I.9	Cancer medicines for children – new indication of low-grade glioma
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Low grade glioma (LGG) are the most frequent paediatric brain tumors and account for around 40% of all CNS tumors. The clinical course of LGG very heterogeneous and is not always predictable at diagnosis. Some LGG are incidental findings on brain imaging, do not grow or only slowly and do not need any treatment. Other types of LGG present with symptoms of increased intracranial pressure and can be life threatening. Some LGG do not need treatment but are followed up to see the clinical course, other types need neurosurgery or chemotherapy only, and other types need a combination of chemotherapy and radiotherapy. Taking all types and manifestations of LGG into account, the survival is very good – but can be associated with high morbidity.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	All drugs used in the treatment of LGG are part of standard of care treatment protocols (SIOP-LGG-2004, vinblastine monotherapy), and already included on the EMLc for other indications.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). SIOP-LGG 2004 trial – 3 arms: observation, chemotherapy, radiotherapy. Standard arm induction chemotherapy: vincristine + carboplatin: OS and EFS very good: The overall survival (OS) of the whole cohort was 0.95 (±0.02) at 5 years but the 5-year event-free survival (EFS) was 0.40 (±0.05). For those 39 patients treated with chemotherapy, either directly after surgery (12/39) or in case of progression or relapse (27/39), the picture is very similar: 5-year OS of 0.89 ±0.05 and 5-year PFS of 0.42 ±0.08. Vinblastine monotherapy, first- and second-line approach. Phase II trials. Demonstrated improvements for PFS and OS in both settings. Vinblastine as primary treatment, overall survival at five years follow-up was 94.4% and progression free

	survival (PFS) 53.2%, where 7 patients progressed on therapy. Patients with NF1 had a significantly better PFS of 85.1% compared with patients without NF1 (42.0%). Treatment time to best response was 52 weeks. Forty-seven of 54 evaluated children experienced a complete, partial, or minor response or stable disease. Vinblastine was reduced primarily because of hematological toxicity. In 17 children to 5 mg/m2, and in 16 children to 4 mg/m2. 13 children tolerated the planed 6 mg/m2. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Vinblastine was reduced primarily because of hematological toxicity.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The evidence presented is not from randomized controlled trials, but that the treatment protocols are associated with relevant benefits and are recognized as the standard of care for treatment of paediatric LGG and this show a favourable overall benefit to risk ratio of Carboplatin, cisplatin, cyclophosphamide, vinblastine, and vincristine for LGG.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Carboplatin, cisplatin, cyclophosphamide, vinblastine, and vincristine are standard of care and essential in the treatment of LGG in children and adolescents. These compounds are already included in the WHO EMLc 2019 for other indications. Therefore these drugs have high overall quality of evidence.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments:
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: All drugs are on the WHO EMLc for another disease and therefore a specific search for evidence was not performed.

Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	All drugs used in the treatment of LGG and included in this application are part of "standard of care" treatment protocols. Therefore their benefits have to outweigh the harms and toxicities. In addition, all drugs are on the WHO EMLc for another disease and therefore a specific search for evidence was not performed.
Any additional comments	
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	The evidence presented, the expansion the listings on the EMLc for carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine to include the indication of low-grade glioma, is not from randomized controlled trials, but that the treatment protocols are associated with relevant benefits and are recognized as the standard of care for treatment of paediatric LGG and this supports their inclusion on the EMLc. Expanding the EMLc indications for these medicines would also support the goals of WHO Global Paediatric Cancer initiative and contribute towards the achievement of the best possible cancer care for children. The availability of clinical evidence in the paediatric context is limited but considered that obtaining the usual level of evidence required for EML listings was unlikely. In this case, efficacy and safety could be accepted based on of extrapolation of the well-known benefits and harms from use of these medicines in adults, for other indications in children, and as part of standard cancer care in children.
References (if required)	Boesten T, Gerber NU, Kandels D, Azizi AA, Schmidt R, Warmuth-Metz M, et al. Management of primary thalamic low-grade glioma in pediatric patients: results of the multicenter treatment studies HIT-LGG 1996 and SIOP-LGG 2004. Neuro-oncology practice. 2017;4(1):29-39. Bouffet E, Jakacki R, Goldman S, Hargrave D, Hawkins C, Shroff M, et al. Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(12):1358-63. Lassaletta A, Scheinemann K, Zelcer SM, Hukin J, Wilson BA, Jabado N, et al. Phase II Weekly Vinblastine for Chemotherapy-Naïve Children With Progressive Low-Grade Glioma: A Canadian Pediatric Brain Tumor Consortium Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(29):3537-43.