Brain Tumour Support NZ submission on Pharmac's proposal to widen access to temozolomide following the discontinuation of lomustine

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Declaration of interest

Brain Tumour Support NZ works with clinicians, researchers, allied health professionals, academia, government and industry to achieve better outcomes for New Zealand brain tumour patients and their families. We are writing to provide feedback on Pharmac's proposal to widen access to temozolomide to manage the impact from the discontinuation of lomustine in the New Zealand market. In doing so, we wish to highlight the significant impact that the unavailability of lomustine will have on people diagnosed with brain tumours in New Zealand.

Summary

Lomustine (CCNU) was first approved by the FDA to treat high-grade gliomas (a type of brain cancer) in 1976, however it remains an important part of the treatment landscape for brain tumours in New Zealand and worldwide. Depending on the type of brain tumour, it is an important first line treatment as a component of PCV (a chemotherapy combination), and as a second line treatment, either as monotherapy or in combination with bevacizumab (Avastin). It is also used in the control arm of many brain tumour clinical trials worldwide.

The importance of lomustine in brain cancer treatment in many ways reflects the dearth of efficacious treatments for brain cancer. Temozolomide (TMZ), another chemotherapy agent used to treat brain cancer, is not a suitable replacement for lomustine in all situations. Oncologists in Aotearoa New Zealand and overseas have limited options available to treat brain cancer patients, particularly when their tumour progresses or recurs. The discontinuation of lomustine will remove another tool from an already depleted toolbox and will leave recurrent brain cancer patients with no funded treatment options.

Brain Tumour Support NZ wishes to make the following recommendations.

1. We support widening access to TMZ so that it is funded for all people with gliomas without restrictions.
2. We recommend that Pharmac enters into further negotiation with Bristol Myers Squibb to delay the discontinuation of CEENU (lomustine) for as long as possible, or at least to June 2025.
3. We recommend that Pharmac makes every effort to source alternative supplies of lomustine so that it remains a funded treatment option for New Zealand brain tumour patients.
4. We recommend that Pharmac funds bevacizumab for people with recurrent high-grade gliomas.

Brain Cancer in New Zealand

- Each year, around 345 people will be diagnosed with brain cancer in New Zealand, and more than 250 will die from the disease. Brain tumours kill more children under 14 years of age than any other disease and more young people under 40 than any other cancer. Survival rates for brain cancer have barely improved in more than 30 years.
- Brain cancer is a high impact cancer which has a sudden and devastating effect on the patient and their loved ones. The symptom burden is high, and can include: severe headaches; nausea and vomiting; decline in cognitive function; physical weakness, fatigue and loss of mobility; changes in behaviour and personality; problems with speech, vision and hearing; and seizures.
- Adding to the clinical symptoms are major psychosocial effects. On top of the stress of the diagnosis, there is the immediate loss of independence (eg. losing the ability to drive), changes in the wider family dynamic (changing roles and relationships), changes in employment status, financial hardship, increased stress, anxiety and depression.
- Caregiver burden is a significant and often under-recognised factor for caregivers of brain tumour patients. Compared with other cancer groups (eg. lung, breast, and prostate), caregivers of patients with brain tumours, particularly GBM, report more severe caregiver burden and poorer health-related quality of life (HRQoL)[1].

Lomustine as first line treatment for grade 3 oligodendroglioma

- Brain cancer consists of several tumour types which are classified and graded under the WHO CNS grading system from 1 to 4.[2] Grade 1 and 2 tumours are classified as low-grade (non-malignant or benign) while grade 3 and 4 tumours are classified as high-grade (malignant or cancerous).
- Gliomas are a type of brain tumour which form in glial cells, the supporting cells of the brain and spinal cord. One type of glioma is Oligodendroglioma, IDH-mutant, 1p/19q co-deleted (grades 2, 3) which arises from oligodendrocytes (another type of glial cell). They are more common in young and middle-aged adults and more likely to occur in men.
- The standard first line treatment for high-grade (grade 3) oligodendroglioma, IDH-mutant, 1p/19q co-deleted is surgery, radiotherapy and adjuvant chemotherapy (PCV). PCV is a chemotherapy regime consisting of three agents - procarbazine, CCNU (lomustine) and vincristine.
- Two phase III clinical trials, EORTC 26951 and RTOG 9402, showed a clear survival benefit for radiotherapy and adjuvant PCV over radiotherapy alone. Long term follow up from these studies demonstrated that a sizeable proportion of patients with these tumours achieve long term survival with this treatment regimen.[3]

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[1] Boele FW, Heimans JJ, Aaronson NK, et al. Health-related quality of life of significant others of patients with malignant CNS versus non-CNS tumors: a comparative study. J Neurooncol. 2013;115(1):87–94. https://pubmed.ncbi.nlm.nih.gov/23824535/

[2] "The 2021 WHO Classification of Tumors of the Central Nervous System: a summary". Neuro-Oncology, Volume 23, Issue 8, August 2021, Pages 1231–1251, https://doi.org/10.1093/neuonc/noab106

[3] "Joint Final Report of EORTC 26951 and RTOG 9402: Phase III Trials With Procarbazine, Lomustine, and Vincristine Chemotherapy for Anaplastic Oligodendroglial Tumors." Journal of Clinical Oncology 2022 40:23, 2539-2545. https://pubmed.ncbi.nlm.nih.gov/35731991/

- NCCN guidelines also list radiotherapy with concurrent and adjuvant temozolomide (TMZ) as a treatment option for these patients, however the efficacy compared with radiotherapy and PCV has yet to be determined in randomised clinical trials.[4]
- PCV is a more toxic chemotherapy regimen than TMZ and it is not uncommon for the PCV protocol to be adjusted mid-cycle to account for toxicities. In New Zealand, PCV is prescribed by oncologists on the expectation that changes may be required following commencement of treatment, for example: dose alterations; removal of one or more of the drugs; or treatment holidays.
- Some patients will opt for the radiotherapy and TMZ regimen on the basis of its lower toxicity, and the assumption that it is equally efficacious as PCV. Although TMZ is currently not funded by Pharmac for this indication, TMZ is a generic drug which is affordable for some.

Lomustine as second line treatment for recurrent high-grade glioma

- The most common type of gliomas are astrocytomas, which account for nearly half of all primary brain tumours. Astrocytomas can develop in adults or children. High-grade astrocytomas include glioblastoma (a WHO grade 4 tumour, also referred to as glioblastoma IDH-wildtype or GBM), and astrocytoma, IDH-mutant (grades 2, 3, 4). Glioblastoma is the most aggressive adult primary brain tumour. It has a median overall survival of 15 months and a 5-year survival rate of around 6 percent (with standard treatments).
- The standard first line treatment for glioblastoma and astrocytoma IDH-mutant grades 3 and 4 is surgery, radiotherapy and chemotherapy (temozolomide, TMZ). However high-grade gliomas almost always recur, at which point the recommended treatment options according to NCCN guidelines include: temozolomide (TMZ), bevacizumab (Avastin), nitrosoureas, such as lomustine (CCNU) and carmustine (BCNU), or a combination of these.[5]
- In New Zealand, the most commonly prescribed funded treatment for recurrent high-grade glioma is lomustine (CCNU). As most patients have already received TMZ as the standard of care first line treatment, re-challenge with TMZ is usually not an option in this situation. In Europe and many other parts of the world, lomustine is the de facto standard of care for recurrent glioblastoma. It is also an important treatment in clinical trials where it is often used in the control arm of randomised clinical trials.[6]
- The most commonly prescribed non-funded treatment in New Zealand is bevacizumab (Avastin), with or without chemotherapy, including lomustine. Bevacizumab is funded in Australia for recurrent high-grade glioma but not in New Zealand, so is only available to those who can afford to pay for it.

[4] CODEL: phase III study of RT, RT + TMZ, or TMZ for newly diagnosed 1p/19q codeleted oligodendroglioma. Analysis from the initial study design. Neuro Oncol. 2021 Mar 25;23(3):457-467. doi: 10.1093/neuonc/noaa168

[5] NCCN Clinical Practice Guidelines in Oncology, Central Nervous System Cancers, Version 1.2023 — March 24, 2023. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

[6] "How did lomustine become standard of care in recurrent glioblastoma?" Cancer Treat Rev. 2020 Jul;87:102029. doi: 10.1016/j.ctrv.2020.102029

Widening the access to temozolomide

- Temozolomide (TMZ) is an alkylating agent which was first approved in 2009 as Temodar/Temodal (Merck Sharpe and Dohme). In 2006 it was funded by Pharmac under special authority for the treatment of newly diagnosed glioblastoma, concurrent with radiotherapy, and 6 cycles of adjuvant treatment.
- As one of the few chemotherapy agents which crosses the blood brain barrier, TMZ is now widely used to treat a variety of brain tumours, including WHO grade 2 and 3 tumours, as both first line (newly diagnosed) and second line (recurrent or progressive) treatments.
- TMZ is now off-patent and several generic brands are available at much lower cost than the original branded drug. Brain Tumour Support NZ believes that TMZ should be fully funded for all types of brain tumours, without restrictions on brain tumour type or duration of treatment.

Bevacizumab for recurrent high-grade glioma

- The choice of single agent lomustine or bevacizumab with or without chemotherapy often comes down to oncologists' personal preference and the ability of the patient to pay for bevacizumab. Some oncologists favour lomustine monotherapy as the drug is administered orally, is generally well tolerated, and requires only a consultation every six weeks, compared with bevacizumab which requires infusions every two to three weeks.
- Bevacizumab has shown in late stage clinical trials to extend progression free survival (PFS) and improve the quality of life of patients with recurrent glioblastoma.[7] [8] These studies were the basis for bevacizumab's accelerated approval by the FDA in 2009. Despite further confirmatory studies failing to show a survival benefit, bevacizumab subsequently achieved full FDA approval in 2017, based on its ability to extend PFS and reduce dependence on steroids, which is an important consideration for patients.[9]
- The combination of bevacizumab and lomustine was also shown to prolong PFS in the phase III clinical trial EORTC 26101.[10]
- Oncologists in New Zealand who regularly prescribe bevacizumab for recurrent high-grade glioma report significant and immediate improvements in the patient's quality of life, often resulting them being able to resume working, exercising and enjoying a generally good quality of life while on treatment.
- The steroid-sparing effects of bevacizumab are also important to brain tumour patients. People taking high dose steroids for symptom control can result in significant side effects, including high blood pressure; weight gain; unstable blood sugar levels; diabetes; muscle weakness; and loss of bone density (osteoporosis). Corticosteroids are also highly immunosuppressive which increases

[7] "Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma". J Clin Oncol. 2009 Oct 1;27(28):4733-40. doi: 10.1200/JCO.2008.19.8721.

[8] "Bevacizumab plus irinotecan in recurrent glioblastoma multiforme." J Clin Oncol. 2007 Oct 20;25(30):4722-9. doi: 10.1200/JCO.2007.12.2440.

[9] https://www.gene.com/media/press-releases/14695/2017-12-05/fda-grants-genentechs-avastin-full-appro

[10] "Lomustine and Bevacizumab in Progressive Glioblastoma." N Engl J Med 2017; 377:1954-1963. DOI: 10.1056/NEJMoa1707358

the risk of infections and may interferes with therapies which require a robust immune system, including many immunotherapies.

- In Australia, bevacizumab is available on the PBS as an unrestricted benefit, meaning that all patients needing this medicine have unrestricted access to it.

Brain Tumour Support NZ Recommendations

The discontinuation of lomustine will remove a safe and efficacious treatment from the oncologist's already limited armamentarium of treatments for brain cancer patients in Aotearoa New Zealand.

It will result in the disastrous situation of high-grade glioma patients not having a viable, funded treatment option when their tumours recur or progress.

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Brain Tumour Support NZ appreciates the opportunity to provide feedback on your proposal and we hope you will consider the points and recommendations made in this submission.

Chris Tse
Chair, Brain Tumour Support NZ