% of all adults with high grade gliomas survive 1 year, with 13% surviving 5 years from initial diagnosis. Treatment following initial diagnosis usually consists of surgical resection, followed by radiotherapy and sometimes systemic chemotherapy. Approximately 80% of patients newly diagnosed with GBM undergo surgery, usually **followed by radiotherapy**. Complete surgical resection of these tumours is **rarely possible**, and relapse is common around 6 to 8 months after initial therapy. Approximately 20% of these people may be suitable for surgical re-intervention followed by chemotherapy. Expert opinion suggests a large proportion of cases will go on to relapse after first and second line treatment. Palliative care aims to improve function and quality of life for those in whom disease recurs. […] **Those patients suitable for such treatment have an improved survival with 12% of GBM patients alive at 4years (as compared with 4% with surgery and radiotherapy alone)**."	The *Background Information* section of the scope has been amended to reflect that the proposed marketing authorisation will be for glioblastoma rather than glioblastoma multiforme. Where appropriate, the suggested rewording specific to glioblastoma multiforme has been incorporated.
	Society of British Neurological Surgeons	Unclear as to extent of additional data concerning single use of bevacizumab, ie that held by the company. This would have considerble bearing on appropriateness of the appraisal at this time.	The technology will be appraised in accordance with its licensed indication.
	Roche Products Ltd.	No comment.	Noted.

Section	Consultees	Comments	Action
	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	It is a concern that the 'background' reads as though it is written by someone without full understanding of the area,; it lacks precision. For example if they are using the WHO grading system the tumour is 'Glioblastoma' not 'Glioblastoma multiforme' according to this classification. Also the tumours are not graded by likely 'rate of growth' rather by their 'proliferative potential' - which is different though often related. The grading also includes consideration of surgical curability and infiltrative properties. The statement that 20% of cases may be suitable for surgical intervention and chemotherapy at relapse suggests that patients are not considered for chemotherapy alone. This is not the case as patients are frequently treated with chemotherapy without further surgery. The incidence data are at variance with those quoted in the recent IOG. Other UK estimates suggest only around 800 patients/year with GBM are suitable for standard first line treatment with chemoradiation and only a proportion of these would be suitable for further chemotherapy. Radiotherapy is usually referred to as a course, not a cycle. There are ongoing studies to address how relapse should be defined, particularly in view of well described phenomenon of radiological psuedo-progression following RT + TMZ. Ideally this needs to be resolved in order to make patient selection for relapse studies appropriate.	Noted. The *Background Information* section of the scope has been amended to reflect the proposed marketing authorisation. Relapse will be defined in accordance with the marketing authorisation.
The technology/ intervention	Society of British Neurological Surgeons	The intervention is described as a 'single' agent process by definiton from the website reference. However examination of the literature with respect to this agent highlights its evaluation as part of a combinational therapy. There is relatively little data in the public domain on single use bevacizumab especially in this group of patients. Is it the intention to broaden the scope to include data from combinational studies as mentioned in the information.	The technology will be appraised in accordance with its licensed indication. If the marketing authorisation includes both monotherapy and combination therapy both may be considered in the appraisal.
	Roche Products Ltd.	Yes.	

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	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	Yes.	Noted.
Population	Society of British Neurological Surgeons	The population of patients is loosely defined as recurrent glioblastome multiforme. The definition of recurrence is now more complicated with the advent of delayed responses from the use of Temozolomide with initial treatment, ie pseudoprogression. Hence the timing of the intervention will have to be assessed in the light of patients who have been through a primary course of Temozolomide. There is a need to consider the position of patients with Anaplastic tumours who recur, and are likely to harbour a higher grade transformation to GBM as a result.	The *Background Information* section of the scope has been amended to reflect the anticipated marketing authorisation. Relapse/recurrence will be defined in accordance with the marketing authorisation.
	Roche Products Ltd.	The population is defined appropriately.	Noted.

Section	Consultees	Comments	Action
	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	Yes, increasingly patients with different MGMT status are treated as separate sub-groups as they respond differently to RT+TMZ. Ultimately some of these patients may not receive TMZ as first line treatment. The relevance of this biomarker to Avastin response is unknown.	The scope has been amended to allow for the inclusion of subgroup analysis based on MGMT status, if evidence allows.
Comparators	Department of Health	Suggest lumostine not be included as comparator. Note that some patients will have already received temozolomide.	Consultees agreed at the scoping workshop that lomustine should remain as a comparator.

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	Society of British Neurological Surgeons	At recurrence the comparators as stated include Temozolomide. This can be given as 5/30 day or as dose intense as reported in some studies, perhaps with lower incidence of SAE at the lower dose rate. Such variations in the use of Temozolomide should be considered where the the beneifts and toxicity of bevacizumab are being compared. If combinational therapy with bevacizumide with temozolomide is being considered, the primary treatment may influence the choice of comparator. For example is there data on bevacizumab and nitrosoureas used together for comparison with temozolomide and bevacizumab?	The cost effectiveness analyses will consider the use of comparator treatments as they are administered in the NHS. This may include variations in their use. Regarding the consideration of bevacizumab combination therapy, the technology will be appraised in accordance with its licensed indication. If the marketing authorisation includes both monotherapy and combination therapy both may be considered in the appraisal.
	Roche Products Ltd.	The comparators are appropriate.	Noted.
	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	Yes.	Noted.

Section	Consultees	Comments	Action
Outcomes	Department of Health	"Overall survival" as outcome measure should be amended to "overall survival at 6 months", as this is an internationally agreed marker for brain treatments.	Consultees agreed at the scoping workshop that overall survival should remain as an outcome measure. This does not exclude the possibility of overall survival at 6 months being additionally reported.
	Society of British Neurological Surgeons	These are the recognised outcome measures for this disease at this stage.	Noted.
	Roche Products Ltd.	These outcomes are appropriate.	Noted.
	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	Yes.	Noted.
Economic analysis	Society of British Neurological Surgeons	For the analysis of patients at recurrence overall survival remains the main measure together with quality of life	Noted.

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	Roche Products Ltd.	The economic analysis will face considerable challenges due to the limitations of existing data within this disease area. 1) The main registration study for bevacizumab used to inform the 'treatment arm' of the economic analysis is a Phase 2 clinical trial which does not include a control arm. 2) Robust comparable data on the alternative treatments in the setting of recurrent glioblastoma multiforme is very limited.	Noted.
	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	In view of overall poor prognosis any agent when scaled up may appear non cost viable unless assessed on better prognostic group	Noted.
Equality and Diversity	Society of British Neurological Surgeons	The other issue to consider here would be that of age particularly where the patient fits a criteria for accessibility for this technology in all but age.	Any criteria determining access to treatment will be based on evidence of differential clinical or cost effectiveness between groups. Age is not normally used to as a criterion for determining treatment.
	Roche Products Ltd.	No comment.	Noted.

Section	Consultees	Comments	Action
Other considerations	Society of British Neurological Surgeons	The recognition that because of the comparators, and current literature, patients and oncologists may have difficulty applying the technology if approved for single agent use only.	Guidance can only be issued in accordance with the marketing authorisation. If the marketing authorisation includes both monotherapy and combination therapy both may be considered in the appraisal.
	Roche Products Ltd.	Due to the unmet need in this rare disease, early engagement on the potential application of the NICE end-of-life supplementary advice would be of great value.	Noted.
	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	Is Avastin intended to be used as a single agent or in combination?	Guidance can only be issued in accordance with the marketing authorisation. If the marketing authorisation includes both monotherapy and combination therapy both may be considered in the appraisal.
Questions for consultation	Society of British Neurological Surgeons	Comments made above address these questions	Noted.

Section	Consultees	Comments	Action
	Roche Products Ltd.	Covered in the sections above.	Noted.
Additional comments on the draft scope.	Society of British Neurological Surgeons	No.	Noted.
	NCRI Brain Tumour Clinical Study Group/Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology	This agent will be entering Phase III studies in the near future. Until these data are available it is difficult to make decisions about its place in glioma treatment. It should be noted that most of the phase II data available on this agent relate to combination treatment with Irinotecan, an agent which is not known to have significant activity in glioma. It is not stated whether this STA will include paediatric or young adult patients, there are studies using Avastin ongoing in these groups too.	The technology will be appraised in accordance with its licensed indication. The manufacturer has indicated that paediatric patients will not be included in the marketing authorisation.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Welsh Assembly Government
Royal Pharmaceutical Society

Royal College of Nursing
Lilly UK
Schering-Plough
Rarer Cancers Forum
ENT UK and the British Association of Otorhinolaryngology – Head and Neck Surgery