National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Carmustine implants for the treatment of recurrent glioblastoma multiforme

Responses to comments received during consultation on draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Brain Tumour UK	This does not refer to BR12 study (ongoing). Data from this study will be be available for a further 12 months but is likely to impact on standards of care at relapse. The FAD on (concomitant therapy)is also relevant. This has been delayed until March 2007.	Comments noted. Details of ongoing trials that do not include the intervention of interest are not usually provided within the scope. Whilst noting the importance of the BR12 trial, it does not include carmustine implants and therefore it is not relevant to this appraisal. Details of the appraisal for newly diagnosed glioma are noted in the 'Related NICE recommendations' section of the scope.

Section	Consultees	Comments	Action
	Society of British Neurological Surgeons (SBNS)	1. With respect to the accuracy and completeness of the background information one of the major issues is definition of recurrence and how this is achieved. Patients are frequently diagnosed with recurrent disease based on clinic deterioration but increasingly the evidence is that early detection by imaging can be more beneficial. In the context of regular surveillance imaging, early recurrence is associated with improved performance and greater likelihood of access to therapy for recurrence. Many older studies have used symptomatic recurrence where inherently the performance level of these patients at recurrence is worse and hence debars patients from either trial entry or expectant treatments. Current treatment should try and maximise the number of patients in whom it should be useful. Imaging surveillance from diagnosis and glioblastoma multiforme especially should be regular and consistent as patients can recur even after prolonged periods of stability. Therefore, imaging should be at between eight weeks to twelve weeks to enable us the greatest chance of picking up recurrence. This is reflected in the recently published Improving Outcomes Guidance which pays particular emphasis to follow-up surveillance. The appraisal should consider the impact of the IOG and definition of recurrence in its deliberations, bearing in mind that image-based deterioration is increasingly the standard by which these patients are managed worldwide. 2. It is incorrect to use a unimodal model defining disease progression in these patients whereby they would have a disease-free interval and then deteriorate to death. Patients with glioblastoma multiforme will always have the disease which can wax and wane during its natural history, sometimes as a result of treatment. Frequently patients will have recurrence based on imaging (or symptoms) which responds to chemotherapy +/- surgery to give prolonged periods of disease control, e.g. greater than a year. Indeed, we have a number of patients from the Queen Elizabeth Hospital series who have had several years of good performance level following from apparent recurrence. Unimodal models of the disease are inadequate to describe uses of treatment, cost benefit, and quality of life. The appraisal should take these issues of disease behaviour into account in any modelling process.	1. The potential importance of early detection of recurrence is noted. As is the comment on the comparability of studies. As the commentator suggests, the issue of appropriate imaging frequency has been discussed by IOG. Details of the IOG are noted in the 'Related NICE recommendations' section of the scope. 2. Comments noted. The outcomes section of the scope has been amended to include measures of functional status.

Section	Consultees	Comments	Action
	Royal College of Nursing (RCN)	There is presently a Phase III study which compares Temozolomide with PCV for patients with glioblastoma with progressive tumour following initial treatment with radiotherapy and who are chemotherapy naïve. There is no mention of this in the draft scope.	We believe the RCN is referring to the BR12 trial which does not consider carmustine implants. Whilst noting the importance of the BR12 study, details of ongoing trials that do not include the intervention of interest are not usually provided within the scope.
	Department of Health (DH)	Figures for incidence are inaccurate. The DH medical advisors are concerned that the documentation does not reflect a full understanding of brain tumours.	The figures for incidence have been amended. In addition, the Institute arranged a discussion with the DH clinical expert regarding this appraisal.
	Link Pharma.	Currently the focus of the background information section is predominantly on newly diagnosed patients and does not reflect the much poorer prognosis for patients with recurrent disease. We would therefore suggest that additional information relating specifically to recurrent GBM and its treatment be included. ***Paragraph Two*** The statement that GBM accounts for approximately 22% of new cases of malignant brain tumours appears to be too low. The information contained within Technology Appraisal No. 23 states GBM accounts for 40-45% which is more consistent with other information sources. [Quinn et al, 2001] Additionally, an even higher number of patients will have progressed to GBM at recurrence. In order to highlight survival in patients with GBM the sentence 'The median survival for patients with GBM is 10 to 12 months' would benefit from clarification that this value is from the time of initial diagnosis of the condition and not from the time of recurrence. Inclusion of the following text will highlight survival following recurrence. *Following initial treatment (i.e. surgery and/or radiotherapy and/or chemotherapy) for a newly diagnosed GBM, virtually all gliomas recur. In*	Background has been revised to include: 40-45% figure for GBM as a proportion of high grade gliomas; To clarify that survival data is estimated from time of initial diagnosis

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		these patients the median survival is closer to 6 months [Dirks et al, 1993; Ammirati et al, 1987; Young et al, 1981] with 6-month and 5-year survival rates of 36% and 4-5% respectively.' [Brem et al, 1995; McLendon et al, 2003] ***Paragraph Three*** As per our previous comment on the focus of the background information the treatment options discussed reflect the situation for newly diagnosed patients only. In order to extend the background information to cover recurrent disease we would recommend the addition of the following text: *At recurrence patients will have surgery, if this is possible, and chemotherapy. The choice of systemic chemotherapy is increasingly temozolomide used at the time of first recurrence, whilst carmustine implants are the local chemotherapy choice.* ***Paragraph four*** Radiotherapy is rarely given to patients with recurrent GBM as in most cases they will have received the maximum tolerated dose as part of their initial treatment regimen.	Reference to progression of tumours to GBM (paragraph 3); Data based on consultation with neuro-oncology expertise and further description of the disease/treatment pathway (now paragraphs 4 and 5). The role of temozolomide in recurrence is described in the last paragraph of the background and in the revised Intervention/population/outcomes tables. Status of radiotherapy at recurrence noted.

The technology/ intervention	Brain Tumour UK	*[Is the description of the technology or technologies accurate?]* Yes	-
	SBNS	[1.] The description of the technology is basically correct but it should be emphasised that it is a surgical treatment with the Gliadel used as an adjunct to surgery to improve effects. The evidence from Brem, Westphal, and more recently from Rikken and others is that this technology is able to realise its effect best where maximal resection (80-90%) is possible. This means that there will inevitably be some degree of selection of patients to affect the best results. It also means that a number of patients will not be eligible for treatment. Recent estimates suggest this may be of the order of around about 20-30% of patients at recurrence. In addition, the surgeon must be able to achieve a watertight closure of the dural layer. 2. The technology is quite different to conventional chemotherapy in that once placed in the patient's intracranial environment does not require bone marrow monitoring or support as there is no evidence of impact on bone marrow from the treatment placed in the intracranial cavity.	1. Comments on adjunctive role of carmustine implants noted. Potential for selection of patients noted. Pathway of care for people with GBM has been expanded in the background; Intervention/population/ outcomes tables have been revised. 2. Noted.
	RCN	No comments	-
	DH	*[Is the description of the technology or technologies accurate?]* Yes	-

	Link Pharma.	<u>Paragraph One</u> It is not clear from the information provided that the implants release carmustine slowly over the period during which the implants dissolve. We would suggest that the third sentence "The wafers release carmustine directly to the tumour site and slowly dissolve over two to three weeks." be replaced with the following sentence: *Immediately from the time of surgery, the implants slowly dissolve over a period of more than three weeks during which time the active ingredient, carmustine, is released directly to the tumour site at high local concentrations.* The statement on the marketing authorisation should actually state the following: Carmustine implants have a UK marketing authorisation as an adjunct to surgery in patients with **recurrent** histologically proved GBM for whom surgical resection is indicated.	Added text: achieving high local concentrations. Added text: recurrent.
Population	Brain Tumour UK	The population should not be limited to patients with gbm histology. Other high grade glioma patients with operable disease may also benefit.	The marketing authorisation for carmustine implants for the treatment of recurrent disease is limited to glioblastoma multiforme. Guidance will only be issued in accordance with the marketing authorisation.
	SBNS	This Technology Appraisal is aimed at patients with recurrent glioblastoma multiforme. Unfortunately, most of the evidence related to the use of Gliadel in recurrent tumours is to patients with High Grade Glial tumours. If the Technology Appraisal only considers glioblastoma multiforme, it will then leave patients with anaplastic astrocytomas or similar high grade tumours in a limbo without formal definition of what they can receive in the way of treatment at recurrence. Therefore, this appraisal process should be expanded to include all patients with high grade glial tumours with specific subsets related to these pathological entities.	The marketing authorisation for carmustine implants for the treatment of recurrent disease is limited to glioblastoma multiforme. Guidance will only be issued in accordance with the marketing authorisation.

	RCN	It would be sensible to include all patients with high grade gliomas (WHO 3 and 4) who undergo surgery and not just limit this to grade 4 as the scope seems to suggest.	The marketing authorisation for carmustine implants for the treatment of recurrent disease is limited to glioblastoma multiforme. Guidance will only be issued in accordance with the marketing authorisation.
	DH	DH feel that it might be useful for NICE to speak with one of the cancer team advisors regarding this. See also comment under 'questions for consultation'.	The Institute arranged a discussion with the DH clinical expert.
	Link Pharma.	The population is appropriately defined. Please see "Other considerations" for examples of subgroups that it would be appropriate to consider.	Subgroups are described in the 'other considerations' section.
Comparators	Brain Tumour UK	As above, there is currently no standard treatment, but the outcome of BR12 and NICE guidance will inform this within the next 12 months.	Noted, however, BR12 does not consider carmustine implants and therefore it is not considered relevant to this appraisal.
	SBNS	This has now become a more complicated process with the Technology Appraisable for Carmustine and Temozolomide at first diagnosis due to report. If the current proposal for Temozolomide becomes the policy, then this would debar patients receiving Temozolomide at recurrence who have received it initially. The patients at recurrence then will be only able to receive PCV therapy and Gliadel will not, therefore, be a suitable comparative for PCV therapy in a chemosensitivity basis because both PCV and Gliadel contain the same active component Lomustine. It is apparent that a number of patients would be suitable for surgery to receive Gliadel and maybe those that couldn't could receive PCV. However, given this complicated situation it might be beneficial if the current Technology Appraisal was postponed until the results of the BR12 study became available at which point it would be possible to decide whether Temozolomide is a more effective treatment than PCV at recurrence. This would then redefine "best alternative care" in this context.	Comments noted. The BR12 trial does not consider carmustine implants and therefore it is not considered relevant to this appraisal.

	RCN	Presently (as far as one is aware) no standard treatment However, regarding first recurrence - most of patients, have had surgery (biopsy or craniotomy), radiotherapy and chemotherapy.	Noted. Noted.
	DH	No - DH medical advisors feel a better understanding of the current patient pathways is needed.	NICE has consulted with the DH clinical expert and considered the comments received from other Consultees during consultation and revised the scope.
	Link Pharma.	The comparators included are appropriate. However, the use of surgery plus temozolomide at first recurrence should be considered as a comparator as this drug is now widely used within the NHS for these patients.	Comparators have been amended following consultation with the DH clinical expert and after considering the comments received from other Consultees .
Outcomes	Brain Tumour UK	Use of progression free survival is problematic because of difficulties defining radiological versus clinical progression in this patient group. Radiology is commonly used, but incidence of progression is then heavily influenced by scanning interval	Noted. The outcomes section has been amended to include functional status.
	SBNS	Progression-free survival is a poor indicator of treatment in patients in whom the disease can wax and wane (see comments on recurrent above). A better measure might be to consider time spent above a threshold performance, e.g. Karnofsky of 60 or 70, as a fraction of total survival. This is a more pragmatic measure and much more workable in the context of patients in whom quality of life assessments are difficult to make.	Comments noted. The outcomes section has been amended to include functional status
	RCN	Unsure as, this may often depend on how individual units follow up methods for their patients.	-
	DH	*[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* Yes	Noted.

	Link Pharma.	The outcome measures suggested are appropriate. However, any results for progression free survival (PFS) which are based solely on radiological imaging should be interpreted with caution and results based on the development of symptoms would be more appropriate. PFS is used as an indicator of patient utility as this is the time when it is assumed that the patient develops symptoms, and therefore a decline in utility. In reality this is not always the case as, for patients with GBM who have had carmustine implants inserted, PFS based on radiological imaging may be confounded by oedema, necrosis and the presence of the implants themselves. Thus a measure of symptoms using functional (performance) status would be a better indicator of patient utility.	Noted. The outcomes section has been amended to include functional status
Economic analysis	Cancer Network Pharmacy Forum	Is it legitimate to include a personal social services perspective when the cost of the treatment will be borne entirely within tertiary care?	The NHS and personal social services perspective form the NICE reference case (See Methods for technology appraisal, section 5.3.1). Whilst it is acknowledged that the majority of costs of treatment are likely to be borne within tertiary care, the costs of some elements of treatment may be borne by social services.
	SBNS	In the current environment there are several new treatments likely to appear for the treatment of patients at recurrence over the next two to five years. For example, the use of Irinotecan or other similar drugs, the use of such compounds as Cerepro, Ark Therapeutics, the use of IL13 linked to a cell toxin (Precise/Neopharm) and other new pharmacological compounds which would need careful scoping. In addition to this is the possibility of using continuous Temozolomide which may have a benefit in a number of patients but have huge economic consideration.	Noted. A review date will be considered by the appraisal Committee (as for other NICE Guidance) and published in the guidance. Consideration of the use of continuous temozolomide is not within the scope of this STA.
	RCN	no comments	-

	DH	As long as the modelling is correct	The economic model developed by the manufacturer will be evaluated by the Evidence Review Group.
	Link Pharma.	As the median survival for recurrent GBM patients is approximately 6 months and 6-month survival is only 36% it is inappropriate to consider the economic analysis over a time horizon greater than 2 years.	Noted. The time horizon should capture all the main costs and benefits to patients.
Other considerations	SBNS	The Scoping Committee should consider the use of Temozolomide over a long-term period, e.g. greater than six months, for patients who show response but therapeutic dependence in terms of their disease on continuous use of this drug. Other issues should deal with whether the patients at recurrence are sensitive to treatment by virtue of their MGMT status.	The focus of this STA is carmustine implants rather than long term temozolomide is outside the scope of this STA. If evidence is provided on MGMT status, the Appraisal Committee may consider this.
	RCN	no comments	-
	Link Pharma.	The use of carmustine implants in subgroups of patients should be considered within the scope. Examples of appropriate subgroups include: ▪ Performance status ▪ Extent of resection	The STA submission template requires that the manufacturers provide information on the make-up of the patient population included in their submission – where possible. The appraisal will consider the use of the treatments for subgroups where these are clinically appropriate and appropriate evidence is available.

Questions for consultation	Brain Tumour UK	There is currently no evidence base to support the use of re-irradiation at relapse, and this question seems beyond the scope of this consultation.	Noted.
	SBNS	1. Definition of recurrence. 2. Appropriate models for patients with recurrent disease. 3. Other measures other than quality of life likely to be more indicative of a successful treatment. 4. Prolonged use of Temozolomide in this situation. 5. Appropriate context in which new treatments could be developed against existing comparators.	See responses to specific comments above.
	RCN	There is presently no role for re-irradiation for patients with recurrent GBM. At present if patients are chemotherapy naïve they would be considered for the BR12 study (see above) and if not suitable for this, PCV will be discussed. Occasionally if the patient is symptomatic and surgery may be beneficial this may be considered (although this often depends on patient's performance status)	Noted. Repeat radiotherapy is not included in the final scope. Description of pathway of care has been revised.
	DH	Would you consider whether you would benefit from an informal discussion with an experienced neuro-oncologist who could brief you on the pathways patients follow? [Contact details removed by NICE]	NICE has consulted with the DH (neuro-oncology) expert and revised the scope accordingly.

	Link Pharma.	What is the role of radiotherapy in the treatment of recurrent GBM? *Radiotherapy has little role in the treatment of recurrent GBM. The vast majority of patients will have received radiotherapy as part of their standard care at the time of first diagnosis. A repeat course of radiotherapy at the time of recurrence is not usually possible, as the maximum cumulative dose will already have been administered.* *Are the comparators listed in the scope appropriate?* As indicated in the section on *Comparators*, the use of temozolomide at the time of first recurrence has become increasingly common in England and Wales. Consequently this should be considered as a valid comparator in combination with surgery. A standardised therapy pathway is not established for the treatment of recurrent GBM…….. Although a standard treatment pathway has not yet been established for the treatment of recurrent GBM, a number of therapies are commonly used. Where the tumour is resectable, surgery is indicated and carmustine implants are already used at this point if the patient is suitable. Several centres include carmustine implants in their treatment protocols for recurrent GBM. Similarly, sales figures would indicate that temozolomide is commonly being given at the time of first recurrence although this is outside the current NICE guidance.	Noted. Repeat radiotherapy is not included in final scope. The intervention/ population/outcomes tables and description of pathway of care have been revised. Noted that a variety of therapies may be used. Description of pathway of care has been revised.

Additional comments on the draft scope.	Brain Tumour UK	When relevant and important information is still awaited, it is surely premature to consider this guideline until the BR 12 (Phase III study) is complete. Also it is premature to consider this guideline until the previous one is complete.	The BR12 trial focuses on the use of PCV or temozolomide in the treatment of recurrent glioma and may not report for some time. Whilst noting the importance of the BR12 trial, it does not include carmustine implants and is therefore not considered relevant to this appraisal.
	SBNS	I draw attention to the fact that the study BR12 which looks at a comparison between the use of Temozolomide and PCV at recurrence has yet to receive full recruitment. This would make a huge impact on what was the appropriate treatment to use in patients at recurrence. In addition to this, the fact that the use of Temozolomide and Gliadel at first diagnosis has not yet been resolved will make further progression of this Technology Appraisal extremely difficult.	Whilst noting the importance of the BR12 trial, it does not include carmustine implants and is therefore not considered relevant to this appraisal.
	RCN	No comments	-
	DH	None	-
	Link Pharma.		

Comment 2: provisional matrix of consultees and commentators

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Comment 3: Regulatory issues

Section	Consultees	Comments	Action
Remit			

Section	Consultees	Comments	Action
Current or proposed marketing authorisation		**What are the current indications for the technology?** Treatment of newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation. For use as an adjunct to surgery in patients with recurrent histologically proved glioblastoma multiforme for whom surgical resection is indicated. **What are the planned indications for the technology?** No new indications are planned.	No action.

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

Brain Tumour Trust
Cancer Backup
Welsh Assembly Government