# Trilaciclib (COSELA)
# National Drug Monograph
# November 2022

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.*

## FDA Approval Information

### Description/Mechanism of Action

- Trilaciclib is a kinase inhibitor of cyclin-dependent kinase (CDK) 4 and 6. Inhibition of CDK 4 and 6 causes a transient G1 phase cell cycle arrest of hematopoietic stem and progenitor cells in the bone marrow that give rise to red blood cells, circulating neutrophils, and platelets.

### Indication(s) Under Review in This Document

- Decrease the incidence of chemotherapy-induced myelosuppression when administered prior to a platinum/etoposide containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SLCL).

### Dosage Form(s) Under Review

- For injection: 300mg/mL Trilaciclib single-dose vial; 240mg/m$^2$ IV over 30 minutes completed within 4 hours prior to the start of chemotherapy.

## Clinical Evidence Summary

### Efficacy Considerations

- This review focuses on 3 small studies: 2 studies in first-line chemotherapy of small-cell lung cancer and one study in the second-line treatment of small-cell lung cancer with topotecan.
- Efficacy data are summarized in Table 1

**Table 1: Efficacy results from clinical trials**

| Study | Study Design | ECOG PS | Treatment | Results |
|---|---|---|---|---|
| **Weiss, at al. 2019**[1] G1T28-02 Study Group **Phase Ib/II DB, PC** | I: ES-SCLC PS 0-2 | 0-2 | Trilaciclib (n=39) IV vs placebo (n=38) day one of chemotherapy Growth factors allowed | Primary EP: Define RP2D and assess safety and tolerability Phase 2: # cycles completed comparable between Trilaciclib and placebo Dose intensities of chemo higher for Trilaciclib |

| | | | | |
|---|---|---|---|---|
| | | | | Reduced duration/severity of neutropenia C1 (0 vs 3%)<br>Rate of G-CSF admin: 11% vs 65% |
| **Daniel, et al. 2020**[2]<br><br>**Phase II DB,PC** | I:<br>ES-SCLC<br><br>E:<br>Symptomatic brain mets<br>Prior systemic chemo for ES-SCLC | 0-2 | Trilaciclib (n=54) IV or placebo (n=53) each day prior to etoposide/carboplatin/atezolizumab (Days 1-3) Every 21 days for 4 cycles, then atezolizumab maintenance<br><br>Primary prophylaxis with G-CSF in C1 prohibited (risk of FN ≤20%) | Primary EP: DSN in C1 and SN throughout treatment<br>Mean DSN C1: 0 vs 4 days<br>Mean SN: 1.9% vs 49.1%<br>G-CSF: 29.6 vs 47.2% (RR 0.646; 95%CI 0.403-1.034) |
| **Hart, et al. 2021**[3]<br><br>**Phase Ib/II DB, PC** | I:<br>ES-SCLC with progression during or after first- or second-line chemo<br>Eligible for topotecan<br><br>E:<br>History of topotecan<br>Brain mets requiring immediate treatment | 0-2 | Trilaciclib 240 mg/m$^2$ IV (n=32) or placebo (n=29) prior to topotecan days 1-5 every 21 days | Primary EP: DSN in C1 and SN throughout treatment<br>Mean DSN C1: 2 vs 7 days<br>SN: 40.6 vs 75.9%<br>G-CSF: 50 vs 65.5% |

DB=double blind; PC=placebo controlled; I=Inclusions; ES-SCLC=Extensive-stage Small Cell Lung Cancer; PS=Performance Status; EP=endpoint; RP2D=recommended phase 2 dose; G-CSF=granulocyte colony stimulating factor; FN=febrile neutropenia; C1=cycle 1; DSN=duration of severe neutropenia; SN=severe neutropenia

Pooled analyses

- Weiss, et al. 2021[4]: Pooled analysis from three phase II trials (in table above)
- Mean Duration of Severe Neutropenia (standard deviation) in C1: 0 days (1.8) vs 4 days (5.1); no difference in rates of febrile neutropenia
- Severe Neutropenia throughout: 11.4 vs 52.9%
- G-CSF administration: 28.5 vs 56.3%
- Hospitalization due to chemo-induced myelosuppression or sepsis: 4.1 vs 13.6%
- Patient Reported Outcomes: For physical well-being, functional well-being, fatigue, anemia trial outcome index, and Functional Assessment of Cancer Therapy-Anemia, subscales and domain scores found that patients treated with trilaciclib improved scores or remained stable while patients who received placebo remained stable or worsened scores.

- Ferrarotti, et al. 2021[5]: Pooled analysis from three phase II trials (in table above)
- Mean DSN in Cycle 1, Severe Neutropenia, and G-CSF administration as reported by Weiss, et al. above.

## Safety Considerations

- **Boxed warnings:** None
- **Contraindications:** History of serious hypersensitivity to trilaciclib
- **Other warnings / precautions**:
  - Injection site reactions: including phlebitis and thrombophlebitis
  - Acute Drug Hypersensitivity Reactions: withhold for moderate reactions, permanently discontinues for severe or life-threatening reactions
  - Interstitial Lung Disease (ILD)/pneumonitis: Permanently discontinue for recurrent symptomatic or severe/life-threatening ILD/pneumonitis
  - Embryo-fetal toxicity
- **Adverse reactions**
    - **Common**: fatigue, hypocalcemia, hypokalemia, hypophosphatemia, ↑ aspartate aminotransferase, headache, pneumonia
    - **Serious Adverse events / Deaths / Discontinuation:**
        - Serious: 30%; respiratory failure, hemorrhage, thrombosis
        - Deaths: 5%; pneumonia, respiratory failure, acute respiratory failure, hemoptysis, cerebrovascular accident
        - Permanent discontinuation 9%; pneumonia, asthenia injection-site reaction, thrombocytopenia, cerebrovascular accident, ischemic stroke, infusion-related reaction, respiratory failure, myositis
    - Drug-drug interactions: effects of trilaciclib on certain substrates of OCT2, MATE1, or MATE-2K; co-administration with trilaciclib may results in increased concentration or accumulation of substrates in kidney (dofetilide, dalfampridine, cisplatin)

## Other Considerations

- Special Populations
  - Pregnancy: make cause fetal harm due to mechanism
  - Lactation: no human data; potential for serious adverse reactions in breast-fed children
  - Patients of reproductive potential: Use effective contraception during therapy and for at least 3 weeks after the final dose
  - Geriatric use: no overall differences in efficacy or safety observed
  - Hepatic impairment: not recommended for moderate or severe hepatic impairment (not studied in patients with moderate or severe hepatic impairment [total bilirubin >1.5 X ULN irrespective of AST]).
- Primary Prophylaxis with growth factors: Generally, primary prophylaxis with granulocyte growth factors is not warranted unless the risk of febrile neutropenia with the first cycle of chemotherapy is ≥20%. If the risk is <20%, primary prophylaxis may be used if the patient has other risk factors for febrile neutropenia. Growth factors are generally not routinely used if the patient is neutropenic but not febrile.

**Risk-Benefit Assessment (for Oncology NMEs only)**

- **Outcome in clinically significant area:** Duration of Severe Neutropenia
- **Effect Size:** 0 vs 4 days (pooled data) with some use of G-CSF needed
- **Potential Harms:** High risk (but expected risk based on mechanism)
- **Net Clinical Benefit:** Minimal

## Other Therapeutic Options

Alternative treatments for prevention of neutropenia are listed in table 3 below

**Table 3 Treatment Alternatives**

| Drug | Formulary status | Clinical Guidance | Other Considerations |
|---|---|---|---|
| **Trilaciclib** | TBD | Decrease the incidence of myelosuppression when used before platinum-etoposide or topotecan for extensive-stage small cell lung cancer | Duration of severe neutropenia was decreased, but use of G-CSF was not eliminated |
| **Filgrastim** | F | G-CSF may be used as a prophylactic option. | Systematic review of G-CSF use in treatment of SCLC has not shown an OS advantage. |

## Projected Place in Therapy

- Small-cell lung cancer (SCLC) comprises approximately 15-20% of lung cancer diagnoses.
- SCLC is very sensitive to cytotoxic chemotherapy administered in the first-line setting; however, most patients relapse after response. After relapse of first-line chemotherapy, topotecan (a topoisomerase 1 inhibitor) is an important treatment option but it is significantly myelotoxic.
- One of the major toxicities of cytotoxic chemotherapy is myelosuppression. Chemotherapy-induced myelosuppression can lead to increased risk for infection, hospitalization, dose reduction, and dose delays. It is currently managed by dose reductions, dose delays, and/or white blood cell growth factors (G-CSF).
- Trilaciclib is a cyclin-dependent kinase 4 and 6 inhibitor given prior to cytotoxic chemotherapy to prevent myelosuppression.
- Trilaciclib was studied in one phase II (Daniel) and two phase Ib/II trials (Weiss and Hart) and two pooled publications (Weiss and Ferrarotto). The Weiss and Daniel trials were in treatment-naïve patients. The Hart trial was in the second line with topotecan.
- In the first-line setting for extensive-stage SCLC, trilaciclib significantly reduced the risk for severe neutropenia compared to placebo.
- In the second line topotecan trial, trilaciclib reduced the risk of severe neutropenia and hospitalizations due to chemotherapy-induced myelosuppression. There was no reduction in mortality seen.
- A May 2022 ICER evaluation of novel agents to prevent chemotherapy-induced myelosuppression included trilaciclib. In ICER's evaluation, the results of the trilaciclib trials are mixed. There is a reduction in duration of severe neutropenia, severe anemia, serious adverse events due to myelosuppression, need for chemotherapy dose reductions, and hospitalizations due to myelosuppression. However, there were no reductions in risk of total hospitalizations, serious adverse events, or deaths due to adverse events. In addition, the HR for overall mortality was 1.00 (95%CI 0.75-1.35). There was moderate certainty that use of trilaciclib is comparable to or has a small net health benefit compared to standard of care.[6]
- ICER incremental cost-effectiveness ratio sensitivity analysis for both first and second-line use of trilaciclib, the incremental cost-effectiveness per QALY exceeded $200,000. Price discounts to achieve the thresholds of $100,000 or $150,000 per QALY would need to be in the range of 67-71%.
- Trilaciclib might be used to prevent long durations of severe neutropenia in patients receiving first-line chemotherapy or second-line topotecan therapy for SCLC in select patients with high risk for prolonged neutropenia.

## References

[1] Weiss JM, Csoszi T, Maglakalidze M, et al. Myelopreservation with the CDK4/6 inhibitor Trilaciclib in patients with small cell lung cancer receiving first-line chemotherapy; a phase Ib/randomized phase II trial. Ann Oncol 2019; 30: 1613-1621.
[2] Daniel D, Kuchava V, Bondarenko I, et al. Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed extensive-stage small cell lung cancer: a multicentre, randomised, double-blind, placebo-controlled phase II trial. Int J Cancer 2020; 1–14. https://doi.org/10.1002/ijc.33453.
[3] Hart LI, Ferrarotto R, Andric ZG, et al. Myleopreservation with trilaciclib in patients receiving topotecan for small cell lung cancer: results from a randomized, double-blind, placebo-controlled, phase II study. Adv Therapy 2021; 38: 350-365.
[4] Weiss J, Goldschmidt J, Andric Z, et al. Effects of trilaciclib on chemotherapy-induced myelosuppression and patient-reported outcomes in patients with extensive-stage small cell lung cancer: pooled results from three phase II , randomized, double-blind, placebo-controlled studies. Clinical Lung Cancer 2021; 22: 449-460.
[5] Ferrarotto R, Anderson I, Medgyasszay B, et al. Trilaciclib prior to chemotherapy reduces the usage of supportive care interventions for chemotherapy-induced myelosuppression in patients wit extensive-stage small cell lung cancer: pooled analysis of three randomized phase 2 trials. Cancer Medicine 2021; 10: 5748-5756.
[6] ICER. Novel agents to prevent chemotherapy-induced neutropenia and other myelosuppressive effects. Revised Evidence Report. May 2022.

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# Appendix A. Acquisition Prices and Cost Considerations

**Refer to VA pricing sources for updated information**