PROPOSAL FOR THE ADDITION OF **TEMOZOLOMIDE** TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN AND THE ESSENTIAL MEDICINE LIST (for patients older than 12 years of age) FOR THE TREATMENT OF PATIENTS WITH HIGH GRADE GLIOMA, RECURRENT OR PROGRESSIVE EWING SARCOMA, RELAPSED OR REFRACTORY NEUROBLASTOMA AND FOR TREATMENT OF CHILDREN IN A PALLIATIVE SETTING (FOR THE ABOVE MENTIONED INDICATIONS)

PROPOSAL FOR THE ADDITION OF **2 NEW INDICATIONS** (RECURRENT OR PROGRESSIVE EWING SARCOMA, RELAPSED OR REFRACTORY NEUROBLASTOMA) FOR **IRINOTECAN** IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN AND THE ESSENTIAL MEDICINE LIST (for patients older than 12 years of age) IN COMBINATION WITH TEMOZOLOMIDE

PROPOSAL FOR THE ADDITION OF **TOPOTECAN** TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN AND THE ESSENTIAL MEDICINE LIST (for patients older than 12 years of age) IN COMBINATION WITH TEMOZOLOMIDE FOR THE TREATMENT OF PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

Revised application addressing comments and requests by EML secretariat

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SECTION 1: SUMMARY STATEMENT OF THE PROPOSAL

This submission advocates for the inclusion of temozolomide as a standalone medicine in the complementary list of the Essential Medicines List for Children (EMLc) for the treatment of paediatric and adolescent patients with high-grade glioma, recurrent or progressive Ewing sarcoma, relapsed or refractory neuroblastoma. It advocates for the inclusion of temozolomide in the Essential Medicine List for patients older than 12 years of age. Additionally, temozolomide is recommended for treatment of paediatric and adolescent patients in a palliative setting (especially for the above mentioned indications).

Temozolomide in combination with radiation therapy is indicated for the treatment of newly diagnosed high grade gliomas for patients older that 3 years of age. Temozolomide is routinely used below the age of 3

Temozolomide in combination with either irinotecan or topotecan is used for the treatment of high risk neuroblastoma, either refractory to first line therapy and in relapse.

Temozolomide in combination with irinotecan is used for the treatment of relapsed Ewing sarcomas.

Temozolomide monotherapy is used as palliative treatment of many pediatric malignancies, including high grade glioma and other brain tumors, neuroblastoma and Ewing sarcoma.

Cancer remains a leading cause of death among children worldwide, with significantly lower survival rates in low- and middle-income countries (LMICs), compared to high-income countries. This disparity is largely due to factors such as limited access to early diagnosis, advanced treatment options, and specialized healthcare services. While more than 80% of children with cancer survive in high-income countries, survival rates in LMICs can be as low as 20%*(1)*. In 2018, the World Health Organization (WHO) launched the Global Initiative for Childhood Cancer, a worldwide effort aiming to increase cure rates for childhood cancer to 60% by 2030. The initiative prioritizes six types of childhood cancer: acute lymphoblastic leukemia, Burkitt lymphoma, Hodgkin lymphoma, retinoblastoma, Wilms tumor, and low-grade glioma. By targeting these specific cancers, which are among the most common and treatable, the initiative seeks to significantly reduce the global disparities in childhood cancer outcomes *(2)*.

Although high-grade glioma, Ewing sarcoma or neuroblastoma are not explicitly prioritized by the Global Initiative for Childhood Cancer, temozolomide remains the only chemotherapeutic option for children with these malignancies. It is often the only chemotherapeutic agent available for treating high-grade gliomas in children, and it is frequently the sole therapeutic option for many relapsed or refractory solid tumors, including Ewing sarcoma and neuroblastoma. The significant role of temozolomide in the paediatric oncology is further underscored by the GAP-F PADO (Paediatric Drug Optimization) Cancer priority list *(3)* including the need for the development of an age appropriate formulation of temozolomide due to the lack of commercially available age appropriate formulation for children so far. We advocate the inclusion of temozolomide to the EMLc to improve the access to care, to extend survival and to improve quality of life for children with these refractory or rare tumours and the inclusion to the EML for patients older than 12 years of age.

Given the high mortality rates of childhood cancer, alongside efforts to increase the cure rates, it's important to have a well established palliative care system. According to the Lancet commission report

there is a huge lack of palliative care services in LMIC *(4)*. Temozolomide with its low and manageable toxicity profile *(5)* as well as its oral administration supports more feasible and comfortable, home-based treatment. Because of these characteristics temozolomide is often used in palliative settings. We advocate the inclusion of temozolomide to the EMLc list to improve the opportunities of palliative care in LMIC. We want to underline the use of temozolomide in a palliative setting for children with the above mentioned indications, but also point out, that due to a lack of diagnostic methods, missing access to healthcare and limited availability of specific medication in LMIC there it is also important to have an available and well tolerated option for medication used for palliative care of children for any refractory malignant solid tumor provided by temozolomide.

The proposal is to add Neuroblastoma and Ewing sarcoma in the list of indications for Irinotecan which is currently on both the WHO EML and the EMLc in combination with temozolomide.

The proposal is to add topotecan in combination with temozolomide to the WHO EML and EMLc for the treatment of patients with relapsed or progressive Ewing Sarcoma.

SECTION 2: CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

The WHO childhood cancer team is part of the SIOP-WHO committee and this proposal has been presented in this committee in September 2024.

Preliminary meetings have been held with the EML secretariat ahead of submission.

In addition, temozolomide is one of the 6 anticancer medicines in the priority list of the GAP-F PADO cancer. The report has been released on October 16, 2024.

SECTION 3: OTHER ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION

Colleagues from the International Society of Paediatric Oncology (SIOP) were consulted to receive an international perspective. The forum consulted was the SIOP Essential Medicines Working Group, a working group of the joint SIOP/WHO committee which includes paediatric oncologists, pharmacists and parents/advocates from the 5 continental branches of SIOP. The proposal to submit temozolomide for the 2025 revision of the EMLc has been validated and endorsed but the SIOP Essential Medicines Working Group on September 16, 2024.

Composition of the SIOP Essential Medicines Working Group Members:

- Prof. Gilles Vassal (Co-Chair), Gustave Roussy, Villejuif, France
- Dr. Avram Denburg (Co-Chair), Sickkids Hospital, Toronto, Canada
- Chi Kong Li Chi Kong Li, Hong Kong Children's Hospital, Hong Kong SAR, China
- Edith Grynszpancholc, President of the Natalí Dafne Flexer Foundation, Argentina
- Federico Antillon-Klussmann, Unidad Nacional de Oncologia Pediatrica and Francisco Marroquin School of Medicine, Guatemala
- Gevorg Tamamyan, Department of Hematology and Pediatric Oncology, Yerevan State Medical University, Armenia & Immune Oncology Research Institute, Armenia
- John Ahenkorah Ghana Parents Association for Childhood Cancers, Ghana
- Joyce Balagadde Kambugu Division of paediatric haematology and oncology, Uganda Cancer Institute, Uganda
- Liliana Vasquez, Department of Noncommunicable Diseases and Mental Health, Pan American Health Organization, Washington D.C., USA
- Maria Otth, Division of Hematology/Oncology, Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland & Department of Oncology, University Children's Hospital Zurich, Zurich, Switzerland
- Ramandeep Singh Arora Max Super Specialty Hospital, New Delhi, India
- Paula Schaiquevich, Hospital JP Garrahan, Argentina
- Helen Irving, Oncology Services Group, Queensland Children's Hospital and University of Queensland, Brisbane, Australia
- Mohammad R. Alqudimat, Department of Nursing, College of Health Sciences, American University of the Middle East, Kuwait, Jordan/Canada.

In addition Pr Maja Beck-Popovic from the Lausanne University Hospital, former President of the SIOPE European Clinical Study Group on Neuroblastoma (SIOPEN) reviewed the application.

SECTION 4: KEY INFORMATION SUMMARY FOR THE PROPOSED MEDICINES

Our problem as pediatric oncologists is, that ICD, which is based on organ systems does not classify properly pediatric malignancies. There is no coding for "relapsed pediatric malignancies" or for "palliative situation" in ICD.

An assessment of the age-appropriateness of dosage forms and strengths was performed. As the oral solution is not a commercial available option, an assessment was not performed. Overall temozolomide solid oral dosage form appears to be acceptable for paediatric patients who are able to swallow them whole, but is not acceptable for young patients; there is no commercial alternative for young patients. GAP-F PADO (Paediatric Drug Optimization) Cancer priority list *(3)* including the need for the development of an age appropriate formulation of temozolomide due to the lack of commercially available age appropriate formulation for children. The product generally contains excipients with acceptable safety profiles. The stability of the product (capsules and i.v. powder) is acceptable in ambient conditions. However, the i.v. powder requires reconstitution and administration by a HCP, so dosage form seems not to be suitable for use in LMICs or children in a palliative setting. It is proposed that is is considered for addition to the EMLc. Attached the documents can be found.

INN	temozolomide		
ATC Code	L01AX03		
ICD-11 code	XH4Q01 Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype		
Indications	High Grade Glioma		
Dosage form(s)	Strength(s)	EML	EMLc
Capsule	5mg, 20mg, 100mg, 140mg, 180mg, 250mg	Yes	Yes
Intravenous Solution	100 mg as lyophilized powder in single dose	Yes	Yes
ICD-11 code	XH8KJ8 Ewing sarcoma		
Indications	Recurrent or progressive Ewing sarcoma		
Dosage form(s)	Strength(s)	EML	EMLc
Capsule	5mg, 20mg, 100mg, 140mg, 180mg, 250mg	Yes	Yes
Intravenous Solution	100 mg as lyophilized powder in single dose	Yes	Yes
ICD-11 code	XH85Z0 Neuroblastoma		
Indications	Relapsed or refractory neuroblastoma		
Dosage form(s)	Strength(s)	EML	EMLc
Capsule	5mg, 20mg, 100mg, 140mg, 180mg, 250mg	Yes	Yes
Intravenous Solution	100 mg as lyophilized powder in single dose	Yes	Yes

Intravenous Irinotecan is used in combination with oral temozolomide for the treatment of refractory or relapsed neuroblastoma as well as relapsed or progressive Ewing sarcoma

INN	Irinotecan
ATC Code	L01CE02

ICD-11 code XH85Z0 Neuroblastoma

Indication refractory or relapsed neuroblastoma

Injection: 40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.

EML EMLc

Yes Yes

ICD-11 code XH8KJ8 Ewing sarcoma

Indication relapsed or progressive Ewing sarcoma

Injection: 40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.

EML EMLc

Yes Yes

Intravenous topotecan is used in combination with oral temozolomide for the treatment of refractory or relapsed neuroblastoma

INN Topotecan

ATC Code L01CE01

ICD-11 code XH85Z0 Neuroblastoma

Indications Relapsed or refractory neuroblastoma

Injection: 1 mg in 1 mL vial; 2 mg in 2 ml vial; 4 mg in 4 ml vial.

EML EMLc

Yes Yes

SECTION 5: LISTING AS AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS / THERAPEUTIC GROUP

Temozolomide (TMZ) belongs to the pharmacological class of alkylating agents, specifically a subclass known as imidazotetrazines. Temozolomide works as a DNA methylating agent, meaning it introduces methyl groups into DNA, which can cause DNA damage and lead to the death of cancer cells. A triazene analog of dacarbazine with antineoplastic activity. As a cytotoxic alkylating agent, temozolomide is converted at physiologic pH to the short-lived active compound, monomethyl triazeno imidazole carboxamide (MTIC). The cytotoxicity of MTIC is due primarily to methylation of DNA at the O6 and N7 positions of guanine, resulting in inhibition of DNA replication. Unlike dacarbazine, which is metabolized to MITC only in the liver, temozolomide is metabolized to MITC at all sites.

Darcarbazine is a closely related agent also belonging to the subclass of imidazotetrazines. It is used in the treatment of Hodgkin Lymphoma in children, however there is no indication for Ewing sarcoma or Neuroblastoma or brain tumour. Dacarbazine is not an alternative to the use of temozolomide.

Irinotecan hydrochloride is a type of chemotherapy drug called a topoisomerase I inhibitor. It causes breaks that cannot be repaired in the DNA of cells. This stops the growth of cancer cells and other rapidly dividing cells and causes them to die. The hydrochloride salt of a semisynthetic derivative of camptothecin, a cytotoxic, quinoline-based alkaloid extracted from the Asian tree Camptotheca acuminata. Irinotecan, a prodrug, is converted to a biologically active metabolite 7-ethyl-10-hydroxy-camptothecin (SN-38) by a carboxylesterase-converting enzyme. One thousand-fold more potent than its parent compound irinotecan, SN-38 inhibits topoisomerase I activity by stabilizing the cleavable complex between topoisomerase I and DNA, resulting in DNA breaks that inhibit DNA replication and trigger apoptotic cell death. Because ongoing DNA synthesis is necessary for irinotecan to exert its cytotoxic effects, it is classified as an S-phase-specific agent. Irinotecan is indicated for the treatment of colorectal cancer in adults. Irinotecan is on the WHO Essential Medicine List for children for the treatment of Metastatic colorectal cancer, Nephroblastoma (Wilms tumour) and Rhabdomyosarcoma.

Topotecan hydrochloride is a chemotherapy drug that damages the DNA of cancer cells and other rapidly growing cells, causing them to die. The hydrochloride salt of a semisynthetic derivative of camptothecin with antineoplastic activity. During the S phase of the cell cycle, topotecan selectively stabilizes topoisomerase I-DNA covalent complexes, inhibiting religation of topoisomerase I-mediated single-strand DNA breaks and producing potentially lethal double-strand DNA breaks when complexes are encountered by the DNA replication machinery. Camptothecin is a cytotoxic quinoline-based alkaloid extracted from the Asian tree Camptotheca acuminate. Toptecan is indicated for cervical, ovarian and small cell lung cancers in adults.

SECTION 6: INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

Information or epidemiological data on childhood cancer in an international context, especially for LMIC is hard to find. There is a lack of diagnostic methods and a lack of data collection in LMIC. The project "international incidence of childhood cancer" from the WHO collected some and disseminated data, we want to refer on *(6)*.

Incidences of CNS and miscellaneous intracranial and intraspinal neoplasms: age specific rates per million (age 0-14) range from 3.4 in Uganda to 49.7 in Italy.

Incidences of Neuroblastoma and other peripheral nervous cell tumors: age specific rates per million (age 0-14) range from 0.4 in Cameroon to 21.5 in Italy.

Incidences of Malignant bone tumors: age specific rates per million (age 0-14) range from 1.4 in South Africa to 16.9 in New Zealand.

High-Grade Gliomas (HGGs) are a group of aggressive brain tumors, including glioblastomas and anaplastic astrocytomas. They are rare in children but are characterized by rapid growth and a poor prognosis.
Incidence rates for HGG in children (0-14 years) in the USA are low. Incidence of anaplastic astrocytoma/glioblastoma: 32/78 per average per year.
Data from the USA as high income country show poor prognosis. The 5- and 10-years relative survival (in the group of patients aged 0-14 years) for anaplastic astrocytoma are 25.5 and 20.4. For glioblastoma even lower with 20.7 and 17.1. Median survival for anaplastic astrocytoma was 21 month and median survival of glioblastoma 9 month*(7)*.
Data from LMIC are not available, but as overall survival of childhood cancer is significantly lower in LMIC, the survival of these very rare tumors might be a lot lower.

Incidences or prognosis for relapsed or refractory tumors, such as Ewing sarcoma or neuroblastoma are hard to find, data for these conditions in LMIC are not available.

Temozolomide (TMZ) holds significant public health relevance due to its critical role in the treatment of refractory and aggressive, hard-to-treat cancers, such as high grade glioma, neuroblastoma and Ewing sarcoma. These tumours are often resistant to conventional therapies and temozolomide has become a cornerstone in their management. Temozolomide is often also used in palliative settings, because it is offering several key public health benefits:

1. Unlike many chemotherapy agents that require intravenous administration, temozolomide can be taken orally. This ease of administration enhances patient compliance, particularly in outpatient settings, and reduces the need for hospital visits, which is especially important for patients with limited access to healthcare facilities or for patients in palliative situations. The oral bioavailability and the predictable pharmacokinetics of temozolomide make it a convenient option for both patients and healthcare provider.

2. As a methylating agent, temozolomide targets cancer cells by inducing DNA damage, which leads to cell death. Its relatively selective mechanism of action, combined with a manageable side effect profile, makes it a viable option for many patients, even those who are frail or have comorbid conditions (such conditions often occur in patients within a palliative setting).

This specificity also reduces the likelihood of severe toxicity, making it safer for long-term use in maintenance therapy.

3. Given its oral administration and relative ease of use, temozolomide has the potential to be more accessible in low- and middle-income countries compared to other chemotherapy agents that require more complex infrastructure. This accessibility can help to reduce global health disparities in cancer treatment, providing an effective option for patients in resource-limited settings.

4. By extending survival and potentially improving quality of life for patients with high grade glioma, relapsed or refractory Ewing sarcoma and neuroblastoma or for patients in palliative settings, temozolomide not only has a direct impact on patient health but also on the broader psychosocial and economic aspects of cancer care. Prolonged survival and reduced hospital stays due to its oral administration can lessen the emotional and financial burden on patients, families, and healthcare systems.

5. In LMIC settings, where many children present with advanced stages of cancer, curative treatment is often not feasible. Based on experience, in Africa more than 75% of patients with solid tumors present with advanced disease. In these cases, effective palliation becomes the best, and sometimes the only treatment option. Temozolomide's oral administration, manageable toxicity, and ease of use in low-resource settings make it an invaluable tool for providing home-based palliative care.

There are no alternative medicines which are currently already included on the Model list for the proposed indications.

Because of the high mortality of childhood cancer beneath increasing the cure rate it's important to have a well-established palliative care system. According to the Lancet commission report there is a huge lack of palliative care services in LMIC, more than a third of children who die have serious health-relates suffering (SHS). More than 98% of the almost 2.5 million children who die with SHS live in LMICs*(4)*. Temozolomide is a drug, which has low toxicity*(5)*, enables oral administration and so the feasibility of a more comfortable, home-based treatment. Because of these characteristics temozolomide is often used in palliative setting.

SECTION 7: TREATMENT DETAILS

Dosage regimen and duration of treatment

Temozolomide (TMZ) is a methylating agent approved for the treatment of malignant glial tumors in both adults and children (8). After oral administration, TMZ is rapidly and fully absorbed, subsequently hydrolyzing into monomethyl 5-triazeno imidazole carboxamide (MTIC). MTIC produces a methyldiazonium ion that methylates DNA, primarily at the O6 position of guanine . These DNA lesions are repaired by the nuclear protein alkylguanine transferase (AGT) and the mismatch repair (MMR) system. There is a noted correlation between the dose and duration of TMZ administration and a reduction in O6 AGT activity in peripheral blood. In vitro studies on tumor cell lines resistant to other anticancer drugs have indicated that TMZ is highly effective *(9)*

The biotransformation of TMZ and MTIC occurs spontaneously—TMZ in a basic environment and MTIC in an acidic one—without the need for an enzymatic system. TMZ has complete oral bioavailability, and its pharmacokinetics (PK) are linear, leading to minimal inter-individual variability in TMZ and its metabolites. Additionally, the likelihood of a pharmacokinetic interaction between TMZ and other drugs is low.

Temozolomide (TMZ) is usually administered to children in the form of oral capsules or a liquid suspension, depending on the child's ability to swallow capsules. The dosing regimen for TMZ in paediatric patients typically depends on the child's body surface area (BSA), and the specific treatment protocol.

Indication: **treatment of newly diagnosed high grade glioma from the age of 3 years in children, adolescents and adults.** Approved indication of temozolomide first authorized in Europe in 1999.

High-Grade Gliomas (HGGs) are a group of aggressive brain tumors, including glioblastomas (GBM) and anaplastic astrocytomas (AA). They are rare in children but are characterized by rapid growth and a poor prognosis. Treatment typically involves a combination of surgery, radiotherapy, and chemotherapy. Despite advances in treatment, outcomes remain unsatisfactory, with a median survival of less than 2 years for most patients. These tumors are known for their infiltrative nature, making complete surgical resection difficult.

Dosage regimen (as in the HIT-HGG 2013 protocol): Temozolomide chemotherapy will start at the first day of radiotherapy and will end at the last day of radiotherapy. It will be given as one single daily dose [75 mg/m^2/d] during the whole duration of radiotherapy including radiotherapy-free days, i.e. on weekend days, holidays etc., but not longer than for 49 continuous days (oral temozolomide treatment may be started in single cases at maximum 7 days before radiotherapy if the 49 days treatment period still fully covers radiotherapy).

It is recommended that temozolomide should be given at night at least one hour after the last meal. However, alternative timing during radiotherapy, e.g. one hour before radiotherapy as often recommended for adult patients with glioblastoma, is also possible.

Temozolomide capsules should be swallowed whole with plenty of water. If in individual cases patients were not be able to swallow the capsules, it would be possible to open the capsules and to

mix the temozolomide powder with orange or apple juice to provide an acid milieu as described in the protocol appendix. For preparation of the oral suspension, the use of Temodal® capsules *(13)* is mandatory. If necessary, temozolomide chemotherapy may be given as intravenous solution, alternatively.

Maintenance chemotherapy with temozolomide will start at earliest 4 weeks after the end of radiochemotherapy. It will be given as one single daily dose of [150-200 mg/m^2/d] on days 1 to 5, repeated every 28 days for up to 12 cycles.

During the first maintenance cycle temozolomide should be dosed at [150 mg/m^2/d]. If this chemotherapy is well tolerated the daily dose of temozolomide may be increased to [200 mg/m2/d] for all following cycles as long as there will be no significant toxic side effects.

Indication: **children with relapsed or refractory neuroblastoma**

Dosage regimen:
Irinotecan regimen: Infants, Children, and Adolescents: Oral: 100 mg/m^2/dose once daily for 5 days, repeat cycle every 21 days for up to 6 cycles; in combination with irinotecan (50 mg/m2 1-hour infusion once daily for 5 days) and; administer temozolomide 1 hour prior to irinotecan *(10)*.
Note: Temozolomide doses were rounded to the nearest capsule size.

Topotecan regimen (TOTEM): Infants ≥6 months, Children, and Adolescents: Oral temozolomide: 150 mg/m2/dose on days 1 to 5 every 28 days; in combination with topotecan (0.75mg/m2 for five consecutive days every 28 days); administer temozolomide prior to the topotecan; continue until disease progression or unacceptable toxicity up to a maximum of 12 months; doses were reduced for hematologic toxicity *(11)*.

Single agent: Children ≥3 years and Adolescents: Oral: Administer doses on days 1 to 5 every 21 to 28 days; continue until disease progression or unacceptable toxicity up to a maximum of 24 cycles; doses were reduced by 25% for grade 4 thrombocytopenia or neutropenia, and grade 3 or 4 mucositis, documented sepsis, pulmonary distress/infiltrate, or seizures requiring prophylaxis *(12)*.
No prior craniospinal irradiation: Oral: 215 mg/m2/day.
Previous craniospinal irradiation or relapse after bone-marrow transplant: Oral: 180 mg/m2/day.

Indication: **patients with recurrent or progressive Ewing sarcoma**

Dosage regimen*(13)*: Limited data available: Children ≥2 years and Adolescents: Oral: 100 mg/m2/dose once daily for 5 days, repeat cycle every 21 days (in combination with irinotecan (50mg/m2 1 hour infusion daily for 5 consecutive days; administer temozolomide 1 hour prior to irinotecan); dosing based on a retrospective review. Rationale: Temozolomide is important for Ewing sarcoma, particularly in cases of relapsed or refractory disease, as it provides a therapeutic option when standard treatments have failed. It is often used in combination with irinotecan, showing activity in patients with recurrent or progressive Ewing sarcoma.

Indication: **children and adolescents with other relapsed or refractory solid tumors**

Dosage regimen: Limited data available; efficacy results variable: Infants, Children, and Adolescents: Oral: 200 to 215 mg/m2/dose days 1 to 5 every 21 to 28 days; dose was decreased to 180 mg/m2/dose for patients who received prior craniospinal irradiation or relapsed after bone marrow transplant; in other trials, lower doses of 160 to 200 mg/m2/dose once daily for 5 days every 28 days were used in patients 3 to 18 years of age.

Requirements to ensure appropriate use of the medicine(s)

Patient Eligibility Criteria

- **Age and Weight Restrictions**:
    - Temozolomide is approved for use in both adult and pediatric patients. However, the dosing must be adjusted according to the patient's body surface area (BSA), which is calculated based on height and weight.
    - For pediatric use, specific dosing regimens have been developed, often with lower starting doses than those used in adults, to reduce the risk of toxicity while maintaining efficacy. In very young children, additional considerations such as the ability to swallow capsules or the need for liquid formulations may influence treatment plans. This is why temozolomide is on the PADO (Paediatric Drug Optimization) Cancer priority list for age appropriate formulation currently.

2. Diagnostic and Monitoring Test Requirements

- **Baseline Laboratory Tests**:
    - **Absolute Neutrophil Count (ANC)**: A baseline ANC of ≥1,500/mm³ is required before starting temozolomide to minimize the risk of severe neutropenia.
    - **Platelet Count**: A platelet count of ≥100,000/mm³ is necessary to reduce the risk of bleeding, as thrombocytopenia is a common side effect of temozolomide.
    - **Liver Fund and Renal Function Tests:** Baseline LFTs and Renal function should be obtained to assess hepatic and renal function.
- **Ongoing Monitoring**:
    - **Complete Blood Count (CBC)**: Regular CBCs are critical during treatment to monitor for myelosuppression. The frequency of these tests typically increases during the first few cycles of treatment and may be weekly or biweekly, depending on the patient's response.
    - **Additional Tests**: Depending on the patient's condition and treatment response, other tests such as MRI scans, electrolyte panels, urinalysis, and additional imaging studies may be warranted.

3. Administration

- **Administration**:
    - **Oral Administration**: Temozolomide is administered orally, and the capsules should be taken on an empty stomach to optimize absorption. Patients are advised to take the medication at the same time each day to maintain consistent drug levels.
    - **Compounding**: For patients who cannot swallow capsules, such as young children or those with swallowing difficulties, temozolomide can be compounded into a liquid suspension by a pharmacist. Temozolomide is on the PADO (Paediatric Drug Optimization) Cancer priority list for age appropriate formulation currently
    - **Missed Dose Protocol**: If a dose is missed, patients should take it as soon as they remember, unless it is almost time for the next dose. They should not double up on doses.
- **Special Considerations**:
    - **Supportive Care**: Anti-emetics are often prescribed to manage nausea and vomiting, which are common side effects. Prophylactic antibiotics or antivirals may also be necessary, particularly in patients at high risk of infections due to myelosuppression.

4. Treatment Administration Requirements

- **Setting**:
    - **Ambulatory Care**: Temozolomide is typically administered in an ambulatory setting, allowing patients to take their medication at home. This approach is convenient for patients and reduces the need for frequent hospital visits.
- **Patient Education**:
    - Patients and caregivers should be educated on the proper handling and administration of temozolomide, potential side effects, and the importance of adherence to the prescribed regimen. They should also be informed about the signs of complications such as infection or bleeding, which require immediate medical attention.

5. Required Skill Levels of Healthcare Providers

- **Laboratory Technicians**:
    - Skilled laboratory technicians are needed to perform and analyze the frequent blood tests required to monitor the patient's response to temozolomide. Accurate and timely results are critical for making necessary adjustments to the treatment plan.

Conclusion

At start of therapy some laboratory tests are necessary, the ongoing monitoring requires only regularly blood count testing. Education of Caregivers and Patients/Parents in handling, administration and potential side effects should be done. Temozolomide is a drug, which has low toxicity*(5)*, enables oral administration (for children a proper formulation is not yet available, but its prioritized on the PADO Cancer list)*. Therefore, the home-based treatment, especially for patients with progressive malignant diseases or in a palliative setting, is feasible. A home-based treatment also could avoid abortion of therapy in LMIC due to in-hospital stays and long ways to the hospital as hurdle for many families.

*The WHO GAP-F PADO cancer report has been publicly released on October 16, 2024. https://iris.who.int/bitstream/handle/10665/379245/9789240101050-eng.pdf

SECTION 8: REVIEW OF EVIDENCE FOR BENEFITS AND HARMS

Summary of available evidence for comparative effectiveness and comparative safety

A systematic literature research has not been performed due to a lack of studies and data. Several studies could be found (only from high income countries). Detailed results are provided below.

Incidences for HGG, for relapsed or refractory tumors, such as Ewing sarcoma or neuroblastoma are low, prognosis is poor, data for these conditions in LMIC are not available.

Temozolomide is the only chemotherapeutic option for children with high grade glioma and temozolomide (in combined treatment regimens) and often is the only therapeutic option in many refractory or relapsed solid tumors, such as Ewing sarcoma or neuroblastoma, as there are no other relevant alternative therapies.

Temozolomide in pediatric high grade gliomas

The rationale for its use in pediatric **HGG**s is supported by studies like HIT-HGG 2007 and HIT-HGG 2013, which have explored its role in combination with radiotherapy. In these ongoing trials, TMZ was used concurrently with radiotherapy to improve tumor control and survival.

HIT-HGG 2007 was a multicentered, prospective, phase II clinical trial design. In HIT-HGG 2007 438 patients from 79 childhood cancer centers in Germany, Austria and Switzerland were included.

In the **HIT-HGG 2007** trial (ISRCTN19852453), TMZ was combined with craniospinal irradiation (CSI) and showed moderate efficacy in controlling disease progression. Although the overall survival benefit was not substantial, TMZ was favored for its manageable toxicity profile and the convenience of oral administration, reducing the need for hospitalizations compared to older chemotherapy regimens such as nitrosoureas *(14)*.

The HIT-HGG 2013 trial (NCT03243461) was a multicentered, prospective, international cooperative Phase III Trial of the HIT HGG study Group for treatment of high grade glioma, diffuse intrinsic pontine glioma and gliomatosis cerebri in children and adolescents <18 years . 198 patients were included in Austria and Germany.

The **HIT-HGG 2013** trial (NCT03243461) aimed to further optimize the treatment of pediatric HGGs by incorporating novel therapeutic approaches in addition to TMZ. The trial explored the potential of adding targeted therapies to the standard radiochemotherapy regimen, with the goal of improving both survival outcomes and quality of life for patients. The results of this trial are contributing to ongoing efforts to refine treatment strategies for pediatric HGGs, ensuring that future protocols can build on the benefits observed with TMZ in terms of tolerability and effectiveness.

While TMZ in combination with radiotherapy remains a cornerstone of treatment for pediatric HGGs, the HIT-HGG trials underscore the need for continued research and innovation to improve outcomes. The non-inferiority design of these trials compared to prior chemotherapy regimens suggests that TMZ offers a more favourable toxicity profile without sacrificing efficacy, making it a reasonable standard treatment option.

Temozolomide in refractory and relapsed neuroblastoma

Temozolomide has been evaluated first as a single agent and then in combination for the treatment of relapsed or refractory high risk neuroblastoma since 2006. For patients with relapsed neuroblastoma who are not eligible or with no access to clinical trials, standard treatment options currently available include temozolomide, a topisomerase 1 inhibitor (irinotecan or topotecan) and a antiGD2 monoclonal antibody (dinutuximab or dinutuximab β).

Temozolomide (TMZ) was initially evaluated as monotherapy for treating relapsed neuroblastoma. In a phase II trial by Rubie et al., TMZ was administered at a dose of 200 mg/m²/day for 5 consecutive days every 28 days to 25 patients, resulting in 10 objective responses (complete, partial, and minor responses) with mild to moderate toxicity (12).

TMZ was then used and evaluated in combination with a topoisomerase I inhibitor, ie topotecan and irinotecan.

In a study by Kushner et al., 49 neuroblastoma patients (36 with assessable disease) received a 5-day courses of irinotecan 50 mg/m2 (1-hour infusion) and temozolomide 150 mg/m2 (oral) every 3 to 4 weeks. Of 19 patients treated for refractory NB and assessable for response, nine showed evidence of disease regression, including two complete responses and seven objective responses. Of 17 patients treated for progressive disease, three showed evidence of disease regression, including one partial response and two objective responses (15).

In a study by Bagatell et al., 55 eligible patients received temozolomide (100 mg/m2/dose for 5 days) and irinotecan (10 mg/m2/dose 5 days a week for 2 weeks) every 3 weeks (10). Two cohorts of patients were defined, one evaluable for response by cross-sectional imaging (stratum 1), and the other assessable by bone marrow aspirate/biopsy or metaiodobenzylguanidine (MIBG) scan only (stratum 2). The objective response rate was 15%. Fourteen patients (50%) on stratum 1 and 15 patients (56%) on stratum 2 had stable disease. Objective responses were observed in three of the first 25 evaluable patients on stratum 1 and five of the first 25 evaluable patients on stratum 2. Less than 6% of patients experienced ≥ grade 3 diarrhea. Although neutropenia was observed, less than 10% of patients developed evidence of infection while neutropenic.

In a study by Di Giannatale et al., 38 children with relapsed or refractory high-risk neuroblastoma received a topotecan + temozolomide (TOTEM) regimen (oral temozolomide at 150mg/m2 followed by intravenous topotecan at 0.75mg/m2 for five consecutive days every 28 days). Tumour control rate (complete response + partial response + mixed response + stable disease) was 68% (95% CI, 63-90%). The 12-months Progression-Free and Overall Survival were 42% and 58% respectively (11) . Upon these results published in 2014, TOTEM was considered as a valid rescue therapy in advanced neuroblastoma.

Having the association of temozolomide with topoisomerase I inhibitor confirmed as solid backbone chemotherapy for relapsed/refractory neuroblastoma, further combination treatments were explored, mainly by adding an anti-GD2 monoclonal antibody (dinutuximab or dinutuximab β):

In a study by Mody R et al, addition of temsirolimus or dinutuximab (an anti-GD2 monoclonal antibody) to the combination of irinotecan and temozomide (oral temozolomide (100 mg/m2 per dose) and intravenous irinotecan (50 mg/m2 per dose) on days 1-5 of 21-day cycles) was compared

in a randomized Phase II trial enrolling 35 eligible patients with relapsed or refractory neuroblastoma. Of the 18 patients assigned to irinotecan-temozolomide-temsirolimus, one patient (6%; 95% CI 0·0-16·1) achieved a partial response (17). Of the 17 patients assigned to irinotecan-temozolomide-dinutuximab, nine (53%; 95% CI 29·2-76·7) had objective responses, including four partial responses and five complete responses. 36 additional patients with first relapsed or refractory neuroblastoma were further nonrandomly assigned to irinotecan, temozolomide, dinutuximab and GM-CSF in this study (18). Objective responses were observed in 13 (36.1%) of these 36 expansion cohort patients (95% CI, 20.4% to 51.8%). Overall, objective responses were seen in 22 (41.5%) of 53 patients overall (95% CI, 28.2% to 54.8%); stable disease was also observed in 22 of 53. One-year progression-free and overall survival for all patients receiving I/T/DIN/GM-CSF were 67.9% ± 6.4% (95% CI, 55.4% to 80.5%) and 84.9% ± 4.9% (95% CI, 75.3% to 94.6%), respectively.

In a subsequent study, Lerman et al., confirmed the interest of combining irinotecan, temozolomide, dinutuximab and GM-CSF in 164 patients with relapsed or progressive neuroblastoma (19). Seventy-one patients (49%) had an objective response (objective response; 29% complete response, 14% partial response, 5% minor response, 21% stable disease, and 30% progressive disease). The median progression-free survival (PFS) was 13.1 months, and the 1-year PFS and 2-year PFS were 50% and 28%, respectively. The median duration of response was 15.9 months; the median PFS off all anticancer therapy was 10.4 months after discontinuation of I/T/DIN/GM-CSF.

In the most recent international trial, the BEACON Neuroblastoma trial (EudraCT 2012-000072-42), 160 patients with relapsed or refractory high risk neuroblastoma were randomly assigned in a 3 × 2 factorial design to temozolomide (T), irinotecan-temozolomide (IT), or topotecan-temozolomide (TTo) with or without bevacizumab. For bevacizumab random assignment (n = 160), the ORR was 26% (95% CI, 17 to 37) with bevacizumab and 18% (95% CI, 10 to 28) without bevacizumab (risk ratio [RR], 1.52 [95% CI, 0.83 to 2.77]; P = .17). Adjusted hazard ratio for PFS and OS were 0.89 (95% CI, 0.63 to 1.27) and 1.01 (95% CI, 0.70 to 1.45), respectively. For irinotecan (n = 121) and topotecan (n = 60) random assignments, RRs for ORR were 0.94 and 1.22, respectively (16). The addition of Bevacizumab to temozolomide-based chemotherapy improved overall response rate in patients with high-risk relapsed/refractory neuroblastoma. Currently the addition of the anti-GD2 monoclonal antibody dinutuximab β to temozolomide + irinotecan combination regimen is under evaluation.

Overall, temozolomide containing regimens provide a 18% to 42% objective responses in patients with relapsed or refractory high risk neuroblastoma, and a 1-year progression-free and overall survival of 67.9% ± 6.4% (95% CI, 55.4% to 80.5%) and 84.9% ± 4.9% (95% CI, 75.3% to 94.6%) for patients receiving temozolomide containing chemo-immunotherapy. Thus, temozolomide containing chemo-immunotherapy is currently a standard treatment option for patients with relapsed neuroblastoma and is being incorporated in front line treatments for patients with a high risk neuroblastoma refractory to initial multi-agent chemotherapy.

Temozolomide in Ewing sarcoma

For patients with **recurrent/relapsed Ewing sarcoma** several studies have demonstrated its efficacy in this setting. S. Salah et al assessed in a retrospective study the efficacy and toxicity of irinotecan and temozolomide (IT) in relapsed Ewing sarcoma (ES) patients, including both paediatric and adult populations. A total of 53 patients were treated, with no significant difference in grade 3/4 hematologic toxicity or diarrhea between paediatric and adult groups. The overall objective response rate was 28%, with no difference in response between the two groups. However, paediatric patients

had significantly better progression-free survival (PFS) compared to adults (7.4 vs. 2.2 months). The study concluded that IT chemotherapy is effective for relapsed ES with manageable toxicity, though the superior PFS in paediatric patients warrants further investigation *(20)*. Another study from Palmerini et al, evaluated in a multi-institutional retrospective study the efficacy of temozolomide (TEM) and irinotecan (IRI) in recurrent Ewing sarcoma (EWS), particularly focusing on both adult and paediatric patients. Among the 51 patients, 66% were adults, and 69% presented with multiple site recurrences. TEMIRI was administered at first relapse in 25% of cases, and for second or subsequent relapse in the remainder. The disease control rate (DCR) was 71%, with 10% achieving complete response, 24% partial response, and 37% stable disease. Six-month progression-free survival (PFS) was 49%, significantly influenced by ECOG performance status and LDH levels. One-year overall survival (OS) was 55%, with response to treatment and ECOG score being independent predictors of outcome. Toxicities were manageable, with neutropenia occurring in 12% of patients. This study confirms the activity of the TEMIRI regimen in both paediatric and adult EWS patients, regardless of treatment line *(21)*. Another earlier study concluded that irinotecan and temozolomide is a well-tolerated and active regimen for recurrent/progressive ES. This retrospective study evaluated the use of irinotecan and temozolomide in 20 patients with recurrent or progressive Ewing sarcoma (ES). Of the 19 evaluable patients, 63% achieved an objective response, including 5 complete and 7 partial responses. The median time to progression (TTP) was 8.3 months overall, and 16.2 months for patients with recurrent ES. TTP was better in patients with a sustained 2-year first remission and those with localized, rather than metastatic, disease. Toxicities included grade 3 diarrhoea, colitis, pneumonitis, and neutropenia, as well as grade 3-4 thrombocytopenia *(13)*.

Temozolomide in other resistant or relapsed pediatric solid tumors

Studies show, that temozolomide can be used in **other resistant or relapsed paediatric solid tumors**. It is an attractive choice as it is well tolerated, has a low incidence of major toxicity and an oral formulation. Most frequent toxicities were neutropenia and thrombocytopenia, nonhematological toxicities were infrequent *(22, 23)*.
De Sio reports on a study, which investigated the use of temozolomide (TMZ) as a single agent in children with relapsed or resistant solid tumors. Fifty-two pre-treated paediatric patients were enrolled, including those with neuroblastoma (NB) (number of included patients = 17), medulloblastoma (n = 8), brain stem glioma (n = 8), and Ewing's sarcoma (n = 4), anaplastic astrocytoma (n = 3), rhabdomyosarcoma (n = 2), ependymoma (n = 2), neuroectodermal tumor ((n=2), hepatocarcinoma (n = 1), osteosarcoma (n = 1). TMZ was administered at a dose of 215 mg/m²/day for 5 days or 180 mg/m²/day for those with prior craniospinal irradiation or autologous bone marrow transplantation. The objective response rate was 13.4%, with 1.9% achieving complete response and 7.7% showing minor response. Stable disease occurred in 38.4%, while 48% had disease progression. Median survival was 7.8 months, and time to progression was 3.4 months. Haematological toxicity, primarily thrombocytopenia, was observed in 21.4% of courses *(22)*. In the treatment of relapsed rhabdomyosarcoma, temozolomide (TMZ) monotherapy has demonstrated limited efficacy, whereas the combination of TMZ with vincristine and irinotecan (VIT) has shown more promising results. Setty et al., in their study on the VIT regimen, reported an overall clinical benefit rate (including complete response, partial response, and stable disease) of 26.7% *(24)*.

SECTION 9: SUMMARY OF RECOMMENDATIONS IN CURRENT CLINICAL GUIDELINES. RECOMMENDATIONS IN EXISTING WHO GUIDELINES

There are no existing WHO guidelines for the indications we refer to.

Also not many other current clinical guidelines could be found. As temozolomide is often used in relapsed or refractory tumors there is often no standardized procedure. It is often an individual decision of the treating pediatric oncologists which therapy is chosen. Choosing temozolomide depends on factors like fragility or morbidity of the patient, which therapies the patient already received, age of the patient, symptoms of the patient and many other factors.

For HGG there is a current (European) clinical guideline:

ESCP (European Standard of Clinical Practice): The SIOPE **HGG**-working group aimed to establish the current management approaches of pedHGG in Europe and UK. Based on the practice in 33 countries, an attempt was made to achieve a consensus on management of these tumors using a Delphi method:
A concomitant daily administration of Temozolomide (TMZ) with a local radiotherapy followed by adjuvant chemotherapy with TMZ has been widely adopted by the paediatric neurooncology community throughout Europe as the preferred treatment option for paediatric patients with newly diagnosed HGG. Sixty percent of the Delphi participants agreed that the recommended treatment regimen is chemoradiation with TMZ followed, after a TMZ treatment break of approximately 4 weeks, by 6-12 cycles of TMZ, irrespective of MGMT promotor methylation status. Treatment should begin approximately 4 weeks after cranial surgery. Alternatively, after irradiation, patients should be enrolled into a clinical trial when available.
Thirty percent of the Delphi participants would support the management of hemispheric high-grade glioma using concomitant and/or adjuvant TMZ as the backbone, but would consider adding Lomustine (CCNU) based on the COG ACNS-0423 trial due to the findings of the difference in survival between the cohort of patients with MGMT-overexpressing tumors in ACNS0126 and ACNS0423.

This European Standard of Clinical Practice has been established by the European Reference Network on Paediatric Cancer (ERN PaedCan), one of the 24 ERNs established by the European Union to improve access to high quality care and treatment for patients with rare disease.

The detailed ESCP on High grade glioma is not publicly available. It is available upon request by pediatric oncologist. A publication is in preparation

SECTION 10: SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST EFFECTIVENESS

Strength	Price 5 pieces (CHF)/Switzerland	Price 1 piece (5 per package) (euro)/Croatia	Price 1 piece (5 per package) (euro)/Slovenia	Price per 1 piece (Canadian Dollar)/Canada
Temozolomid 5 mg, Capsule	27.80	2	/	1.9500
Temozolomid 20 mg, Capsule	61.15	8.4	30.81	7.8000
Temozolomid 100 mg, Capsule	209.90	37.1	152.43	39.0015
Temozolomid 140 mg, Capsule	341.20	44.2	189.33	54.6025
Temozolomid 180 mg, Capsule	382.95	64	235.25	/
Temozolomid 250 mg, Capsule	500.40	91.7	299.92	97.5010
Oral Solution 1,25mg/ml, 10mg/ml	NA	NA	NA	NA
Intravenous Solution	NA	NA	NA	NA

NA, not available

Strength	Price 1 piece (5 per package) (USD)/India	Price 1 piece (5 per package) (USD)/Argentina	Price 1 piece (5 per package) (PEN)/Peru	Price per 1 piece (USD)/Guatemala
Temozolomid 5 mg, Capsule	/	/	/	/
Temozolomid 20 mg, Capsule	5-10	/	/	/
Temozolomid 100 mg, Capsule	20-30	500-2500	1290.00	16.00
Temozolomid 140 mg, Capsule	/	/	/	/
Temozolomid 180 mg, Capsule	/	/	/	/
Temozolomid 250 mg, Capsule	30-50	/	/	/
Oral Solution 1,25mg/ml, 10mg/ml	NA	NA	NA	NA
Intravenous Solution	NA	NA	NA	NA

NA, not available

Strength	Price (CHF)	Strength	Price (USD)
IRINOTECAN Accord 40 mg/2ml L01CE02 Irinotecan	57.25	Solution (Camptosar Intravenous) 40 mg/2 mL (per mL):	$16.59

IRINOTECAN Accord 100 mg/5ml L01CE02 Irinotecan	115.40	Solution (Camptosar Intravenous) 100 mg/5 mL (per mL):	$9.90
IRINOTECAN Accord 300 mg/15ml L01CE02 Irinotecan	283.55	Solution (Camptosar Intravenous) 300 mg/15 mL (per mL):	$9.10
IRINOTECAN Accord 500 mg/25ml L01CE02 Irinotecan	405.70	Solution (Irinotecan HCl Intravenous) 40 mg/2 mL (per mL):	$5.40 - $138.08
IRINOTECAN Fresenius Inf Konz 40 mg/2ml L01CE02 Irinotecan	57.55	Solution (Irinotecan HCl Intravenous) 100 mg/5 mL (per mL):	$4.32 - $138.07
IRINOTECAN Fresenius Inf Konz 100 mg/5ml L01CE02 Irinotecan	116.25	Solution (Irinotecan HCl Intravenous) 300 mg/15 mL (per mL):	$8.00 - $8.96
IRINOTECAN Fresenius Inf Konz 300 mg/15ml L01CE02 Irinotecan	283.55	Solution (Irinotecan HCl Intravenous) 500 mg/25 mL (per mL):	$7.73
IRINOTECAN Fresenius Inf Konz 500 mg/25ml L01CE02 Irinotecan	416.70		
IRINOTECAN Labatec 40 mg/2ml L01CE02 Irinotecan	57.60		
IRINOTECAN Labatec 100 mg/5ml L01CE02 Irinotecan	116.25		
IRINOTECAN Labatec 300 mg/15ml L01CE02 Irinotecan	283.55		

IRINOTECAN Sandoz eco 40 mg/2ml L01CE02 Irinotecan	57.60		
IRINOTECAN Sandoz eco 100 mg/5ml L01CE02 Irinotecan	116.25		
IRINOTECAN Sandoz eco 300 mg/15ml L01CE02 Irinotecan	283.55		
IRINOTECAN Sandoz eco 500 mg/25ml L01CE02 Irinotecan	410.50		
IRINOTECAN Teva liquid 40 mg/2ml L01CE02 Irinotecan	57.85		
IRINOTECAN Teva liquid 100 mg/5ml L01CE02 Irinotecan	115.85		
IRINOTECAN Teva liquid 300 mg/15ml L01CE02 Irinotecan	283.55		
IRINOTECAN Teva liquid 500 mg/25ml L01CE02 Irinotecan	405.70		

Strength	**Price (CHF)**	**Strength**	**Price (USD)**
TOPOTECAN Accord Inf Konz 1 mg/ml L01CE01 Topotecan	90.55	Capsules (Hycamtin Oral) 0.25 mg (per each)	$145.65
TOPOTECAN Accord Inf Konz 4 mg/4ml L01CE01 Topotecan	280.55	Capsules (Hycamtin Oral) 1 mg (per each)	$582.59
		Solution (Topotecan HCl Intravenous)	$20.79 - $129.81

		4 mg/4 mL (per mL)	
		Solution (reconstituted) (Hycamtin Intravenous) 4 mg (per each)	$1,526.51
		Solution (reconstituted) (Topotecan HCl Intravenous) 4 mg (per each)	$168.00 - $358.25

SECTION 11: REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOEIA STANDARDS

Temozolomide is marketed as a generic medicine.

In the European Union, temozolomide is authorized for the treatment of adults and children three years of age and over with malignant glioma such as glioblastoma multiforme or anaplastic astrocytoma, when the tumor has returned or got worse after standard treatment (approved indication of temozolomide first authorized in Europe in 1999) *(25)*

In the US, temozolomide was granted a FDA (U.S. Food and Drug Administration, last update 2023) approval for use in adults exclusively *(26)*.

In Canada, temozolomide is approved for adult indications by Health Canada but not approved for pediatric use, "given lack of safety and efficacy data in the pediatric population" as stated in the manufacturer summary of product characteristics. Temozolomide is used off-label for paediatric indications in Canada.

In India, temozolomide is available and approved for paediatric and adult malignant glioma.

In Peru, temozolomide is included in Peru's National Essential Medicines List (Petitorio Nacional Único de Medicamentos Esenciales, PNUME), as approved by Ministerial Resolution No. 633-2023-MINSA on July 5, 2023. This inclusion signifies its approval and availability for the treatment of malignant gliomas, for patients older than 3 years old, in Peru.

In Argentina, Temozolomide is approved for the treatment of malignant glioma in adults and children.

In Guatemala, Temozolomide is approved for the treatment of malignant glioma in adults and children.

Generic equivalents of temozolomide are available, international brand names:

(AE) United Arab Emirates: Tegozol | Temodal;
(AR) Argentina: Clitech | Kemtax | Rumalar | Temodal | Temola | Temonova | Temoxan | Temozolomida gp pharm | Terbai | Tezulina | Varizolamida | Zolom;
(AT) Austria: Temodal | Temomedac | Temozolomid accord | Temozolomid ratiopharm | Temozolomid sandoz | Temozolomid stada;
(AU) Australia: Apo temozolomide | Astromide | Orion temozolomide | Temizole | Temodal | Temolide | Temozolomide alphapharm | Temozolomide an | Temozolomide juno;
(BD) Bangladesh: Temonix;
(BE) Belgium: Temodal | Temomedac | Temozolomide accord | Temozolomide EG | Temozolomide hospira | Temozolomide Mylan | Temozolomide sandoz | Temozolomide teva;
(BG) Bulgaria: Blastomat | Nogron | Temodal;
(BR) Brazil: Telma | Temodal | Temolida | Temozod | Temozolomida | Zabrux;
(CH) Switzerland: Temodal | Temozolomid accord | Temozolomid devatis | Temozolomid labatec | Temozolomid Medac | Temozolomid teva;
(CL) Chile: Dralitem | Mozola | Temodal | Varizolomida;
(CN) China: Di qing | Temodal;
(CO) Colombia: Dralitem | Hb oncobrain | Tedolix | Temaz | Temitoma | Temodal | Temozolomida | Tensacton | Tripzol;
(CZ) Czech Republic: Apo temozolomid | Temodal | Temomedac | Temozolomide accord | Temozolomide glenmark | Temozolomide sandoz | Temozolomide sun | Temozolomide teva;

(DE) Germany: Temodal | Temomedac | Temozo cell | Temozolomid accord | Temozolomid Fair Med | Temozolomid Hexal | Temozolomid Hospira | Temozolomid ratiopharm | Temozolomid teva | Temozolomide fair med | Temozolomide ratiopharm | Temozolomide sun;
(DO) Dominican Republic: Dralitem | Telamid-100 | Telamid-20 | Temodal;
(EC) Ecuador: Gliotem | Mozola | Nilactin | Temaz | Temodal | Temorel | Temozolamida | Temozolomida | Tocitrap | Varizolomida;
(EE) Estonia: Blastomat | Temodal | Temozolomide accord | Temozolomide teva;
(EG) Egypt: Temodal;
(ES) Spain: Temodal | Temomedac | Temozolomida hospira | Temozolomida sun | Temozolomida teva;
(ET) Ethiopia: Temozol;
(FI) Finland: Temodal | Temomedac | Temozolamid ratiopharm | Temozolomid ratiopharm | Temozolomid teva | Temozolomide accord | Temozolomide hospira | Temozolomide sandoz | Temozolomide sun | Temozolomide teva;
(FR) France: Temodal | Temozolamide teva | Temozolomide accord | Temozolomide Mylan | Temozolomide sun;
(GB) United Kingdom: Temodal | Temomedac | Temozolomide accord | Temozolomide Actavis;
(GR) Greece: Ridoca | Temodal | Temomedac | Temozolomide accord | Temozolomide sandoz | Temozolomide/Teva | Tezolamet;
(HK) Hong Kong: Temodal;
(HR) Croatia: Blastomat | Temazol | Temodal;
(HU) Hungary: Blastomat | Nogron | Temodal | Temostad | Temozolomide pharmacenter | Temozolomide sandoz | Temozolomide sun | Temozolomide teva;
(ID) Indonesia: Temodal | Temotero | Teroza;
(IE) Ireland: Temodal | Temozolomide accord | Temozolomide clonmel | Temozolomide teva;
(IL) Israel: Temodal;
(IN) India: Gbmt | Gliogen | Gliotem | Glioz | Glisoma | Glistroma | Strimodal | Tabze | Temcad | Temcure | Temo trust | Temodal | Temoglan | Temolon | Temoloz | Temonat | Temorel | Temoside | Temotec | Temotero | Temoway | Temozam | Temozol | Zolotem;
(IT) Italy: Temodal | Temozolomide accord | Temozolomide Crinos | Temozolomide sandoz | Temozolomide sun | Temozolomide teva;
(JO) Jordan: Tegozol;
(JP) Japan: Temodal;
(KE) Kenya: Emzolam | Temodal | Temotero;
(KR) Korea, Republic of: Astrodal | Temodal | Temolam | Temolde | Temozol;
(LB) Lebanon: Accotim | Temodal | Temozolomide accord;
(LT) Lithuania: Blastomat | Temodal | Temozolomide accord | Temozolomide sandoz | Temozolomide teva;
(LU) Luxembourg: Temodal | Temozolomide accord | Temozolomide sandoz | Temozolomide teva;
(LV) Latvia: Blastomat | Temodal | Temozolomide accord | Temozolomide sandoz | Temozolomide teva;
(MA) Morocco: Temodal | Temozolomide zenith;
(MX) Mexico: Byaimid | Niman | Paxublin | Rubrum asf | Temodal | Temozolomida | Tera caz | Termozepal | Timzomide | Zuriphar;
(MY) Malaysia: Temodal | Temozam;
(NL) Netherlands: Temodal | Temozolomide hospira | Temozolomide ratiopharm | Temozolomide sandoz;
(NO) Norway: Temodal | Temomedac | Temozolomid ratiopharm | Temozolomide accord | Temozolomide hospira | Temozolomide sun | Temozolomide teva;
(NZ) New Zealand: Apo temozolomide | Orion temozolomide | Temaccord | Temodal | Temozolomide accord | Temozolomide amneal;
(PE) Peru: Dralitem | Mozola | Nilactin | Temodal | Temozolomida | Tocitrap;
(PH) Philippines: Emzolam | Gliotem | Temodal | Temosanz 100 | Temotero | Temovex | Temozam;
(PK) Pakistan: Midizol | Temoeirgen | Temomedac | Temonat;
(PL) Poland: Blastomat | Temodal | Temomedac | Temostad | Temozolomide accord | Temozolomide fair med | Temozolomide glenmark | Temozolomide polpharma | Temozolomide sun | Temozolomide teva;
(PR) Puerto Rico: Temodar;
(PT) Portugal: Temodal | Temomedac | Temozolomida accord | Temozolomida Stada | Temozolomida teva;
(PY) Paraguay: Dralitem | Temola | Temolon | Temozolamida libra | Temozolomida imedic | Temozolomida varifarma | Temozolomida vmg | Tezulina | Tocitrap | Zolom;
(QA) Qatar: Temodal;
(RO) Romania: Blastomat | Brastoryn | Temozolomida accord | Temozolomida teva;
(RU) Russian Federation: Astroglif | Temcital | Temodal | Temomid | Temozoleks | Temozolomide rus | Temozolomide teva | Temozolomide tl | Tezalom;
(SA) Saudi Arabia: Lagona | Tegozol | Temodal;
(SE) Sweden: Temodal | Temomedac | Temozolomi accord | Temozolomid Ebb | Temozolomid stada | Temozolomide accord | Temozolomide hospira | Temozolomide sandoz | Temozolomide sun | Temozolomide teva;
(SG) Singapore: Temodal;
(SI) Slovenia: Temodal | Temomedac | Temozolomid accord | Temozolomid sandoz | Temozolomide teva;
(SK) Slovakia: Nogron | Temodal | Temomedac | Temostad | Temozolomid ratiopharm | Temozolomide accord | Temozolomide sandoz | Temozolomide sun | Temozolomide teva;
(TH) Thailand: Temodal | Zolotem;
(TN) Tunisia: Tegozol | Temo | Temodal | Temomedac;
(TR) Turkey: Midizol | Temodal | Temomid | Temozolid;
(TW) Taiwan: Tamos | Temodal;
(UA) Ukraine: Glyosomid | Temodal | Temozolomid accord | Temozolomide teva;
(UY) Uruguay: Temozolamida | Temozolomida | Tocitrap;
(ZA) South Africa: Accord Temozolomide | Temintas | Temoxol | Tezmyl;

(ZM) Zambia: Temodal;
(ZW) Zimbabwe: Temotero

Pharmacopoeial standards

Pharmacopoeial standards for temozolomide are available in the British, European, International and United States Pharmacopoeias. Attached the information leaflet Ph. Eur. Reference Standard can be found.

Irinotecan hydrochloride is marketed as a generic compound worldwide.

- Manufacturer: ACCORD HLTHCARE
  Approval date: November 21, 2008
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]
- Manufacturer: ACTAVIS TOTOWA
  Approval date: February 27, 2008
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]
- Manufacturer: EPIC PHARMA LLC
  Approval date: September 16, 2009
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]
- Manufacturer: EUGIA PHARMA
  Approval date: November 2, 2020
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP], 300MG/15ML (20MG/ML) [AP]
- Manufacturer: FRESENIUS KABI USA
  Approval date: February 27, 2008
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]
- Manufacturer: GLAND PHARMA LTD
  Approval date: November 18, 2019
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]
- Manufacturer: HENGRUI PHARMA
  Approval date: December 16, 2011
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]
- Manufacturer: HIKMA
  Approval date: December 24, 2008
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]
- Manufacturer: HIKMA FARMACEUTICA
  Approval date: December 20, 2010
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]
- Manufacturer: HOSPIRA
  Approval date: February 27, 2008
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]

- Manufacturer: INTAS PHARMS USA
  Approval date: August 31, 2017
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]
- Manufacturer: NOVAST LABS
  Approval date: May 26, 2017
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]
- Manufacturer: QILU PHARM HAINAN
  Approval date: May 3, 2016
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP], 300MG/15ML (20MG/ML) [AP]
- Manufacturer: SHILPA
  Approval date: December 28, 2018
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]
- Manufacturer: SHILPA
  Approval date: August 16, 2019
  Strength(s): 300MG/15ML (20MG/ML) [AP]
- Manufacturer: ZENNOVA
  Approval date: May 13, 2011
  Strength(s): 40MG/2ML (20MG/ML) [AP], 100MG/5ML (20MG/ML) [AP]

Topotecan

Hycamtin if the brand name of topotecan approved by the FDA and the EU. There are many generics.

Mylan-topotecan Hydrochloride for Injection Powder, for solution 4 mg / vial Intravenous Mylan Pharmaceuticals Inc.

PMS-topotecan Powder, for solution 1 mg / vial Intravenous Pharmascience Inc

PMS-topotecan Powder, for solution 4 mg / vial Intravenous Pharmascience Inc

Teva-topotecan Powder, for solution 1 mg / vial Intravenous Teva Italia S.R.L.

Teva-topotecan Powder, for solution 4 mg / vial Intravenous Teva Italia S.R.L.

Topotecan Injection, powder, lyophilized, for solution 4 mg/4mL Intravenous Ingenus Pharmaceuticals,

Topotecan Injection, powder, lyophilized, for solution 4 mg/15mL Intravenous Meitheal Pharmaceuticals Inc.

Topotecan Injection, solution, concentrate 1 mg/1mL Intravenous Mylan Institutional Inc.

Topotecan Injection 1 mg/1mL Intravenous Accord Healthcare, S.L.U.

Topotecan Hydrochloride Injection, powder, lyophilized, for solution 4 mg/4mL Intravenous Pfizer Laboratories Div Pfizer Inc

Topotecan Hydrochloride Injection, powder, lyophilized, for solution 4 mg/4mL Intravenous Cipla USA Inc.

Topotecan Hydrochloride Injection, powder, lyophilized, for solution 4 mg/4mL Intravenous Sagent Pharmaceuticals

Topotecan Hydrochloride Injection, powder, lyophilized, for solution 4 mg/4mL Intravenous Sagent Pharmaceuticals

Topotecan Hydrochloride Injection, powder, lyophilized, for solution 4 mg/1mL Intravenous Mylan Institutional Inc.

Topotecan hydrochloride Injection, powder, lyophilized, for solution 4 mg/4mL Intravenous Actavis Pharma, Inc.

Topotecan Hydrochloride Injection, powder, lyophilized, for solution 4 mg/4mL Intravenous Accord Healthcare, S.L.U.

Topotecan Hydrochloride Injection, powder, for solution 4 mg/4mL Intravenous Three Rivers Pharmaceuticals Ltd

Topotecan hydrochloride Injection, powder, lyophilized, for solution 4 mg/4mL Intravenous Sun Pharmaceutical Industries (Europe) B.V.

Topotecan Hydrochloride Injection, powder, lyophilized, for solution 4 mg/4mL Intravenous Bedford Laboratories

Topotecan Hydrochloride Injection, powder, lyophilized, for solution 4 mg/4mL Intravenous Fresenius Kabi Italia S.R.L.

Section 12: Reference list

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Appendix

1. Assessment of the age-appropriateness of dosage forms and strengths for temozolomide
2. Information Leaflet Ph. Eur. Reference Standard Temozolomide