NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA23; Temozolomide for the treatment of recurrent malignant glioma, and TA121; Carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma

These pieces of guidance were issued in April 2001 (TA23) and June 2007 (TA121).

The review date for both pieces of guidance is 2015.

1. Recommendation

TA23

Recommendation 1.1 of TA23 should be changed to reflect current conventions and the guidance should be transferred to the 'static guidance list'. The existing recommendations 1.2 and 1.3 should be withdrawn because they were superseded by TA121, which considered the use of temozolomide in newly-diagnosed malignant glioma.

The updated wording for TA23 will read as follows:

1.1 Temozolomide is recommended as an option for treating malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy only if the patient has Karnofsky performance status greater than or equal to 70 and a projected life expectancy of 12 weeks or more.

1.2 When using Karnofsky performance-status score, clinicians should be mindful of the need to secure equality of access to treatment for patients with disabilities. Clinicians should bear in mind that people with disabilities may have difficulties with activities of daily living that are unrelated to their prognosis with respect malignant glioma. In such cases clinicians should make appropriate judgements of performance status taking into account the person's usual functional capacity and requirement for assistance with activities of daily living.

TA121

TA121 should be placed on the static list.

That we consult on these proposals.

2. Original remit(s)

TA23

Clinical and cost effectiveness of temozolomide for brain cancer.

TA121

To appraise the clinical and cost effectiveness of carmustine implants for the treatment of recurrent glioblastoma multiforme (GBM) and newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation and to appraise the clinical and cost effectiveness of temozolomide within its licensed indications for glioblastoma multiforme (GBM) as an adjunct to surgery and radiation.

3. Current guidance

TA23

1.1 Patients with recurrent malignant glioma (brain cancer) who have failed first-line chemotherapy treatment with other agents (either because of lack of efficacy or because of side effects) may be considered for treatment with temozolomide. Such patients must have a histologically proven malignant glioma (WHO grades III and IV, or transformed grade II) at first relapse, recurrence or progression (as assessed by imaging), Karnofsky performance status greater than or equal to 70 and a projected life expectancy of 12 weeks or more, at initiation of temozolomide treatment. (See Appendix D for definition of Karnofsky status and Appendix E for definition of WHO tumour grading).

1.2 Temozolomide is not recommended for first-line chemotherapy treatment for patients with malignant glioma who have failed primary therapy (surgery and/or radiotherapy), except in the context of a randomised controlled trial against a standard-treatment comparator.

1.3 As temozolomide is not currently licensed for adjuvant chemotherapy treatment of malignant glioma, its use in this indication has not been considered in this appraisal.

TA121

Temozolomide and carmustine implants have been appraised separately for the treatment of newly diagnosed high-grade glioma. On the basis of the evidence presented to the Committee, no recommendation can be made regarding the sequential use of these treatments for newly diagnosed high-grade glioma.

1.1 Temozolomide, within its licensed indications, is recommended as an option for the treatment of newly diagnosed glioblastoma multiforme (GBM) in patients with a World Health Organization (WHO) performance status of 0 or 1.

1.2 Carmustine implants, within their licensed indications, are recommended as an option for the treatment of newly diagnosed high-grade glioma only for patients in whom 90% or more of the tumour has been resected.

1.3 Treatment with carmustine implants should be provided only within specialist centres that in general conform to guidance in ‘Improving outcomes for people with brain and other central nervous system tumours’ (NICE cancer service guidance 2006; www.nice.org.uk/csgbraincns), and should be supervised by

specialist neurosurgeons who spend at least 50% of their clinical programmed activities in neuro-oncological surgery. The specialists should also have access to:

- multidisciplinary teams to enable preoperative identification of patients in whom maximal resection is likely to be achievable
- magnetic resonance imaging (MRI) to enable preoperative identification of patients in whom maximal resection is likely to be possible, and
- image-directed technology, such as neuronavigation, for use intraoperatively to assist the achievement of maximal resection.

1.4 Carmustine implants are not recommended for the treatment of newly diagnosed high-grade glioma for patients in whom less than 90% of the tumour has been resected.

4. Rationale[1]

TA23

It is expected that, since temozolomide is recommended as a first line treatment in TA121, only a small number of patients would have treatment with temozolomide for recurrent disease as recommended in TA23. Therefore, although there is new evidence available, it is expected that the number of people having temozolomide at recurrence would be too small to warrant a review of the guidance.

The wording of recommendation 1.1 should be changed to reflect current conventions.

Recommendations 1.2 and 1.3 were outside the scope of the original appraisal and have been superseded by TA121 and should be withdrawn.

TA121

There is no new evidence to change the recommendations in TA121. TA 121 should be moved to the static list.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

6. New evidence

The search strategy from the original Assessment report (for MTAs) was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from July 2010 onwards were reviewed. Additional searches of clinical trials registries and

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

When the appraisal of temozolomide for the treatment of recurrent malignant glioma (TA23) was conducted, temozolomide was indicated for the treatment of patients showing recurrence or progression with standard therapy. At that time, there had been only 1 randomised controlled trial comparing temozolomide with procarbazine alone in patients with recurrent glioblastoma multiforme (GBM; 1 of 3 forms of malignant gliomas). There had been no trials of temozolomide in anaplastic astrocytoma (AA; another of the 3 forms of malignant gliomas). Based on the evidence available at the time, TA23 recommends temozolomide as an option for second-line treatment of patients with recurrent malignant glioma (and further disease-specific criteria; see recommendation 1.1). It does not recommend temozolomide as an option as first-line chemotherapy after surgery/radiotherapy, except in the context of a clinical trial (see recommendation 1.2), but it appears that first-line use was outside the marketing authorisation at the time (the marketing authorisation was not extended to first-line use until September 2005). As temozolomide was not licensed for adjuvant chemotherapy treatment of malignant glioma, its use in this indication was not considered in the original appraisal (see recommendation 1.3).

When the appraisal of carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma (TA121) was carried out, the marketing authorisation for carmustine implants was for the treatment of newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation, and for the treatment of recurrent GBM as an adjunct to surgery. At the time of publication of TA121, the indication for temozolomide had expanded to include treatment of newly diagnosed GBM concomitantly with radiotherapy, and subsequently as monotherapy treatment. Based on the evidence available at the time, TA121 recommends temozolomide as an option for the treatment of newly diagnosed GBM in patients with a World Health Organization (WHO) performance status of 0 or 1 (see recommendation 1.1) superseding recommendation 1.2 and 1.3 in TA23. Carmustine implants are also recommended as an option for the treatment of newly diagnosed high-grade glioma only for patients in whom 90% or more of the tumour has been resected (see recommendation 1.2) but not recommended if less than 90% of the tumour has been resected (see recommendation 1.4). Carmustine implants were recommended only under specific criteria (see recommendation 1.3).

Generic formulations of temozolomide have become available since publication of TA23 and TA121. The marketing authorisation and the acquisition cost for carmustine implants have remained unchanged.

In 2010, a decision to review TA121 was deferred until 2015 until the results from a number of relevant trials were reported. TA23 was considered for review in 2004 and 2011 when it was decided to defer the decision to review until 2015 so that the decision was taken alongside to review TA121 so that the option to combine the review of the 2 appraisals could be considered.

Newly-diagnosed high grade glioma (TA121)

At the time of the publication of TA121, no evidence on the sequential use of temozolomide and carmustine implants was identified. To date no randomised clinical trial has been identified investigating this. Dixit et al. 2011 noted in its review that few prospective and retrospective studies have been published reporting on the sequential use of carmustine implants and temozolomide. Results seem to indicate extension in survival in comparison with the published results using carmustine implants or temozolomide regimen alone and complications seem to be manageable. The evidence highlighted in this review does not appear to be sufficient to warrant a review of TA121 and the sequential use of these treatments should be best determined in a clinical guideline.

No recommendations on the concurrent use of carmustine implants and temozolomide were made in TA121. There is some evidence on the combination of these treatments in people with newly-diagnosed high grade glioma (La Rocca and Mehdorn 2009; McGirt et al. 2010). The marketing authorisations for carmustine implants and temozolomide do not specifically cover the combination therapy. Therefore, the combined use of carmustine implants and temozolomide seems to fall outside the scope of this review.

Treatment with temozolomide

In 2013, Hart el al published a Cochrane systematic review on temozolomide for high grade glioma concluding that temozolomide is an effective primary treatment in GBM compared with radiotherapy alone when given in both concomitant and adjuvant phases, as it prolongs survival and delays progression. The authors also noted that temozolomide does not have an impact on quality of life and it does increase early adverse events. These results are in line with the conclusions in TA121. Observational studies carried out in the UK in people having adjuvant and concurrent temozolomide also concluded that results in clinical practice are comparable to those observed in the clinical trials (Hargreaves et al 2010; Haylock et al 2010; Rock et al 2012). In TA121, the Committee also noted that a trial was planned that will compare low-dose temozolomide with dose-intense temozolomide, and that this trial was expected to include stratification of patients by MGMT promoter methylation status (a predictive molecular marker). The Cochrane review presents the results of a trial investigating this (Clarke et al. 2009) noting that there was no statistically significantly difference in overall survival between treatment groups. Another trial comparing these different doses of temozolomide also found no statistically significant differences in efficacy but noted the significance of MGMT methylation as a prognostic factor in GMB (Gilbert et al. 2011). At the time of TA121, there was no evidence related to the use of the technologies (temozolomide or carmustine implants) in children, and the Committee considered that the evidence based on adults was likely to apply to children, however. the marketing authorisation for temozolomide for treating newly diagnosed GBM is currently only for adults.

Treatment with carmustine implants

In 2011, Hart el al published a Cochrane systematic review on chemotherapy wafers for high grade glioma. There were no new studies included in the review compared with those already included in TA121. The literature search identified 1 study

concluding on the benefits of carmustine implants in the preservation of neurocognitive function (Brem et al. 2013).

Recurrent malignant glioma

The research recommendations included in TA23 call for research into the effect of temozolomide on children and refer to usefulness of a planned trial of temozolomide in comparison with procarbazine, lomustine and vincristine in patients with GBM, AA and other malignant gliomas.

The Cochrane systematic review on temozolomide for high grade glioma (Hart et al 2013) concludes that in recurrent GBM, temozolomide compared with standard chemotherapy improves time-to-progression and may have benefits on quality of life without increasing adverse events but it does not improve overall survival. The review included 2 randomised controlled trials, Yung 2000 and Brada et al 2010, comparing temozolomide with procarbazine and with procarbazine, lomustine and vincristine respectively. The study from Yung was the basis of the evidence considered in TA23. Brada et al 2010 corresponds to the planned trial mentioned in the research recommendations included in TA23. The results showed that temozolomide did not demonstrate a clear benefit compared with procarbazine, lomustine and vincristine in people with different types of high grade gliomas. TA23 states that the cost per life year gained (and quality-adjusted life years gain) of temozolomide compared with procarbazine, lomustine and vincristine was unknown. Given the new evidence available, it seems now possible to estimate the cost effectiveness of temozolomide compared with procarbazine, lomustine and vincristine. However, it is expected that since the publication of TA121, most people have treatment with temozolomide when newly-diagnosed (i.e. as first line treatment) and therefore, the number of eligible patients who may have temozolomide at recurrence (i.e. as second line treatment) is expected to be too small to warrant a review of TA23 in light of the new evidence.

Conclusion

In summary, the new evidence available since the publication of TA121 seems to support the recommendations in the guidance. However, the wording of the guidance should be updated in line with the current wording of the marketing authorisation of temozolomide. Although there has been new evidence published since the publication of TA23, it is expected that the number of people having temozolomide at recurrence would be too small to warrant a review of the guidance given that as a result of TA121, most people have the option of having temozolomide as first line treatment. The wording of the recommendations in TA23 should be amended in line with current conventions and a note in the webpage of TA23 should be added stating that the recommendations in TA121 supersede recommendations 1.2 and 1.3 in TA23.

8. Implementation

A submission from Implementation is included in Appendix 3.

Temozolomide and carmustine implants are both predominantly used in the hospital setting. A reduction on estimated spend associated with these treatments is observed in 2013/14 compared with 2012/13.

Update data from published literature shows that 33% of the patients who are selected for maximal resection of the tumour have subsequent treatment with carmustine implants and that implementation of TA121 regarding carmustine implants is extremely variable in different multidisciplinary teams across the UK

9. Equality issues

No equalities issues were raised in TA23 and TA121. The review of TA23 carried out in 2011 states that recommendation 1.1 of TA23 refers to Karnofsky performance status. Karnofsky performance status relates to the person's level of functional impairment and their need for care and assistance. People with disabilities could have lower scores for reasons that are unrelated to their prognosis with respect to malignant glioma. For this reason more recent guidance that has referred to performance status has normally included a statement to the effect that clinicians should make appropriate judgements taking into account the person's usual functional capacity and requirement for assistance with activities of daily living.

GE paper sign off: Janet Robertson, 8 December 2015

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the [specify STA or MTA] process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	TA 121 should be transferred to the static guidance list. The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The wording of the guidance should be amended without the need for a full review, and the guidance should be re-issued.	TA 23 should be reworded as suggested in section 1 above and transferred to the static guidance list,	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise

- There is evidence of unjustified variation across the country in access to a treatment

- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Service guidance for improving outcomes for people with brain and other central nervous system tumours (2006) NICE guideline CSGBRAINCNS

Suspected cancer: recognition and referral (2015) NICE guideline 12

Brain Cancers (2015) NICE pathway

Suspected cancer: recognition and referral (2015) NICE pathway

Suspended/terminated

Carmustine implants for the treatment of recurrent glioblastoma multiforme (2008) NICE technology appraisal guidance 149

Bevacizumab for the treatment of recurrent glioblastoma. NICE technology appraisal guidance. Suspended

Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
TA23 Temozolomide (Temodal) is an alkylating agent derived from dacarbazine and first synthesised in 1984. It is indicated for the treatment of patients with malignant glioma showing recurrence or progression after standard therapy. The UK price of this drug was £1,176 per 5-day cycle for a daily dose of 340 mg for those who have not had prior chemotherapy, and £934 for those who have, where the dose is usually reduced by 25%. **TA121** Carmustine implants have a UK marketing authorisation for the treatment of newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation, and for the treatment of recurrent GBM as an adjunct to surgery. The cost of one carmustine implant was £650.38 (excluding VAT; 'British national formulary [BNF]' 52nd edition). Up to eight implants may be used simultaneously, depending on the shape and size of the resection cavity. Costs may vary in different settings because of negotiated procurement discounts. Temozolomide has a UK marketing authorisation for the treatment of newly diagnosed GBM concomitantly with radiotherapy, and subsequently as monotherapy treatment. It also has a UK marketing authorisation for the treatment of malignant glioma showing recurrence or progression after standard therapy. The cost of temozolomide was £17.30 for 5 x 5 mg tablets, £69.20 for 5 x 20 mg tablets, £346.00 for 5 x 100 mg tablets and £865.00 for 5 x 250 mg tablets (excluding VAT; BNF 52). Costs may vary in different settings because of negotiated procurement discounts.	**TA23** Temodal is indicated for the treatment of: children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy. Temodal (MSD) Capsules**,** temozolomide 5 mg, net price 5-cap pack = £10.59; 20 mg, 5-cap pack = £42.35; 100 mg 5-cap pack = £211.77; 140 mg (blue/white), 5-cap pack = £296.48; 180 mg (orange/white), 5-cap pack = £381.19; 250 mg (white), 5-cap pack = £529.43. Temozolomide (Non-proprietary) Capsules**,** temozolomide 5 mg, net price 5-cap pack = £16.00; 20 mg, 5-cap pack = £60.30; 100 mg, 5-cap pack = £320.80; 140 mg, 5-cap pack = £451.40; 180 mg, 5-cap pack = £580.37; 250 mg, 5-cap pack = £806.08. Brands include *Temomedac* **TA121** GLIADEL Implant is indicated in newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation. GLIADEL Implant is indicated for use as an adjunct to surgery in patients with recurrent histologically proved glioblastoma multiforme for whom surgical resection is indicated. Temodal is indicated for the treatment of: adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment. Gliadel (Archimedes) Implant**,** carmustine 7.7 mg, net price = £650.38 Temozolomide prices are listed above

Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Rindopepimut (Celldex Therapeutics Inc)	Phase III Clinical Trials Method of Administration: Intradermal [redacted]	Topic ID 7546 Rindopepimut with GM-CSF for Glioblastoma multiforme (GBM) Newly diagnosed glioblastoma multiforme expressing epidermal growth factor receptor variant III Status: Topic prioritised for potential technology appraisal guidance production
Paclitaxel poliglumex (CTI BioPharna)	Phase II Clinical Trials (with radiotherapy and temozolamide) Method of Administration: Intravenous [redacted]	Topic ID 7076 Status: Topic has been scoped
Bevacizumab (Roche)	Phase III Clinical Trials Method of Administration: Intravenous infusion [redacted]	Topic ID 8104 Bevacizumab as monotherapy or in combination with lomustine for glioblastoma – second line
Brain Cancer Vaccine (Northwest Biotherapeutics)	Phase III Clinical Trials Method of Administration: Intradermal [redacted]	Topic ID 3015 Glioblastoma multiforme (newly diagnosed) - DCVax-L

Nivolumab (Bristol-Myers Squibb)	Phase III Clinical Trials Method of Administration: Intravenous [redacted]	Topic ID 7887 Nivolumab; Medarex/Ono; BMS-936558; MDX-1106; ONO-4538; Opdivo for Recurrent glioblastoma (GBM); second line, monotherapy
ABT-414 (AbbVie)	Phase II Clinical Trials (multiforme, relapsed - second and subsequent line) Method of Administration: Intravenous Infusion [redacted]	-
Bevacizumab (Roche)	Phase III Clinical Trials (newly diagnosed - 1st-line (with temozolomide + radiation) Method of Administration: Intravenous [redacted]	-
ICT-107 (ImmunoCellular Therapeutics)	Phase III Clinical Trials (First-line therapy – vaccine) Method of Administration: Intradermal [redacted]	-
Monoclonal antibody TNT-1 (Peregrine Pharmaceuticals)	Phase II Clinical Trials Method of Administration: Intratumoural [redacted]	-

Olaptesed Pegol (Noxxon Pharma)	Phase II Clinical Trials (in conjunction with radiotherapy) Method of Administration: Intravenous [redacted]	-
VB-111 (VBL Therapeutics)	Phase II Clinical Trials (for recurrent glioblastoma multiforme) Method of Administration: Intravenous [redacted]	-
Vitespan (Agenus)	Phase II Clinical Trials (for newly diagnosed glioblastoma multiforme) Method of Administration: Intradermal [redacted]	-
Nivolumab (Oncoscience)	Phase III Clinical Trials (first-line therapy in children Method of Administration: Intravenous [redacted]	-

Registered and unpublished trials

Trial name and registration number	Details
Radiation Therapy Combined With Chemotherapy in Treating Patients With Anaplastic Astrocytoma or Mixed Gliomas Phase 3 NCT00004259	This randomized phase III trial is studying radiation therapy and temozolomide to see how well they work compared to radiation therapy and carmustine or lomustine in treating patients with anaplastic astrocytoma or mixed gliomas. Status: Active, not recruiting Enrollment: 230 Estimated Primary Completion date: March 2020
Vorinostat, Temozolomide, or Bevacizumab in Combination With Radiation Therapy Followed by Bevacizumab and Temozolomide in Young Patients With Newly Diagnosed High-Grade Glioma Phase 2/3 NCT01236560	A Randomized Phase II/III Study of Vorinostat and Local Irradiation OR Temozolomide and Local Irradiation OR Bevacizumab and Local Irradiation Followed by Maintenance Bevacizumab and Temozolomide in Children With Newly Diagnosed High-Grade Gliomas Status: Active, not recruiting Enrollment: 268 Estimated Primary Completion date: March 2019
A Phase III Trial on Adjuvant Temozolomide With or Without Interferon-alpha in Newly Diagnosed High-grade Gliomas Phase 3 NCT01765088	This study is being conducted to help determine whether the addition of Interferon-alpha(α-IFN),which were determined sensitized the activity of Temozolomide (TMZ) in vivo and vitro, when given along with Temozolomide during the monthly cycles that follow radiation, is able to delay tumor growth, shrink tumors, or impact how long people with newly diagnosed high-grade glioma. Status: Recruiting Estimated Enrollment: 300 Estimated Study Completion date: September 2015

Trial name and registration number	Details
Radiation Therapy With Concomitant and Adjuvant Temozolomide or Radiation Therapy With Adjuvant PCV or Temozolomide Alone in Treating Patients With Anaplastic Glioma Phase 3 NCT00887146	Status: Active, not recruiting Estimated Enrollment: 520 Estimated Primary Completion date: December 2018
Temozolomide and Radiation Therapy With or Without Bevacizumab in Treating Patients With Newly Diagnosed Glioblastoma Phase 3 NCT00884741	Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma Status: Active, not recruiting Enrollment: 978 Primary Completion date: March 2013
Temozolomide With or Without Veliparib in Treating Patients With Newly Diagnosed Glioblastoma Multiforme Phase 2 / Phase 3 NCT02152982	A Phase II/III Randomized Trial of Veliparib or Placebo in Combination With Adjuvant Temozolomide in Newly Diagnosed Glioblastoma With MGMT Promoter Hypermethylation Status: Recruiting Eestimated Enrollment: 440 Estimated Primary Completion date: June 2022
Efficacy and Safety Study of Lomustine/Temozolomide Combination Therapy vs. Standard Therapy for Glioblastoma Patients Phase 3 NCT01149109	Phase III Trial of CCNU/Temozolomide (TMZ) Combination Therapy vs. Standard TMZ Therapy for Newly Diagnosed MGMT-methylated Glioblastoma Patients Status: Active, not recruiting Enrollment: 128 Estimated Study Completion date: December 2015

Trial name and registration number	Details
Standard Temodal (Temozolomide) Regimen Versus Standard Regimen Plus Early Postsurgery Temodal for Newly Diagnosed Glioblastoma Multiforme (Study P05572) Phase 4 NCT00686725	Status: Completed, has Results Enrollment: 99 Study Completion date: September 2011
Radiation Therapy (RT) and Temozolomide (TMZ) in Treating Patients With Newly Diagnosed Glioblastoma or Gliosarcoma Phase 3 NCT00304031	Phase III Trial Comparing Conventional Adjuvant Temozolomide With Dose-Intensive Temozolomide in Patients With Newly Diagnosed Glioblastoma Status: Active, not recruiting, has Results Enrollment: 1173 Primary Completion date: February 2011
Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Methylated Gene Promoter Status Phase 3 NCT00689221	Status: Completed, has Results Enrollment: 545 Study Completion date: August 2013
Radiation Therapy With or Without Temozolomide in Treating Older Patients With Newly Diagnosed Glioblastoma Multiforme Phase 3 NCT00482677	Status: Active, not recruiting Enrollment: 562 Estimated Primary Completion date: March 2016
Phase III Study of Rindopepimut/GM-CSF in Patients With Newly Diagnosed Glioblastoma Phase 3 NCT01480479	Status: Active, not recruiting Estimated Enrollment: 700 Estimated Primary Completion date: November 2016

Trial name and registration number	Details
A Study of Avastin® (Bevacizumab) in Combination With Temozolomide and Radiotherapy in Patients With Newly Diagnosed Glioblastoma Phase 3 NCT00943826	Status: Completed, has Results Enrollment: 921 Study Completion date: September 2015
Supra-early Post-Surgery Chemotherapy in the Treatment on GBM Patients Phase 4 NCT02520635	A Clinical Study of Supra-early Post-Surgery Chemotherapy Plus Standard TEMODAL® Regimen Versus Standard TEMODAL® Regimen in the Treatment on Patients With Newly Diagnosed Glioblastoma Multiforme Status: Recruiting Estimated Enrollment: 100 Estimated Primary Completion date: December 2016
Phase III Study Comparing 2 Brain Conformational Radiotherapy in Combination With Chemotherapy in the Treatment of Glioblastoma Phase 3 NCT01507506	Phase III Randomized Study Comparing 2 Brain Conformational Radiotherapy in Combination With Chemotherapy in the Treatment of Glioblastoma : Standard 3D Conformational Radiotherapy Versus Intensity-modulated Radiotherapy With Simultaneous-integrated Boost Guided by Magnetic Resonance Spectroscopic Imaging Status: Recruiting Estimated Enrollment: 220 Estimated Primary Completion date: March 2016
Carmustine implant (Gliadel Wafer) plus adjuvant and concomitant Temozolomide in combination with radiotherapy in primary glioblastoma patients. EUCTR2008-003905-15-IT	Status: Ongoing

Relevant services covered by NHS England specialised commissioning
Specialised Services Commissioning Transition Team (2012) Manual for prescribed

specialised services

NHS England (2013) Neurosurgery (Adult)

NHS England (2013) Radiotherapy (All Ages)

NHS England (2013) Cancer Chemotherapy (Adult)

NHS England (2013) Cancer Chemotherapy (Children, Teenagers and Young Adults)

NHS England (2013) Cancer Brain and Central Nervous System (Adult)

Additional information

Medicines and Healthcare products Regulatory Agency (2014) Drug Safety Update: Temozolomide: risk of hepatic injury, including fatal hepatic failure—updated warnings and monitoring guidance

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La Rocca RV, Mehdorn HM. (2009) Localized BCNU chemotherapy and the multimodal management of malignant glioma. Current Medical Research and Opinion 25 (1):149–60

McGirt MJ, Than KD, Weingart JD, et al. (2009) Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. Journal of Neurosurgery 110 (3): 583–8

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Appendix 3 – Implementation submission

Routine healthcare activity data

This section presents data from the Hospital Prescribing data for 2013/14 (produced by the HSCIC). This is based on the IMS Hospital Pharmacy Audit Index (HPAI), and shows the estimated spend, and the trend in comparison to 2012/13.

Table 1: Estimated cost (£000's) in 2013/14

	Primary care		Hospital		Total	
	£000's	YOY change	£000's	YOY change	£000's	YOY change
Temozolomide	0.4	-89%	14,230	0%	14,230	0%
Carmustine implants			478	-45%	47%	-45%

As shown in table 1, both temozolomide and carmustine implants are predominantly used within a hospital setting. As a result, no relevant activity was available through the electronic prescribing analysis and cost tool (ePACT).

Uptake data from published literature

There is one uptake datapoint relating to TA121 recorded on the uptake database, dating from October 2010:

Recommendation: 1.2 Carmustine implants, within their licensed indications, are recommended as an option for the treatment of newly diagnosed high-grade glioma only for patients in whom 90% or more of the tumour has been resected.

Audit standard: Patients who were selected for maximal resection and who subsequently received carmustine wafers - 94/285 (33%)

Price, S. J. et al. (2012) NICE guidance on the use of carmustine wafers in high grade gliomas: a national study on variation of practice. British Journal of Neurosurgery. Vol 26 (3) pp 331-335

Healthcare activity data definitions

IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI)

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.