The European Society for Paediatric Oncology (SIOP Europe)

Clos Chapelle-aux-Champs 30, Bte 1.30.30, B-1200
Brussels, Belgium

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Application for the Inclusion of Low Grade Glioma and related Essential Medicines on the WHO Essential Medicines List for Children 2021

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1. Summary statement

Low grade glioma 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. Age at diagnosis, histological subtype and biological tumor characteristics have an impact on the clinical course. As broad as the clinical presentation is also the treatment of LGG. 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.

2. Relevant WHO technical department and focal point

This application has been pre-discussed with Bernadette Cappello, Lorenzo Moja, Albert Figueras, Elizabeth de Vries and Andrea Bondi and was additionally reviewed by Bernadette Cappello.

3. Name of the organisation(s) consulted and/or supporting the project

European Society for Paediatric Oncology (SIOPE)

SIOPE Brain Tumor Group (SIOPE BTG)

4. Methodological approach

Following the Joint Action on Rare Cancers (JARC, 724161, EU Health Programme) Conclusions, the European Society for Paediatric Oncology (SIOP Europe) has initiated a pan-European project to develop a list of anticancer medicines that are essential to treat children and adolescents with cancer in Europe by mobilising the pan-European community of clinicians, researchers, and parents to take part in the project. Activities were led by a leading clinicians and researchers from the SIOP Europe Board, Young SIOP Europe members, senior mentors from European Clinical Trial Groups, and

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parent representatives from CCI-Europe. Synergies are ensured with the European Reference Network for Paediatric Cancers (ERN PaedCan) and the WHO Global Initiative for Childhood Cancer. A total of 54 SIOP Europe members (Young SIOP Europe members and their mentors), divided into 16 tumour groups, worked on this project. Low Grade Glioma was one of these 16 tumour groups.

Identified anticancer medicines to treat LGG in children and adolescents derive from a systematic collection and screening of all national and international European standard treatment protocols, registries and treatment regimens. For LGG, anticancer medicines in the standard arm of upfront treatment protocols were defined as "essential" for the purpose of this project.
These medicines were compared to the WHO cEML 2017 list. For all identified medicines, which were not on the WHO cEML 2017 list, a thorough literature search was performed to collect data on the efficacy and relevance of these medicines. Last, a designated reviewer and expert in LGG in children and adolescents reviewed the list of suggested drugs and approved on them. For drugs considered essential in the treatment of LGG and already on the WHO EMLc 2017 list (e.g. Carboplatin), no literature search was performed, as they are already considered essential by the WHO for at least one other tumour entity and their efficacy and safety in the treatment of LGG is proofed by the inclusion in standard treatment protocols (= "standard of care").

5. International Nonproprietary Names (INN) of drugs needed in the treatment of paediatric Low Grade Glioma

Generic name	**INN**	**ATC**
Carboplatin	Carboplatin	ATC: L01XA02
Cisplatin	Cisplatin	ATC: L01XA01
Cyclophosphamid	Cyclophosphamide	ATC: L01AA01
Vinblastine	Vinblastine	ATC: L01CA01
Vincristine	Vincristine	ATC: L01CA02

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6. Dose forms and strengths proposed for inclusion

All five drugs (carboplatin, cisplatin, cyclophosphamide, vinblastine and vincristine) are administered intravenously only and in the following doses:

- Carboplatin (Carbo): 550mg/m^2/dose
- Cisplatin (Cis): 30 mg/m^2/dose
- Cyclophosphamid (CYC): 1500 mg/m^2/dose
- Vinblastine (VBL): 6 mg/m^2/dose (max. single dose 10mg)
- Vincristine (VCR): 1.5 mg/m^2/dose (max. single dose 2mg)

	Drug	**Strengths and available vials**
SIOP-LGG-2004		
Induction	Carboplatin Vincristine	Strengths 10mg/ml; Vials of 5, 15, 45, and 60ml Strengths 1mg/ml; Vials of 1 and 2ml
Consolidation	Carboplatin Vincristine	
Consolidation in case of allergy or early progression	Cyclophosphamide Cisplatin Vincristine	Powder for injection of 200, 500, 750, 1000, and 2000mg Strengths 1mg/ml; Vials of 10, 25, 50, 100ml
Vinblastine monotherapy	Vinblastine	Strengths 1mg/ml; Vials of 10ml

As the dose is calculate based on body surface area, and this varies widely from infancy to adolescence (see table below), we listed all vial volumes.

Age category	Age	Body surface area
Neonate		0.25 m^2
Child	2 years	0.5 m^2
	9 years	1.07 m^2
	10 years	1.14 m^2
	12-13 years	1.33 m^2
Women		1.6 m^2
Men		1.9 m^2

7. Whether listing is requested as a new entity, an individual medicine or an example of a therapeutic group?

We request to add all drugs mentioned under point 5 to be listed to the WHO EMLc for the new indication of paediatric LGG.

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8. Description of Low Grade Glioma (LGG) in children (1-3)(1-3)(1-3)(1-3)(1-3)(1-3)

Brain Tumors are the largest group of solid tumors in children and represent approximately one quarter of all cancers in children below 15 years of age. Table 1 shows a categorisation of the different types of brain tumors in children.

Tumor type	Frequency
Low Grade Glioma	40%
High Grade Glioma (including DIPG)	17%
Medulloblastoma	8%
Ependymoma	6%
Craniopharyngioma	4%
Intracranial Germ Cell Tumors	4%
Atypical teratoid rhabdoid tumor	2%
Others*	19%

Table 1: Categorisation of brain tumor in children

* meningioma, oligodendroglioma, sarcoma, primitive neuroectodermal tumor, choroid plexus tumor etc. (1)

Low grade glioma (LGG) (1, 4)

Low grade glioma are the most frequent paediatric brain tumors and account for around 40% of all CNS tumors. The annual incidence is 10 per 1 million children below < 15 years in western countries. The incidence varies between high, middle and low income countries and is even not available for some regions. This is because imaging modalities essential to diagnose LGG are not available or no centralized recording (e.g. cancer registry) are available (5). The average age at diagnosis ranges from 6.5 to 9 years. Boys are affected more often than girls.

The term "LGG" refers to the WHO grade I and II tumors of glial origin and are rather slow growing tumors. LGG can occur anywhere in the brain and spinal cord, but the majority appears in the cerebral and cerebellar hemispheres. Dissemination develops in a very small proportion of patients only (5-10%). LGG can be associated with cancer predisposition syndromes, such as Neurofibromatosis type 1 (NF1) and Tuberous Sclerosis Complex (TSC). Subependymal giant cell astrocytoma (SEGA) are characteristic for TSC. The mutation underlying TSC leads to an activation of the mammalian target of rapamycin complex 1 (mTORC1). Targeted drugs, such as Everolimus, inhibit directly this mTOR

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pathways (6, 7). Activation of the mitogen-activated protein (MAP) kinase pathway is another factor with a critical role in the development of LGG and can be treated with targeted drugs (7). However, less evidence is available for inhibitors of the MAP kinase pathway in children today and we therefore do not focus on these compounds at this stage.

Knowledge about the natural course of LGG is in part based on small series collected throughout long periods of time. At diagnosis, the clinical course of LGG is not always predictable, but knowledge on biological tumor characteristics which have an impact on the clinical course are emerging. BRAF V600E is such a biological marker. Low grade glioma with a BRAF V600E mutation or fusion show a worse progression free survival and overall survival compared to those with BRAF wild type (8). The mutation was detected in 17% of paediatric LGG in a cohort of 405 patients (8). In a review, the average BRAF V600E positivity lies between 0-51% and varies largely between histological subgroups of LGG (9). The mutation can be targeted by BRAF inhibitors and treatment results in reduction in tumor size and increase in progression free survival (10-12).

LGG have a high 10-years overall survival rate of 90-95% and 10 years progression free survival rate around 44% (1, 4). Of course, this might differ for some subtypes or additional risk factors, such as BRAF V600E mutation mentioned previously. Due to its behaviour, LGG are considered a chronic disease with periods of stable disease, followed by tumor growth needing treatment, followed by a stable period again. The effectiveness and feasibility of repeated chemotherapy in progressive LGG could be shown in a study, including 38 patients with a 5-year OS and PFS were 86±6% and 37±8%, respectively (13).

9. Treatment details and trials for LGG

SIOP-LGG-2004

The SIOP-LGG-2004 trial is a cooperative multicenter study for children and adolescents with Low Grade Glioma. Pediatric oncology societies from Germany, Austria, Italy, United Kingdom, France, Spain, the Nordic countries (NOPHO), Belgium, Switzerland and the Netherlands participated in this

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trial. Besides these countries, many more treat their patients according to the SIOP-LGG-2004 trial. The trial consists of three arms:

1. Observation after initial diagnosis/surgery
2. Chemotherapy
    a. Standard induction (Vincristine, Carboplatin) or intensified induction (Vincristine, Carboplatin, Etoposide)
    b. Consolidation: Vincristine, Carboplatin
    c. Alternative consolidation (Vincristine, Cyclophosphamide and Vincristine, Carboplatin) in case of allergy or early progression
3. Radiotherapy

One of the aims of the SIOP-LGG-2004 trial was to determine if etoposide (VCE) added to standard induction with carboplatin and vincristine (VC) increased progression free survival. The trial could show no difference in term of survival and radiological response between the two arms. The 5-year Progression-Free Survival (PFS) and Overall Survival (OS) were 46% and 89% (SD 2.1) in the VC arm and 45% (SD 3.5) and 89% (SD 2.1) in the VCE arm (14). If the same PFS and OS can be reached with a two-drug regimen, this is preferred over a three-drug regimen. Especially because etoposide is also known to cause considerable late effects, such as secondary haematological malignancies. As a result, etoposide is not standard of care in pediatric LGG. Hypersensitivity reaction was the most frequent side effect in the VC regimen. The Kaplan-Meier curve of this trial underlines the high overall survival in children diagnosed with LGG and recruited in the SIOP-LGG-2004 trial (**Figure 1**).

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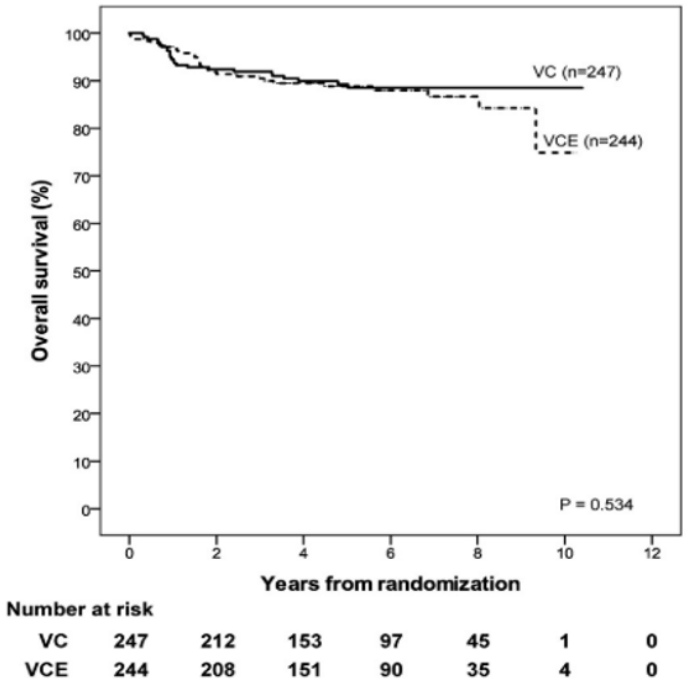

Figure 1: Overall survival in children included in SIOP-LGG-2004 trial, stratified by randomisation arm; VC, vincristine carboplatin; VCE, vincristine carboplatin etoposide (14)

Publications looking into subgroups of LGG underline the character of a chronic disease, shown with a high overall survival rate but lower event free survival. **Figure 2** shows this in a cohort of 116 patients diagnosed with LGG of the brainstem (pons and medulla oblongata), where 100 patients (86%) were in the observational arm after initial surgery and did not receive any chemo- or radiotherapy. Of those, 41 patients progressed in the course of their disease and switched to either receive chemo- or radiotherapy. Together with those patients (n=16) who needed treatment directly following surgery, a total of 39 patients received chemotherapy, 18 radiotherapy, and 59 received surgery only through the whole course of the disease. 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) (15). 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. Treatment with chemotherapy was initiated after a median od 0.7 years (range 0.0-5.9 years). This underlines that

treatment with chemotherapy (vincristine and carboplatin) shows considerable benefits in the treatment of LGG, also in those with relapsed or progressive disease.

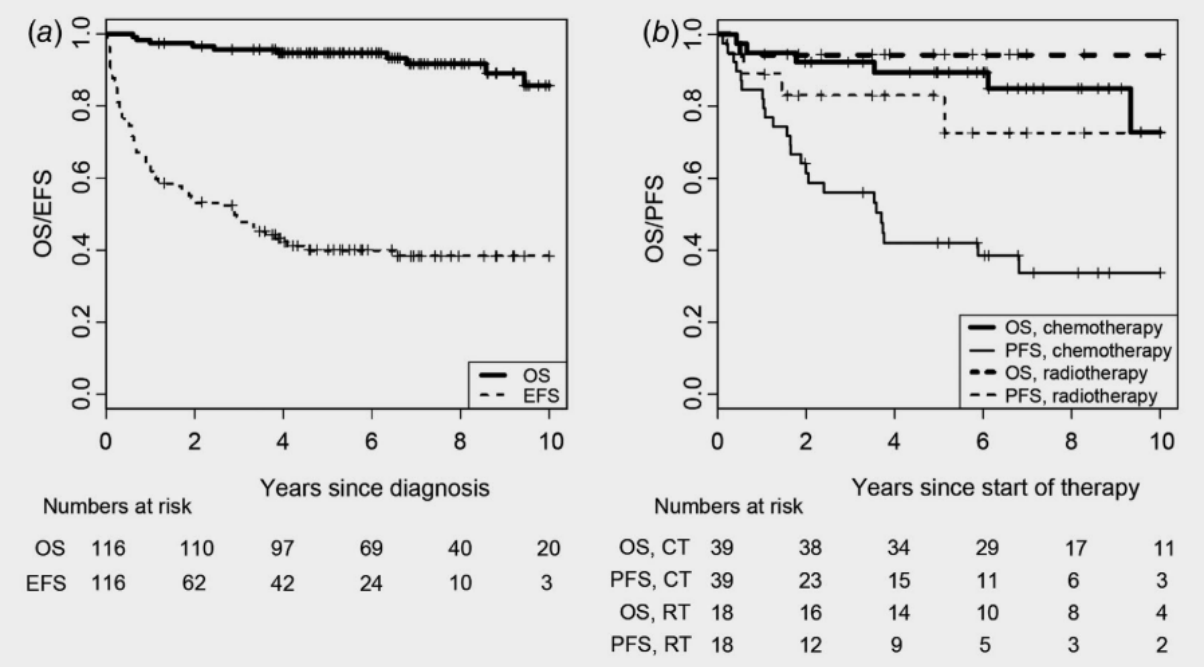

Figure 2: Overall (OS) and event-free survival (EFS) in children diagnosed with brainstem low-grade glioma and treated in the SIOP-LGG-2004 trial. A) entire group; B) stratified by treatment group (15)

A similar pattern as in LGG located in the brain stem is seen in children diagnosed with tectal plate LGG (**Figure 3**) and thalamic LGG (**Figure 4**). All patients from both studies were registered as trial patients on the SIOP-LGG-2004 trial, but 41 (58%) of the study by Kaufmann et al (16) and 47 (46%) by Boesten (17) et al did not receive chemotherapy or radiotherapy. This again underlines the nature of LGG.

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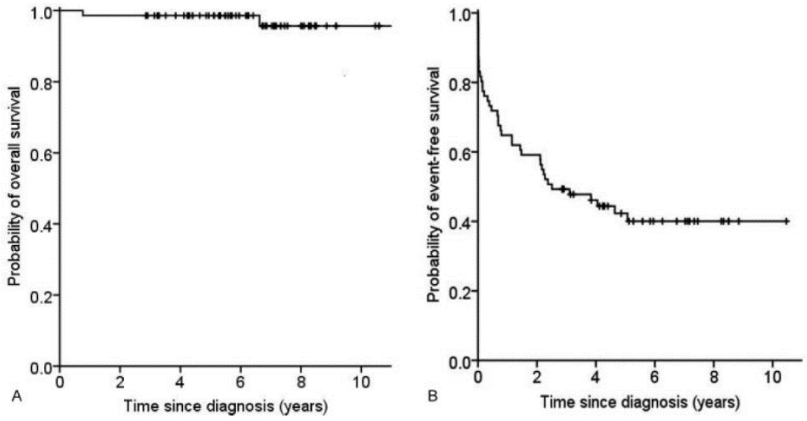

Figure 3: Overall (A) and event-free survival (B) in children diagnosed with tectal plate LGG and treated in the SIOP-LGG-2004 trial; n=71 (16)

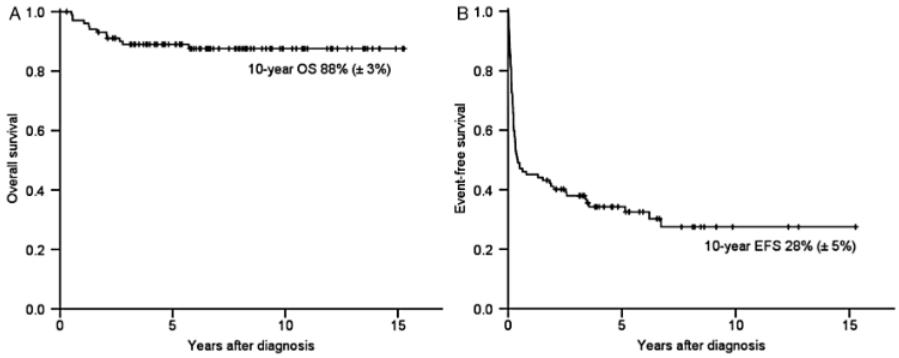

Figure 4: Overall (A) and event-free survival (B) in children diagnosed with thalamic LGG and treated in the SIOP-LGG-2004 trial; n=102 (17)

The next treatment protocol (SIOP LGG LOGGIC) has not opened yet and will compare three randomised arms: vincristine and carboplatin vs. weekly vinblastine vs. trametinib.

Vinblastine monotherapy

Vinblastine monotherapy is used as first- and second-line approach in the treatment of LGG and has been established by the Canadian Pediatric Brain Tumor Consortium. In 2012 Bouffet et al. published the results from the phase II trial of single agent vinblastine as second line treatment in LGG (18). Vinblastine was administered as an iv infusion at 6mg/m^2 once a week in 50 children. Dose reduction

was needed in 18 children due to neutropenia. Median follow-up was 67 months and five-year overall survival was 93.2%, with a 42.3% 5-year progression-free survival. During the study, two children showed early progression but later a partial response, arguing for the longer time to best response. Eighteen children (36%) experienced a complete, partial, or minor response. In addition, 19 children had stable disease. The following study by Lassaletta et al. used vinblastine as primary treatment (19). 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/m^2, and in 16 children to 4 mg/m^2. 13 children tolerated the planed 6 mg/m^2.

10. Information supporting the public health relevance of Low Grade Glioma

Low Grade Glioma represents a relevant proportion of brain tumors in children with a high 10-years overall survival rate of 90-95% and 10 years progression free survival rate around 44% (1, 4). These proportions include all LGG and therefore include patients that need no treatment, those who need surgery only, and those who need a combination of different treatment modalities.

Surgery is a key element in the treatment of LGG, but the possible extent of surgical resection can be a limiting factor. In addition, tumor location, extension of disease, tumor biology and genetic alterations, patient-related factors, and treatment-related factors, can affect the curability. Due to the different biological behaviours of LGG, the following three treatment approaches and clinical courses are possible:

- Some patients never need treatment if the tumor makes no clinical symptoms and does not grow over time.
- Some patients can be treated with surgery only and even residual tumor can be monitored without need of additional chemotherapy.

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- Some patients can be treated with surgery and need additional systemic chemotherapy or in very rare cases radiotherapy.

The very high long-term survival means that survivors can experience not only symptoms related to the tumor, but also late effects due to the treatments applied. In addition, LGG is often also a chronic disease with periods of stable disease, followed by tumor growth needing treatment, followed by a stable period again. The course is often not predictable at initial diagnosis. We only know a few prognostic features, i.e diagnosis before 1 year of age, diencephalic syndrome, dissemination at diagnosis or BRAF V600E mutation or fusion, which have a worse outcome, but still with 10 years over all survival of 50%-80% (4).

11. Review of benefits, harms, and toxicities

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 we therefore did not perform a specific search for evidence (see section 4 "Methodological approach").

12. Summary on available data on comparative cost and cost-effectiveness of the medicine

Cost

As LGG are chronic diseases, the treatment duration can vary largely between patients. In case of treatment according to the SIOP-LGG-2004 protocol, some patients need one cycle of induction and consolidation only, others need several cycles.

The below mentioned table summarizes the costs if a patient receives only one treatment course. The patient in this example as a body surface area of $1m^2$ and the costs per vial are taken from the Netherlands.

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	Drug (per dose)	Cumulative dose	Duration of cycle	Costs per dose	Costs per course
SIOP-LGG-2004					
Induction	Carboplatin (550 mg/m^2)	3850 mg/m^2	24 weeks	Strengths 10mg/ml 1 vial à 45ml: €154.93 2 vials à 5ml : €34.42	€1325.45
	Vincristine (1.5 mg/m^2)	19.5 mg/m^2		Strengths 1mg/ml 1 vial of 2ml: €22.18ml	€288.34
Consolidation	Carboplatin (550 mg/m^2)	5500 mg/m^2	55 weeks	Strengths 10mg/ml 1 vial à 45ml: €154.93 2 vials à 5ml : €34.42	€1893.50
	Vincristine (1.5 mg/m^2)	45mg/m^2		Strengths 1mg/ml 1 vial of 2ml: €22.18ml	€665.40
Consolidation in case of allergy or early progression	Cyclophos-phamide (1500 mg/m^2)	7500 mg/m^2	55 weeks	Powder for injection 1x1000mg: €18.04 1x500mg: €10.79	€71.99
	Cisplatin (30 mg/m^2)	150 mg/m^2		Strengths 1mg/ml 3 vials à 10ml: €13.74	€68.7
	Vincristine (1.5 mg/m^2)	45 mg/m^2		Strengths 1mg/ml 1 vial of 2ml: €22.18ml	€665.40
Vinblastine monotherapy	Vinblastine (6 mg/m^2)		52 weeks	Strengths 1mg/ml 1 vials à 10ml: €38.15	€1983.80

- ➔ The chemotherapy of a child of 1m^2 receiving one course of induction and one course of consolidation according to SIOP-LGG-2004 protocol would cost approximately €4162.69
- ➔ The chemotherapy of a child of 1m^2 receiving one course of vinblastine monotherapy would cost approximately €1983.80

Comparative cost-effectiveness

For the treatment of pediatric LGG with the regimens mentioned in this proposal, it is not possible to show cost-effectiveness or post-marketing data. First, the drugs are used for many decades already and before they were approved by major regulatory agencies, because they did not exist at this time. Second, LGG is a chronic disease and treatment duration and costs may differ largely between patients. As mentioned previously, some need never chemotherapy and others repeated times.

13. Summary and conclusion on Low Grade Glioma the use of Everolimus to treat children and adolescent sin Europe

i. Brain tumors are the most frequent solid tumors in children. Low Grade Glioma represent the most frequent brain tumor entity with a very high 10-year overall survival rate of 90-95%.

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ii. According to the SIOPE Essential Medicines working group 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.

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