Appendix E

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Health Technology Appraisal

Carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma

Comments received from Consultees and Commentators on the draft scope

Consultee Name	Comment	TL suggested action
APPRAISAL OBJECTIVE – EXTENSION TO AA (GRADE III GLIOMA)		
Professor Michael Brada Institute of Cancer Research	This is a well set out draft scope with appropriate appraisal objectives. In the management of patients with malignant glioma, the predominant tumour type, glioblastoma multiforme (GBM), is frequently considered alongside the less frequent anaplastic astrocytoma (AA – WHO grade III glioma). The appraisal objective aims only at glioblastoma multiforme. While this is reasonable, the trial testing the efficacy of carmustine implants has included both tumour types and the wider clinical community tends to consider treatment for AA by analogy with results in GBM. May I therefore suggest that you add to the appraisal objectives something like "consider the implications of the appraisal for the treatment of anaplastic astrocytoma".	The scope has been amended so that the appraisal will consider high grade gliomas; however recommendations regarding temozolomide will only apply to patients with GBM in line with its anticipated marketing authorisation.
Tenovus	No.23 guidance covers other malignant gliomas WHO III, IV and transformed II) but this draft scope is limited to glioblastoma multiforme. This will therefore be leaving unanswered questions about the appropriate treatment for other newly diagnosed brain tumours under the malignant umbrella. Can this be addressed or is this not possible due to the extent of UK approval of Gliadel?	The scope has been amended to include other high grade gliomas (see above).
PenTAG	The scope is concerned with "newly diagnosed GBM", however the license indication is for newly diagnosed high grade glioma. Could this be clarified? For example are grade 3 tumours considered to be "high grade"? What about tumour types other than	See above.

	astrocytoma?	
Link Pharma	The draft scope as it is currently proposed only covers the use of carmustine implants for the treatment of newly diagnosed glioblastoma multiforme (grade IV glioma), which is not congruent with either the current UK licence or the associated clinical trial data. Link Pharmaceuticals therefore believes that this scope is too restrictive and would suggest that it be expanded to include the use of carmustine implants in newly diagnosed patients with high-grade (grade III and IV) malignant gliomas. A suggestion for the title of this widened scope is: **Carmustine implants for the treatment of newly diagnosed malignant glioma and temozolomide for the treatment of newly diagnosed glioblastoma multiforme.** The reasons that we feel that this is important are as follows: **1. Licensed Indication** Carmustine Implant was granted an extended indication in September 2004 for use in patients with newly diagnosed high-grade malignant gliomas as an adjunct to surgery and radiotherapy. NICE has stated that interventions will be appraised according to their licensed or anticipated indications. The expanded scope would therefore include all patients covered by the licensed indication for carmustine implants, i.e. all patients with grade III and IV malignant gliomas and not just the glioblastoma multiforme sub-group. **2. Disadvantageous to a group of patients in whom benefit has been demonstrated** The benefit of carmustine implants has been demonstrated in a large, randomised, double-blind, placebo-controlled, multicentre, phase III study that recruited patients with both grade III and IV gliomas. If the scope is restricted to only glioblastoma multiforme (grade IV tumours), it will exclude a group of patients in whom there is proven benefit. Expanding the scope, as we have suggested, to cover the licensed indications does not exclude glioblastoma multiforme patients, but does extend the	See above.

	appraisal to all patients for whom a benefit with carmustine implants has been shown. **3. Difficulty of implementation at a local level** If guidance for carmustine implants was issued according to the draft scope, consultant neurosurgeons would have great difficulty in local implementation. This is because, in the majority of neurosurgical units, it is not possible to make an intra-operative histological differentiation between glioblastoma multiforme and grade III tumours. However, it is possible to make a diagnosis of high-grade malignant glioma at the time of resection. Therefore expanding the scope, as we have suggested, will ensure that any guidance issued can be implemented locally with the histopathological services currently available.	
Schering-Plough	We have reviewed the scope for the NICE appraisal: Carmustine implants and temozolomide for the treatment of newly diagnosed glioblastoma multiforme and agree with the main contents. However we would like to make the following minor points of clarification, particularly around the wording for the indications of temozolomide described under "The technology". **Appraisal Objective** Insert the phrase "and for temozolomide concomitantly with radiotherapy and then as adjuvant treatment after radiotherapy." so it would read as; ".....(GBM) as an adjunct to surgery and radiation and for temozolomide, concomitantly with radiotherapy and then as adjuvant treatment after radiotherapy.", and to provide....."	The scope currently reads 'as adjunct to surgery **and** radiation' as indicated in the remit. This implies that the appraisal will consider TMZ given after radiotherapy. No change necessary.
BACKGROUND		
Douglas Guerroro Royal College of Nursing	Page 1 Section: Background Paragraph 3 Line 3. Reads 'Complete surgical resection of these tumours is difficult, and patients with malignant glioma etc' - it would be more accurate to say 'complete surgical resection of these tumours is difficult, and SOME patients with malignant glioma etc'. Presently not all patients with malignant gliomas undergo more than one surgical procedure.	Amended. Added word 'some' and removed word 'usually'.

TECHNOLOGY		
Schering-Plough	The license information for temozolomide should be amended; ".....concomitantly with radiotherapy and then as adjuvant treatment after radiotherapy." The proposed wording for the license extension for temozolomide is detailed below; Temodal capsules are indicated for the treatment of patients with - newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as adjuvant treatment - malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy The proposed dosing regimen is 42 days consecutive treatment during the 6 week radiotherapy phase, followed by 5 days of treatment in 28-day cycles.	Amended.
INTERVENTION		
Schering-Plough	Please refer to our previous wording in 'Appraisal Objective'	Amended to read “Both are used as adjuncts to surgery and/or radiotherapy”
POPULATION		
Schering-Plough	This should include patients who do not have surgery but for whom radiotherapy is indicated "Adults with newly diagnosed GBM for whom surgery and/or radiotherapy is indicated."	No change. The scope is in line with the remit, which states that TMZ should be appraised as an adjunct to surgery and radiation.
Douglas Guerroro Royal College	Page 2 Section: Population. 'Adults with newly diagnosed GBM for whom surgery is indicated' - It would help if the type of surgery is specified e.g. partial tumour resection or complete tumour resection. Biopsy although a type of surgical intervention would not allow for the procedure to be undertaken but would in some	No change. All types of surgery are included in the appraisal, although we recognise that carmustine implants will only be appropriate if

of Nursing	situations indicate further surgery pending final histology.	the extent of surgery has been adequate. It is noted in the 'Other Considerations' section that the data will be analysed by subgroups defined according to the type of surgery if the evidence allows.
SDRT	We are concerned about your phrase 'Adults with newly diagnosed GBM for whom surgery is indicated' Patients in the Temozolomide study did not all have surgery (beyond a biopsy that is). Whilst in the subpopulation analysis it was the operated group who did best, and recommendations might come out in favour of restricting a drug in this group, never the less we think the whole population who might potentially benefit should be examined. That is patients who have a biopsy proven diagnosis of GBM. For Gliadel of course it is only operated patients because that is how it is given.	The definition of the population is in line with the remit, which states that the technologies must be given as adjunct to surgery and radiation. However, as noted in the other considerations section, if the evidence allows the appraisal will consider subgroups according to the extent of surgery received. No change
COMPARATORS		
Professor Michael Brada Institute of Cancer Research	These are appropriate. While the two interventions have not been compared head to head, it would be of value to attempt some comparison.	No action necessary.
Dr Rodney Burnham Royal College of Physicians	The only appropriate comparator is with the standard UK treatment, ie surgery and radiotherapy alone. PCV or chemotherapy, other than temozolomide, are not given concomitantly with radiotherapy in the UK. The major US study that supports concomitant temozolomide and radiotherapy in glioblastoma compared these treatments with surgery and radiotherapy.	If there is evidence that relates to surgery and radiotherapy combined with other antineoplastic agents other than TMZ, this should also be included in the appraisal. No change.
Schering-	Surgery alone or radiotherapy alone would be appropriate comparators as the trials for carmustine implants and temozolomide ran against one or other comparators but	The comparators are in line with the remit which is to appraise the

Plough	not both - for carmustine implants the comparator was surgery and for temozolomide the comparator was radiotherapy	technologies as adjunct to surgery and radiation. The evidence base includes trials in patients who had received surgery and were eligible for radiotherapy. No change.
SDRT	In the 'comparators' then you could compare: • Radiotherapy alone • Surgery and radiotherapy alone • Surgery, radiotherapy combined with ……	The remit states that the technologies must be given as adjunct to surgery and radiation. No change.
PenTAG	Can the comparators also be clarified. They are too open-ended as they are and could result in a large number of potential comparators some of which may not be relevant to the UK.	If there is evidence that relates to surgery and radiotherapy combined with other antineoplastic agents other than TMZ, this should also be included in the appraisal. No change.
OUTCOMES		
Schering-Plough	- survival; the importance of long-term survival should be made explicit. Consideration should also be given to the variation in prognosis between the different trial populations - Progression free survival; clarification is required on how progression is defined in the two trials - Adverse events - Health-related quality of life	The trial data will be evaluated during the course of the appraisal. The aim of the scope is not to evaluate the data. No change.
SDRT	When you say 'survival' we presume you mean a variety of survival measures: mean, median, 1, 2, 3 year etc.	The type of survival measures will depend upon the evidence available and are not usually defined in the scope. No change.

OTHER CONSIDERATIONS		
Professor Michael Brada Institute of Cancer Research	It would be of value if the appraisal were to recommend further research strategy in relation to the two methods of treatment. This would be particularly appropriate when the relative worth of the two techniques are to be compared.	The Committee will consider requirements from future research and make recommendations as appropriate. No change.
Link Phama	Please note, that in the "Other Considerations" section, it states that the manufacturers of both technologies currently have a licence application pending for the treatment of newly diagnosed high-grade malignant glioma. The wording of this section should be amended to reflect the current position that carmustine implants are already licensed for this extended indication.	Amended.
	In other 'considerations' no 4 beginning 'the manufacturers….' You talk about high grade glioma (HGG), however in the population you talk only about GBM. It concerns us that even here you are not clear in your minds what you are looking at. All GBM are HGG but not all HGG are GBM.	The scope has been amended so that the appraisal will consider high grade gliomas, however recommendations regarding temozolomide will only apply to patients with GBM in line with its anticipated marketing authorisation.
SDRT	In 'Other considerations' you may like to consider 'Flexibility of Treatment' by which we mean: • Applicability to resectable and non-resectable patients. • Ability of the patient to decide post biopsy they wish adjuvant treatment. • Ability to abandon treatment part through (if appropriate) with cost savings. • Choose treatment base on pathology or molecular biology.	We welcome information from patient groups in their submissions regarding patients' experiences and preferences towards the technologies of interest (for example, if patients have wished to abandon treatment part through but have been unable to do so). However, this level of detail is not usually provided within the scope. No change.

Schering-Plough	a.. The appraisal should require presentation of data from sub-groups - we suggest the following parameters to define these sub-groups · type of resection/surgery · Histology, ie, GBM vs. non-GBM b.. The data on 2-year survival for patients within the temozolomide trial are achieved despite the relatively poor prognosis of this patient population when compared with that of the carmustine implant trial population. Any comparison between these technologies should take account of the difference in baseline characteristics of the trial populations c.. Where data exists in this area on the treatment of children, this should be incorporated into the review	a. The scope states that subgroups will be considered if the evidence allows. The Assessment Group's protocol will define the subgroups to be considered. b. The trial data will be evaluated during the course of the appraisal. The aim of the scope is not to evaluate the data. c. If data for children are available, this will be considered within the appraisal. The population has been amended to read 'people'.
SDRT	1. Temozolomide is currently authorised for the use nationally for patients with relapsed glioblastoma multiforme and grade 3 gliomas. This is a very restrictive guidance for this drug in a disease where no chemotherapy is really of proven benefit. This very restrictive guidance is limiting the availability of this drug to patients beyond its specific indications according to the NICE guidance which is not compatible with its use in other first world countries. UK patients, therefore, are being denied access by the NICE guidance to Temozolomide in its expanding role in gliomas in adults and children. 2. Temozolomide has also been shown in phase II trails to be highly effective in low grade gliomas. This high response rate requires further investigation through phase III trials but is supportive of Temozolomide being available beyond the specific relapse indications that are currently in force. 3. The selection of patients suitable for chemotherapy with high grade glioma would be massively enhanced if there was a system of being able to detect 1p and 19q deletion abnormalities in the chromosomal make-up of these tumours at diagnosis. Presently, there are a limited number of centres in the UK where such genetic tests of tumour tissue can be undertaken and as of autumn 2004, none of those centres felt that their testing system was of high	This appraisal will consider newly diagnosed disease. A review of the existing Guidance on recurrent disease is currently being considered. The anticipated UK marketing authorisation for TMZ is for newly diagnosed high grade gliomas. The Institute does not issue guidance outside of the licensed indications of technologies. Comments noted, but the appraisal will not alter the licensed indications of the technologies. The remits are to appraise and issue guidance regarding TMZ and carmustine implants, rather than the diagnostic tests described. However,

	enough quality to perform tests for other centres for governance reasons. This means that there is a postcode lottery for optimal assessment of tumours at diagnosis because of the lack of dissemination of this specific genetic technology for biological tumour assessment which links directly to their sensitivity to chemotherapy and therefore should be included within the scope of the NICE guidance currently circulating. 4. Carmustine implants, or Gliadel wafers, have been subjected to randomised control trials and shown to prolong survival. It is clearly very important that patients are given access to these devises as soon as possible as the current situation of no funding means that people are not being given the benefit of this potential prolonged survival through financial restrictions and licensing.	it is standard to consider issues around diagnosis within the appraisal. Comments noted. Comments noted.

Comments received from:
Institute of Cancer Research
Link Pharmaceuticals
PenTAG
Royal College of Nursing
Royal College of Physicians
Samantha Dickson Research Trust
Schering-Plough
Tenovus

Statements of 'no comment' received from:
Association of British Neurologists
Board of Community Health Councils in Wales
British National Formulary
Marie Curie
Royal College of General Practitioners
Royal College of Surgeons
Royal Pharmaceutical Society of GB & I
Society of British Neurological Surgeons