CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MULTI-DISCIPLINE REVIEW

Project Renewal Assessment Aid

NDA 021029 and NDA 022277

Temodar (temozolomide) capsules
Temodar (temozolomide) for injection

Version date: September 2021 (ONLY for Project Renewal sNDA reviews)

Disclaimer: The FDA's recommendations and opinions are limited to this Assessment Aid and do not extend to other documents regarding this application. In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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1.0 EXECUTIVE SUMMARY

1.1 Product Introduction and Relevant U.S. Regulatory History

Temodar (temozolomide) is an alkylating agent. New Drug Application (NDA) 021029 for Temodar capsules initially received accelerated approval on August 11, 1999, under Subpart H of Part 314, as a single agent indicated for the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine. The accelerated approval was based on response rate in a single arm trial conducted in patients with anaplastic astrocytoma at first relapse.

On March 15, 2005, FDA approved Temodar capsules for the treatment of adult patients with newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy (RT) and then as maintenance treatment. The approval was based on the results of an international, multi-center randomized controlled trial demonstrating the benefit of temozolomide in combination with RT and followed by maintenance therapy, compared with radiotherapy alone (European Organisation for Research and Treatment of Cancer [EORTC] trials 22981/26981). Results of this study were used to fulfill accelerated approval requirements for refractory anaplastic astrocytoma under 21 CFR 314.510 in Subpart H. On February 27, 2009, FDA approved an injectable formulation, Temodar for injection, under NDA 022277.

This Project Renewal Assessment Aid for Temodar (NDAs 021029 and 022277) provides a summary of the key proposed FDA recommendations for updates to the information related to approved uses for Temodar to align with 21 CFR 201.56 and 201.57 and applicable guidances,[1,2] as well as proposed recommendations for adding or modifying an indication(s) or other conditions(s) of use based on certain data and information, such as published literature.

In addition, FDA's independent assessment to support proposed recommendations for labeling modifications included published literature review, FDA Adverse Event Reporting System data, and assessment of the existing Temodar labeling for adherence to current guidance and regulations. FDA's key proposed recommended labeling modifications are described below. Rationale for additional proposed labeling updates are provided in annotated comments to the Applicant, including references where appropriate, within the proposed draft labeling.

1.2 Information to Support the Proposed Changes to Labeling

The published literature cited in the annotated labeling support FDA's proposed updates to the Temodar product labeling. The Applicant should submit any additional data or information relevant to the labeling updates proposed in the above-referenced sNDAs. If some of the

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/indications-and-usage-section-labeling-human-prescription-drug-and-biological-products-content-AND.
[2] https://www.fda.gov/media/72142/download.

evidence supporting the updates is derived from information for which the Applicant does not own or have a right of reference, the Applicant would need to submit the supplements pursuant to section 505(b)(2) of the FD&C Act.

Based on the evaluation of information identified through this process and as further assessed by FDA in conjunction with a review of additional published literature (as annotated in the proposed labeling), the following key labeling modifications, including new indications or modifications to existing indications and to dosage and administration, are proposed for inclusion in the Temodar labeling.

Any additional new indication(s) that the Applicant would like to propose that are not reflected in this Assessment Aid are outside the scope of Project Renewal and should be discussed individually with the appropriate FDA oncology review division.

2.0 PROPOSED REVISIONS TO INDICATIONS AND DOSAGE AND ADMINISTRATION

2.1 Newly Diagnosed Glioblastoma

Summary of Proposed Changes

- The pre-existing indication for newly diagnosed glioblastoma remains intact, however "adult patients" was changed to "adults" in the indication statement to be consistent with contemporary labeling practices.
- The recommended dosage and dosage modifications for the existing indications have been modified as follows:
    - Removal of "60 Gy administered in 30 fractions"
    - Addition of administering TEMODAR once daily for 42 to 49 days for the concomitant use phase
    - Addition of "other administration schedules have been used"
    - Removal of "no dose reductions are recommended during the concomitant phase"
    - Specified that dose modifications are "due to adverse reactions"
    - Table 1 modified to note that TEMODAR is to be resumed at the same dose when interrupted if certain hematologic parameters are met
    - Table 2 modified to note dose modifications also apply to adjuvant use of temozolomide for patients with anaplastic astrocytoma
    - The word "use" was added after "maintenance" and "concomitant" to further specify these use phases
    - "Lymphocytopenia" revised to "lymphopenia"
    - Important instructions for dosage and administration moved to separate sub-section, now Section 2.1, to avoid redundancy

Section 1.1: Newly Diagnosed Glioblastoma

TEMODAR is indicated for the treatment of adults with newly diagnosed glioblastoma, concomitantly with radiotherapy and then as maintenance treatment.

Section 2.2: Recommended Dosage and Dosage Modifications for Newly Diagnosed Glioblastoma

Administer TEMODAR either orally or intravenously once daily for 42 consecutive days during the concomitant use phase with focal radiotherapy, and then once daily on Days 1 to 5 of each 28-day cycle for 6 cycles during the maintenance use phase.

Provide *Pneumocystis* pneumonia (PCP) prophylaxis during the concomitant use phase and continue in patients who develop lymphopenia until resolution to Grade 1 or less *[see Warnings and Precautions (5.3)]*.

Concomitant Use Phase:

The recommended dosage of TEMODAR is 75 mg/m^2 either orally or intravenously once daily for 42 days to 49 days in combination with focal radiotherapy. Focal radiotherapy includes the tumor bed or resection site with a 2 to 3 cm margin.

Other administration schedules have been used.

Obtain a complete blood count weekly. The recommended dosage modifications due to adverse reactions during concomitant use phase are provided in **Table 1**.

TABLE 1: Dosage Modifications Due to Adverse Reactions During Concomitant Use Phase

Adverse Reaction	Interruption	Discontinuation
Absolute Neutrophil Count	Withhold TEMODAR if ANC is greater than or equal to 0.5 x 10^9/L and less than 1.5 x 10^9/L. Resume TEMODAR at the same dose when ANC is greater than or equal to 1.5 x 10^9/L.	Discontinue TEMODAR if ANC is less than 0.5 x 10^9/L.
Platelet Count	Withhold TEMODAR if platelet count is greater than or equal to 10 x 10^9/L and less than 100 x 10^9/L. Resume TEMODAR at the same dose when platelet count is greater than or equal to 100 x 10^9/L.	Discontinue TEMODAR if platelet count is less than 10 x 10^9/L.
Non-hematological Adverse Reaction (except for alopecia, nausea, vomiting)	Withhold TEMODAR if Grade 2 adverse reaction occurs. Resume TEMODAR at the same dose when resolution to Grade 1 or less.	Discontinue TEMODAR if Grade 3 or 4 adverse reaction occurs.

Single Agent Maintenance Use Phase:

Beginning 4 weeks after concomitant use phase completion, administer TEMODAR either orally or intravenously once daily on Days 1 to 5 of each 28-day cycle for 6 cycles. The recommended dosage of TEMODAR in the maintenance use phase is:

- Cycle 1: 150 mg/m^2 per day
- Cycles 2 to 6: May increase to 200 mg/m^2 per day before starting cycle 2 if no dosage interruptions or discontinuations are required (Table 1). If the dose is not escalated at the onset of Cycle 2, **do not** increase the dose for Cycles 3 to 6.

Obtain a complete blood count on Day 22 and then weekly until the ANC is above 1.5 x 10^9/L and the platelet count is above 100 x 10^9/L. Do not start the next cycle until the ANC and platelet count exceed these levels.

The recommended dosage modifications due to adverse reactions during the maintenance use phase are provided in **Table 2**.

If TEMODAR is withheld, reduce the dose for the next cycle by 50 mg/m^2 per day. Permanently discontinue TEMODAR in patients who are unable to tolerate a dose of 100 mg/m^2 per day.

TABLE 2: Dosage Modifications Due to Adverse Reactions During Maintenance and Adjuvant Treatment

Adverse Reactions	Interruption and Dose Reduction	Discontinuation
Absolute Neutrophil Count	Withhold TEMODAR if ANC less than 1 x 10^9/L. When ANC is above 1.5 x 10^9/L, resume TEMODAR at reduced dose for the next cycle.	Discontinue TEMODAR if unable to tolerate a dose of 100 mg/m^2 per day.
Platelet Count	Withhold TEMODAR if platelet less than 50 x 10^9/L. When platelet count is above 100 x 10^9/L, resume TEMODAR at reduced dose for the next cycle.	Discontinue TEMODAR if unable to tolerate a dose of 100 mg/m^2 per day.
Nonhematological Adverse Reactions (except for alopecia, nausea, vomiting)	Withhold TEMODAR if Grade 3 adverse reaction occurs. When resolved to Grade 1 or less, resume TEMODAR at reduced dose for the next cycle.	Discontinue TEMODAR if recurrent Grade 3 adverse reaction occurs after dose reduction, if Grade 4 adverse reaction occurs, or if unable to tolerate a dose of 100 mg/m^2 per day.

Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Glioblastoma is the most common and aggressive primary central nervous system tumor with an age-adjusted incidence rate of 3.22 per 100,000 population, which accounts for 57.3% of all gliomas and 48.3% of all malignant brain tumors. (Mehta 2017, Ostrom 2020a)	Newly diagnosed glioblastoma is relatively common among primary brain tumors and is a serious condition with poor survival and an area of unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Median overall survival is 14.6 months from diagnosis with standard of care therapy. (Stupp 2005)	
Current Treatment Options	• Maximal surgical resection has been shown to improve survival for patients with newly diagnosed glioblastoma. (Lacroix 2001) • Adjuvant concurrent temozolomide (75 mg/m^2/day for 42 days) and radiation therapy (60Gy in 30 fractions) followed by maintenance temozolomide (200 mg/m^2/day on days 1-5 of a 28-day cycle) have been shown to improve survival for patients with newly diagnosed glioblastoma. (Stupp 2005) • Tumor-treating fields, using the Optune device, when administered with maintenance temozolomide have been shown to increase survival. (Stupp 2017)	Maximal surgical resection followed by adjuvant concurrent temozolomide and radiation therapy and maintenance temozolomide is considered standard of care for the treatment of newly-diagnosed glioblastoma.
Benefit	• In the trial evaluating adjuvant concurrent temozolomide with RT noted above (Stupp 2005), temozolomide was administered at a dose of 75 mg/m^2 per day, given 7 days per week from the first day of radiotherapy until the last day of radiotherapy, but for no longer than 49 days. • Alternative radiation therapy protocols, including short-course radiation or hypofractionation, have demonstrated improved outcomes in specific subpopulations (e.g. elderly patients with glioblastoma). (Malmstrom 2012,	The product labeling should not restrict the radiation therapy to 60Gy in 30 fractions for select populations with newly diagnosed glioblastoma (e.g. elderly, low baseline performance status) where alternative radiation therapy paradigms may result in improved survival. Concurrent temozolomide may be administered for 42 and up to 49 days in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Minniti 2012, Perry 2017) • Hypofractionated radiation therapy (30Gy in 6 fractions) has been associated with improved overall survival over standard radiotherapy (60Gy in 30 fractions) in a randomized controlled study in patients older than 70 years with newly-diagnosed glioblastoma (hazard ratio 0.59, 95% confidence interval 0.37-0.93, p=0.02). (Malmstrom 2012)	combination with RT, as was evaluated in Stupp 2005.
Risk and Risk Management	• Increased risks with alternative radiation therapy paradigms (e.g. hypofractionation) have not been demonstrated.	The risk of removing a specific radiation therapy dose and schedule from the product label is acceptable for the intended population.

The Applicant's Position

The Applicant agrees with all the FDA proposed revisions to section 2.1 Newly Diagnosed Glioblastoma.

The FDA's Assessment

The FDA agrees with the Applicant's position. This is an existing indication that has been previously reviewed by the FDA, with the phrase "adult patients" changed to "adults". FDA reviewed evidence in the published literature on the recommended dosage and dosage modifications for adults with newly diagnosed glioblastoma. The FDA review team's determination is that there is substantial evidence for the updated dosage and dosage and administration for TEMODAR for patients with newly diagnosed glioblastoma.

2.2 Anaplastic Astrocytoma

Summary of Proposed Changes for Anaplastic Astrocytoma

- A new indication for the adjuvant treatment of adults with newly diagnosed anaplastic astrocytoma has been added
- The pre-existing indication of refractory anaplastic astrocytoma has been modified to remove the stipulation that patients should have experienced disease progression on a drug regimen containing nitrosourea and procarbazine
- The recommended dosage and dosage modification for the new indication of newly diagnosed anaplastic astrocytoma has been added to Section 2
- The pre-existing dosage and dosage modifications for refractory anaplastic astrocytoma were modified to remove the language "In the clinical trial, treatment could be continued for a maximum of 2 years, but the optimum duration of therapy is not known."

Section 1.2: Anaplastic Astrocytoma

TEMODAR is indicated for the:

- adjuvant treatment of adults with newly diagnosed anaplastic astrocytoma;
- treatment of adults with refractory anaplastic astrocytoma.

Section 2.3: Recommended Dosage and Dosage Modifications for Anaplastic Astrocytoma

Adjuvant Treatment of Newly Diagnosed Anaplastic Astrocytoma

Beginning 4 weeks after the end of radiotherapy, administer TEMODAR orally in a single dose on days 1-5 of a 28-day cycle for 12 cycles. The recommended dosage of TEMODAR is as follows:

- Cycle 1: 150 mg/m^2 per day
- Cycles 2 to 12: 200 mg/m^2 per day if patient experienced no or minimal toxicity in cycle 1. If the dose was not escalated at the onset of Cycle 2, do not increase the dose during Cycles 3 to 6.

The recommended complete blood count testing and dosage modifications due to adverse reactions during adjuvant treatment are provided above and in Table 2 *[see Dosage and Administration (2.2)]*.

Refractory Anaplastic Astrocytoma

The recommended initial dosage of TEMODAR is 150 mg/m^2 once daily on Days 1 to 5 of each 28-day cycle. Increase the TEMODAR dose to 200 mg/m^2 per day if the following conditions are met at the nadir and on Day 1 of the next cycle:

- ANC is greater than or equal to 1.5 x 10^9/L, and
- Platelet count is greater than or equal to 100 x 10^9/L.

Continue TEMODAR until disease progression or unacceptable toxicity.

Obtain a complete blood count on Day 22 and then weekly until the ANC is above 1.5 x 10^9/L and the platelet count is above 100 x 10^9/L. Do not start the next cycle until the ANC and platelet count exceed these levels.

If the ANC is less than 1 x 10^9/L or the platelet count is less than 50 x 10^9/L during any cycle, reduce the TEMODAR dose for the next cycle by 50 mg/m^2 per day. Permanently discontinue TEMODAR in patients who are unable to tolerate a dose of 100 mg/m^2 per day.

Benefit-Risk Assessment for Anaplastic Astrocytoma

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Anaplastic astrocytoma accounts for 1-2% of all primary brain tumors. The incidence rates of anaplastic astrocytoma by age group are 2.6 in young adults, 4.7 in adults, 8.4 in elderly per million per year. (Ostrom 2020b) • Median overall survival (OS) with anaplastic astrocytoma is approximately 4 years (Chang 2017).	Anaplastic astrocytoma is a serious condition and area of unmet medical need. The study used to support labeling recommendations classified tumors according to the 2016 World Health Organization (WHO) Central Nervous System Tumors nomenclature.
Current Treatment Options	• Initial therapy for newly diagnosed anaplastic astrocytoma is maximal safe resection. • The only currently FDA-approved therapy for newly diagnosed anaplastic astrocytoma is carmustine (BCNU),	No contemporary drugs are currently approved specifically for the treatment of newly diagnosed anaplastic astrocytoma. BCNU is approved broadly for brain

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	which is approved broadly for brain tumors including astrocytoma. • Treatment options for refractory anaplastic astrocytoma include surgical resection for local recurrence and re-irradiation or systemic chemotherapy. • The only currently FDA-approved therapy for refractory anaplastic astrocytoma is temozolomide, which is currently restricted to adults who had disease progression on a drug regimen containing a nitrosourea and procarbazine.	tumors including astrocytoma; however, its safety risks (e.g., pulmonary fibrosis, myelosuppression) have limited its use in this population and it is no longer recommended by the National Comprehensive Cancer Network as a preferred treatment regimen for this indication (Nabors 2020). Surgical resection, re-irradiation, or systemic chemotherapy (i.e., regimens based on alkylating agents) are considered standard of care for recurrent anaplastic astrocytoma.
Benefit	• The CATNON trial (NCT00626990) studied the use of radiation therapy with concurrent, adjuvant, and concurrent followed by adjuvant temozolomide for patients with anaplastic astrocytomas without 1p/19q co-deletions. (van den Bent 2021) The 4 arms (n=186 to 189 per arm) in this study were compared using a 2x2 analysis. A prespecified interim analysis of the CATNON trial demonstrated an overall survival benefit for radiation therapy followed by adjuvant temozolomide (median OS 82.3 months) compared to no adjuvant temozolomide (median OS 46.9	Data from the CATNON trial support the OS benefit of adjuvant temozolomide for patients with newly diagnosed anaplastic astrocytoma without 1p/19q co-deletions, using the 2016 WHO classification criteria for central nervous system tumors. The 2021 WHO classification of tumors of the central nervous system differentiate gliomas by

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	months, hazard ratio 0.64 [95% confidence interval 0.52-0.79], p<0.0001). (van den Bent 2021) No statistically significant benefit was observed for concurrent temozolomide. • The pivotal data supporting accelerated approval for refractory anaplastic astrocytoma came from a multi-center, single-arm trial of patients with recurrent anaplastic glioma (anaplastic astrocytoma and anaplastic mixed oligoastrocytoma) treated with temozolomide 150 mg/m2 – 200 mg/m2 on days 1-5 of a 28-day cycle. The primary endpoint was progression-free survival at 6 months (PFS) with OS and response rate as secondary endpoints. All patients had received RT, and 60% (97/162 patients) had received a nitrosourea based regimen. (Yung WK 1999) • Accelerated approval was based on subgroup analysis of patients who had previously received both a nitrosourea and procarbazine, with a response rate of 22%. • A recent study has demonstrated efficacy of adjuvant temozolomide in the first-line setting in patients who did not receive prior procarbazine or nitrosourea. (see Section 2.2, van den Bent 2021)	IDH status. IDH-wildtype gliomas are classified as glioblastomas, and IDH-mutant gliomas are further sub-classified based on 1p/19q co-deletion status. Oligodendrogliomas are IDH-mutant and 1p/19q co-deleted, and astrocytomas are IDH-mutant and 1p/19q non-co-deleted. The CATNON study utilized the 2016 WHO classification criteria for central nervous system tumors and looked at patients with 1p/19q non-co-deleted anaplastic gliomas, which is an anaplastic astrocytoma using the 2016 and 2021 WHO classification. The primary benefit in CATNON was identified in the subgroup of patients with IDH 1/2 tumor mutations. Although no clinical benefit was identified for patients with IDH-wildtype tumors, these tumors would be classified as glioblastomas under 2021 WHO classification, which is already an FDA-approved indication. To avoid restricting the indication, this subgroup was not

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		specified in labeling. The product labeling should not restrict treatment of refractory anaplastic astrocytoma with temozolomide to patients who have previously received both a nitrosourea and procarbazine. Procarbazine, nitrosoureas, and temozolomide are all alkylating agents. The CATNON trial supports not requiring prior treatment with drugs of the same class, as patients in the adjuvant setting who did not receive prior procarbazine or nitrosourea achieved benefit.
Risk and Risk Management	• No new safety signals emerged for temozolomide in CATNON. (van den Bent 2021) • The most common grade 3 or 4 adverse events were thrombocytopenia (10%) and neutropenia (7%) in the adjuvant temozolomide arm. (van den Bent 2021) • In the adjuvant temozolomide arm, 8% of patients discontinued therapy due to	The safety profile of adjuvant temozolomide in patients with newly-diagnosed anaplastic astrocytomas without 1p/19q co-deletions is acceptable and is manageable with current labeling. Thrombocytopenia and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	toxicity. (van den Bent 2021) • Temozolomide, nitrosoureas, and procarbazine are all alkylating agents. Therefore, having the requirement that patients progress on an alkylating agent (nitrosourea) with a worse toxicity profile prior to treatment with temozolomide puts patients at risk of developing myelotoxicity that may preclude subsequent treatment with temozolomide or other agents (including investigational agents on clinical trials).	neutropenia are currently included under a myelosuppression subsection in the Warnings and Precautions section of the product labeling. The risk of removing specific drug products as required previously-received therapies from the product label is acceptable for the intended population.

The Applicant's Position

The Applicant agrees with all the FDA proposed revisions to section 2.2 Anaplastic Astrocytoma.

The FDA's Assessment

The FDA agrees with the Applicant's Position.

CATNON (NCT00626990) was an adequate and well-controlled randomized, open-label, multicenter trial, based on a critical evaluation of the stated methods from the published literature. The clinical meaningfulness and objectivity of overall survival as the major efficacy outcome measure and the observed results provides confidence in the effect demonstrated. This trial is supported by a well-established safety profile and mechanism of action, with confirmatory evidence of antitumor effects of temozolomide demonstrated in clinical trials in other brain tumors. Within this context, the review team's determination is that there is substantial evidence of effectiveness of temozolomide for the adjuvant treatment of adults with newly diagnosed anaplastic astrocytoma.

The existing indication of temozolomide for the treatment of adults with refractory anaplastic astrocytoma was updated to remove the stipulation that patients should have experienced disease progression on a drug regimen containing nitrosourea and procarbazine, based on FDA's review of the published literature and determination that the CATNON trial supports not requiring prior treatment with drugs of the same class, as patients in the adjuvant setting who did not receive prior procarbazine or nitrosourea achieved benefit.

3.0 NONCLINICAL PHARMACOLOGY/TOXICOLOGY PERTINENT TO PROPOSED UPDATED LABELING

TEMODAR is an alkylating agent.

Non-clinical pharmacology and toxicology information was revised; refer to sections 5, 8, and 17 of the proposed annotated product labeling for rationale and references, where applicable.

- Section 5, Warnings and Precautions, Section 5.5, Embryo-Fetal Toxicity: minor editorial changes revised to be consistent with current labeling practices
- Section 8, Use in Specific Populations, Section 8.1, Pregnancy: minor editorial changes to be consistent with current labeling practices
- Section 17, Patient Counseling Information, Embryo-Fetal Toxicity: minor editorial changes revised for consistency with current labeling practices under FDA's Pregnancy and Lactation Labeling Rule (PLLR)

The Applicant's Position

The Applicant agrees with all the FDA proposed revisions to the non-clinical pharmacology and toxicology information as outlined above.

The FDA's Assessment

Refer to the temozolomide labeling for updates pertinent to non-clinical pharmacology and toxicology.

4.0 CLINICAL PHARMACOLOGY PERTINENT TO PROPOSED UPDATED LABELING

Clinical pharmacology information in the proposed annotated labeling Section 12 was revised to conform with the Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance. Proposed clinical pharmacology-related changes and supporting published literature are provided in the annotated labeling.

- Section 12, Clinical Pharmacology, Section 12.1, Mechanism of Action: Revised to include that DNA alkylation at 06 and N7 positions of guanine leads to double strand breaks and programmed cell death
- Section 12, Clinical Pharmacology, Section 12.2, Pharmacodynamics: This subsection was added based on FDA's regulations at 21 CFR 201.57(c)(13)(B), which requires this subsection.
- The presentation of Drug Interaction studies was revised to reflect FDA's best labeling practices to enhance consistency, readability, and utility of this information by the healthcare provider.

The Applicant's Position

The Applicant agrees with all the FDA proposed revisions to section 12 Clinical Pharmacology as outlined above.

The FDA's Assessment

Refer to the temozolomide labeling for updates pertinent to clinical pharmacology.

5.0 SAFETY PERTINENT TO PROPOSED UPDATED LABELING

Existing safety data was reviewed and any proposed safety-related changes and supporting published literature are provided in the proposed annotated labeling.

Substantive proposed changes to the safety sections of the TEMODAR labeling include the following:

- Section 5 was reordered to reflect the relative clinical significance of the adverse reactions.
- Information on Myelosuppression from trial MK-7365-006 was moved from Section 6 to Section 5, to better characterize these adverse reactions.
- The warning and precaution for embryo-fetal toxicity was modified to advise not only pregnant women, but also females of reproductive potential, of this risk.
- A new warning and precaution for "(b) (4) exposure to opened capsules" was added (b) (4) and to align with labeling for other orally administered cytotoxic products. This risk does not apply to the intravenous formulation of TEMODAR.
- Section 6 was updated to include the sub-heading "Newly diagnosed anaplastic astrocytoma" and includes a statement on the safety findings for TEMODAR in this patient population.
- Section 6 Tables 3 and 4 were updated to use a threshold of >10% for inclusion of adverse reactions. Clinically relevant adverse reactions occurring in <10% of patients were included as text under each respective table.
- Other formatting changes were implemented throughout Section 5 and 6 to align with contemporary labeling practice.

The Applicant's Position

The Applicant agrees with the proposed safety revisions outlined above except for the following:

A new warning and precaution for "(b) (4) exposure to opened capsules."

The Applicant acknowledges the FDA recommendation, however, respectfully disagrees with the inclusion of the proposed text in the Warning and Precaution section (b) (4)

(b) (4)

Moreover, the proposed statement, "If TEMODAR capsules must be opened (b) (4) this should be done by a professional trained in safe handling of hazardous drugs using appropriate equipment and safety procedures" can be misleading. There are no available pharmacodynamics and pharmacokinetics data of the opened capsules, and therefore the Applicant does not recommend opening or crushing them.

However, in acknowledgment of the FDA recommendation, the Applicant proposes to include the following text:

5.6 Exposure to Opened Capsules

(b) (4)

This text aligns with the information in the current USPI sections:

2.4 Preparation and Administration

Swallow TEMODAR capsules whole with water. Advise patients not to open, or chew or dissolve the contents of the capsules [see Warnings and Precautions (5.6)].

17. PATIENT COUNSELING INFORMATION

(b) (4)

Although FDA proposed to delete, the Applicant respectfully requests to retain the precautionary statement shown below in Section 2.4 to provide instructions to follow if capsules are accidently opened or damaged and to be aligned with the proposed text in Section 5.6.

2.4 Preparation and Administration

If capsules are accidentally opened or damaged, take precautions to avoid inhalation or contact with the skin or mucous membranes. In case of powder contact, the hands should be washed.

The Applicant's text provides consistency in the information presented across Temozolomide labeling. The Applicant will continue to monitor the safety profile of temozolomide under routine pharmacovigilance activities.

Section 6 Tables 3 and 4

The Applicant agrees with the Section 6 Tables 3 and 4 revisions to use a threshold of >10% for inclusion of adverse reactions and include the clinically relevant adverse reactions occurring in <10% of patients as text under each respective table. The Applicant proposes editorial revisions to the text under each respective table for clinically relevant adverse reactions occurring in <10% of patients to ensure consistency of presentation by system organ class and relocation of footnote referring to the terms included in the adverse reaction of blurred vision as shown.

For the clinically relevant adverse reactions in <10% of patients included as text under Table 3 for Newly Diagnosed Glioblastoma the following revisions are proposed:

Central & Peripheral Nervous System: memory impairment, confusion

Eye: vision blurred

Gastrointestinal System: stomatitis, abdominal pain, (b) (4)

(b) (4)

General: weakness, dizziness

Immune System: allergic reaction

Injury: radiation injury not otherwise specified

Musculoskeletal System: arthralgia

Platelet, Bleeding, & Clotting: thrombocytopenia

Psychiatric: insomnia

Respiratory System: coughing, dyspnea

Special Senses Other: taste perversion

Skin & Subcutaneous Tissue: dry skin, pruritus, erythema

For the clinically relevant adverse reactions in <10% of patients included as text under Table 4 for Refractory Anaplastic Astrocytoma the following revisions are proposed:

Central and Peripheral Nervous System: paresthesia, somnolence, paresis, urinary incontinence, ataxia, dysphasia, convulsions local, gait abnormal, confusion

Endocrine: adrenal hypercorticism

Gastrointestinal System: abdominal pain, anorexia

General: back pain, [redacted] (b) (4)

Metabolic: weight increase

Musculoskeletal System: myalgia

Psychiatric: anxiety, depression

Reproductive Disorders: breast pain female

Respiratory System: upper respiratory tract infection, pharyngitis, sinusitis, coughing

Skin & Appendages: rash, pruritus

Urinary System: urinary tract infection, micturition increased frequency

*Vision: diplopia, vision abnormal**

** This term includes blurred vision; visual deficit; vision changes; and vision troubles.*

The FDA's Assessment:

FDA agrees with the Applicant's proposed Section 5 and 6 changes. Warnings and Precautions Section 5.6 title has been updated to "Exposure to Opened Capsules" and the wording has been updated for clarity. The Applicant's proposed changes in Section 6 are acceptable and reflect adverse reactions by system.

6.0 PEDIATRIC INFORMATION PERTINENT TO PROPOSED UPDATED LABELING

Pediatric information was reviewed; proposed changes related to pediatric information and supporting published literature are discussed in the pediatric sections in the proposed annotated labeling, including section 8.4 and other sections, where applicable.

The Applicant's Position

The Applicant has reviewed the pediatric information in the label and did not identify any FDA proposed revisions. The Applicant does not propose any revisions to the pediatric information in the label.

The FDA's Assessment

Refer to the temozolomide labeling for updates pertinent to pediatric information.

7.0 ADDITIONAL PROPOSED LABELING CONSIDERATIONS

Full Prescribing Information: Following review of the existing product labeling, and independent FDA review of available evidence, FDA included additional proposed modifications in the proposed annotated product labeling attached to the Supplement Request Letter to adhere more closely to current guidance and regulations.

Where applicable, format and content of the labeling were updated to conform to the Physician Labeling Rule (PLR) and current labeling guidances.

HIGHLIGHTS

- The Applicant should update Highlights to reflect final labeling proposal.

TABLE OF CONTENTS

- The Applicant should update the Table of Contents to reflect final labeling proposal.

Section 2

- Section 2.1, Important Instructions for Dosage and Administration: FDA proposes to add this section as a stand-alone subsection by incorporating the relevant information previously included in other subsections of Section 2.
- In Section 2.1, a revision was made regarding having adequate hematologic parameters (e.g., absolute neutrophil count, platelet count) prior to dosing. Language was revised to avoid implying a contraindication when interpreted as previously written.
- Section 2.4, Preparation and Administration: FDA proposes to add "parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit" per 21 CFR 201.57(c)(3)(iv).

(b) (4)

Section 3

- Minor editorial change to note that for injection, 100 mg white to light tan or light pink lyophilized powder for reconstitution in a single-dose vial.

Section 4

- **Contraindications:** FDA recommends adding "serious" to avoid having a contraindication for patients who may experience only mild hypersensitivity reactions.

Section 5

- Information on risks associated with safe handling for patients was added to Section 5.6, which is a new warning and precaution.

Section 6

- Refer to Section 5.0 of this review for changes proposed to Section 6 of the USPI,

Section 8

- Section 8.1, Pregnancy: minor editorial changes to be consistent with current PLLR labeling practices,
- Section 8.5, Geriatric Use: The information contained in this subsection must pertain to use of the drug in persons 65 years of age and older. If available, the incidence in patients 75 and older should be added. If available, the Applicant should consider revising the incidence of Grade 4 neutropenia and thrombocytopenia to reflect experience in patients over 75. This subsection should also contain a summary of observed differences in safety for geriatric patients.

Section 11

- Minor editorial change to note that for injection, 100 mg white to light tan or light pink lyophilized powder for reconstitution in a single-dose vial.

Section 12

- The presentation of Drug Interaction studies was revised to reflect FDA's best labeling practices to enhance consistency, readability, and utility of this information by the healthcare provider.

Section 14

- Refer to Sections 1.0 and 2.0 of this review for changes proposed to Section 14 of the USPI

Section 17

- Revisions made to be consistent with current PLLR labeling practices

Patient Labeling: FDA will propose updates to the existing PPI as part of labeling negotiations.

(b) (4) **Labeling:** FDA proposes removing (b) (4) (b) (4)

Package and Container Labeling: The Applicant should submit copies of all container/carton labeling with any necessary updates to ensure adherence to current regulations and guidances.

The Applicant's Position

Full Prescribing Information:

The Applicant agrees with the additional proposed labeling considerations except for those previously mentioned in Section 5 of the Assessment Aid and the geriatric information in Section 6.1 and Section 8.5 in the Full Prescribing Information as described below. The Applicant also proposes additional revisions to Section 17 as shown below. Furthermore, the Applicant has updated the Highlights and Table of Contents to reflect the final labeling proposal, as requested.

Section 6.1 and 8.5

Reference is made to the April 11, 2023, teleconference between the Applicant and the FDA which addressed the requested revisions to the geriatric information in Sections 6.1 and 8.5 to reflect the safety profile in patients ≥65 and <65 years of age. During the meeting, the FDA was informed that the Applicant is relying solely on the data presented in the published literature (van den Bent 2021) and does not have access to the data for the CATNON trial. Per the van den Bent publication (2021), the age stratification factor used for the primary efficacy analysis in the CATNON Trial included participants aged older than 50 (>50) versus those 50 years and younger (≤50). The publication reports the results from the second interim analysis. There were 751 participants randomized to treatment. As reported in the Supplementary Appendix to the publication, specifically in Supplementary Table 2, there were 233 (31.0%) participants older than 50 years. Given the age stratification factor used in the study and the fact that we do not have access to the data, the Applicant could not determine the number (and/or percentage) of geriatric patients (defined as 65 years and older) nor confirm the statement regarding safety and efficacy across the age groups. Therefore, the Applicant proposes to provide the percentage of patients aged older than 50 years and delete the additional statement regarding safety and efficacy across groups.

During the same teleconference, the proposed revision to include a statement in the label regarding the incidence of reports of Grade 4 neutropenia or thrombocytopenia in patients ≥65 and <65 was addressed. The Applicant informed the FDA that given the age of the studies (initial approval in August 1999 for treatment of adult patients with refractory anaplastic astrocytoma, and subsequent approval in March 2005 for treatment of patients with glioblastoma multiforme), it would be difficult to reanalyze the data.

The FDA agreed with the Applicant's proposals during the meeting. The Applicant appreciates the FDA flexibility in updating the geriatric information across sections of the label and

considering the difficulties noted, proposes to retain the data in patients ≥70 vs <70 in both Section 6.1 to Section 8.5.

Section 17

The Applicant agrees with the proposed FDA content revisions to Section 17. However, proposes to reorganize the content to align to the order of presentation of information in Section 5 as shown.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression

Inform patients that TEMODAR can cause low blood cell counts and the need for frequent monitoring of blood cell counts. Advise patients to contact their healthcare provider immediately for bleeding, fever, or other signs of infection [see Warnings and Precautions (5.1)].

Hepatotoxicity

Advise patients of the increased risk of hepatotoxicity and to contact their healthcare provider immediately for signs or symptoms of hepatoxicity [see Warnings and Precautions (5.2)].

(b) (4)

Pneumocystis Pneumonia

Advise patients of the increased risk of Pneumocystis pneumonia and to contact their healthcare provider immediately for new or worsening pulmonary symptoms. Inform patients that prophylaxis for Pneumocystis pneumonia may be needed [see Dosage and Administration (2.1), Warnings and Precautions (5.3)].

(b) (4)

(b) (4)

Secondary Malignancies

Advise patients of the increased risk of myelodysplastic syndrome and secondary malignancies [see Warnings and Precautions (5.4)].

(b) (4)

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5), Use in Specific Populations (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with TEMODAR and for 6 months after the last dose [see Use in Specific Populations (8.3)].

Advise male patients with pregnant partners or female partners of reproductive potential to use condoms during treatment with TEMODAR and for 3 months after the last dose [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)].

Advise male patients not to donate semen during treatment with TEMODAR and for 3 months after the last dose [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)].

Lactation

Advise women not to breastfeed during treatment with TEMODAR and for 1 week after the last dose [see Use in Specific Populations (8.2)].

Infertility

Advise males of reproductive potential that TEMODAR may impair fertility [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)].

Patient Labeling:

Although the FDA plans to propose updates to the existing PPI as part of labeling negotiations, the Applicant has reviewed the Patient Labeling and proposed revisions to align with the proposed revisions in the Full Prescribing Information.

(b) (4) Labeling

The Applicant agrees with the FDA proposal (b) (4)

Package and Container Labeling

Temodar (temozolomide) for Injection

The Applicant has reviewed the Package and Container Labeling and proposes changes to the container carton for Temodar for Injection (b) (4) The primary vial label does not include (b) (4) (b) (4) Therefore, no changes are proposed to the primary vial label.

Temodar (temozolomide) Capsules

The Applicant has discontinued sales of all Temodar capsule strengths, and all product has reached expiry as of December 2022. As Temodar Capsules are no longer in distribution, the Package and Container Labeling will not be updated.

The FDA's Assessment

For section 8.5, Geriatric Use, the Applicant notes that information specifically on patients defined by the cutoff of 65 years of age is limited, and thus proposes to use 50 years as a cutoff since this was a stratification used in the van den Bent trial. FDA does not use age 50 or over in the geriatric use section of labeling. Additionally, given that only ~30% of patients were over the age of 50 and the median age was 42 years of age in the van den Bent study, the original language will be maintained. This states that 31% of patients in the CATNON trial were 65 years

and older and this study did not include a sufficient number of patients aged 65 and older to determine differences in safety or effectiveness from younger patients.

For Section 17, FDA agrees with the Applicant's proposed revisions to reorder events to be consistent with most recent updates to Section 5.

8.0 FDA'S RECOMMENDATIONS

8.1 Clinical and Labeling

The FDA review team recommends approval.

8.2 Non-Clinical

The FDA review team recommends approval.

8.3 Clinical Pharmacology

The FDA review team recommends approval.

9.0 FDA REVIEW TEAM SIGNATURE PAGE

X	X
Amy Skinner, Ph.D. Pharmacology/Toxicology Primary Reviewer	Claudia Miller, Ph.D. Pharmacology/Toxicology Team Lead
X	X
Runyan Jin, Ph.D. Clinical Pharmacology Primary Reviewer	Jeanne Fourie Zirkelbach, Ph.D. Clinical Pharmacology Team Lead
X	
Sundeep Agrawal, MD Clinical Reviewer Cross Disciplinary Team Lead	

Disclaimer: The FDA's recommendations and opinions are limited to this Assessment Aid and do not extend to other documents regarding this application. In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

X	X
William Pierce, Pharm.D., MPH	Elizabeth Everhart, MSN, RN, ACNP
Associate Director for Labeling	Associate Director for Labeling

10.0 OFFICE DIRECTOR

X

Jennifer Gao, MD

Associate Director

Oncology Center of Excellence

11.0 APPENDICES

See annotated package insert containing FDA's recommended updates**.**

11.1 Sources of Clinical Data and Review Strategy

The Project Renewal Support Team reviewed information regarding potential unapproved uses in the post-marketing setting as described in multiple drug compendia.[3] Following identification of potential labeling changes regarding new/updated indications and dosage regimens, the Project Renewal Support Team obtained agreement from the new drug application holder for participation in this process. The Project Renewal Support Team then identified Research Team Members (RTMs), defined as subject matter experts and key opinion leaders with expertise in these disease areas based on recommendations by relevant professional organizations.[4] Medical hematology/oncology fellows were also included as part of the educational component of this project; both RTMs and hematology/oncology fellows evaluated scientific literature identified through a python-based tool of PubMed describing such unapproved uses, including both positive and negative studies.

Research teams were formed with relevant disease-specific expertise; the teams discussed the available data in a series of meetings to reach consensus regarding proposals for labeling modifications. Specifically, the teams considered existing labeling including dose, safety, pharmacology and special populations, and whether there were adequate data to establish the effectiveness of the drug for any new uses. For new uses, the RTMs provided recommendations for the proposed indication(s) and recommended dosage regimen.

The final Project Renewal Assessment Aid documents FDA's independent assessment of data sources to support proposed recommendations for labeling modifications including Project Renewal review above, additional published literature review, FDA Adverse Event Reporting System data, and assessment of the existing Temodar labeling for adherence to current guidance and regulations.

[3] Center for Medicare and Medicaid Services-designated compendia; Lexicomp Online (Walters Kluwer Lexi-Drugs); Micromedex (Truvent Analytics Micromedex Drug DEX), and the National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium.
[4] Professional organizations include, but are not limited to, the American Society for Clinical Oncology (ASCO); American Society for Hematology (ASH); American Association for Cancer Research (AACR).

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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Amy Skinner, PhD	OOD/DHOT	Sections: 3, 5, 7 and subsection 8.2	**Select one:** ☐ Authored ☒ Approved
	Signature: Amy M. Skinner -S Digitally signed by Amy M. Skinner -S Date: 2023.09.08 12:10:31 -04'00'			
Nonclinical Team Leader	Claudia Miller, PhD	OOD/DHOT	Sections: 3, 5, 7 and subsection 8.2	**Select one:** ☐ Authored ☒ Approved
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Clinical Pharmacology Reviewer	Runyan Jin, PhD	OCP/DCPII	Sections: 4, 7 and subsection 8.3	**Select one:** ☐ Authored ☒ Approved
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Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach, PhD	OCP/DCPII	Sections: 4, 7 and subsection 8.3	**Select one:** ☐ Authored ☒ Approved
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Clinical Reviewer and Cross-Disciplinary Team Leader (CDTL)	Sundeep Agrawal, MD	OOD/DO1 and OCE	Sections: All	**Select one:** ☒ Authored ☒ Approved
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