



Positive Quality Intervention: Copanlisib (Aliqopa) Toxicity Management

Description: Copanlisib is an intravenous (IV) phosphatidylinositol 3-kinase (PI3K) inhibitor indicated for the treatment of relapsed follicular lymphoma (FL) in patients that have received at least two prior systemic therapies.¹ This PQI will review how to manage select toxicities associated with copanlisib.

Background: Copanlisib is a pan-class I PI3K inhibitor with preferential inhibitory activity against PI3K- α and PI3K- δ isoforms, which are expressed in malignant B-cells.² Accelerated approval of copanlisib was based on the results of a phase II trial in relapsed or refractory indolent B-cell lymphomas; overall response rate (ORR) of 59% and complete response (CR) rate of 12% were observed.³ The adverse events associated with copanlisib can be explained by the PI3K isoform targets with the most common adverse events being hyperglycemia, hypertension, infections, and diarrhea.¹⁻³ Hyperglycemia is an expected on-target effect of PI3K- α inhibition with systemic inhibition of PI3K- α .⁴ Blood glucose typically peaked 5 to 8 hours post-infusion with grade 3 or 4 hyperglycemia (blood glucose \geq 250 mg/dL) occurred in 41% of patients treated with serious hyperglycemic events occurring in 2.8% of patients.¹ Hypertension associated with copanlisib peaks 2 hours post-infusion and resolves within 24 hours.¹ Grade 3 hypertension (\geq 160/100 mmHg) occurred in 26% of patients with serious hypertensive events occurring in 0.9% of patients.¹ Infections occurred in patients receiving copanlisib with 19% of patients experiencing serious infections.¹ Diarrhea has been commonly seen with various other PI3K-inhibitors and was also seen in copanlisib trials with diarrhea developing in 36% of patients with Grade 3 in 5% of patients.¹ There are currently no black box warnings and both hypertension and hyperglycemia were observed to be transient. Follicular lymphoma RR was 59%, CR was 20%, and ORR was 60%.⁵ Below we will review the prevention and management of common toxicities associated with copanlisib including hyperglycemia, hypertension, infections, and diarrhea.

PQI Process:

- Hyperglycemia prevention and management¹:
 - Check blood glucose prior to copanlisib infusion and withhold dose unless the following parameters have been met:
 - Fasting plasma glucose \leq 160 mg/dL OR random glucose \leq 200 mg/dL
 - If pre-dose blood glucose \geq 500 mg/dL then withhold until above parameters have been met and reduce copanlisib from 60 mg to 45 mg
 - On subsequent occurrences, reduce to 30 mg when above parameters have been met
 - Nondiabetic patients⁴:
 - Consider checking HbA1c prior to copanlisib treatment and re-checking once treatment is discontinued.
 - Patients who develop an increase in HbA1c during copanlisib treatment should be re-tested in 3 months to determine if HbA1c has returned to baseline
 - Post-infusion monitoring is not needed for nondiabetic patients
 - Insulin is discouraged in nondiabetic patients due to the increased risk of hypoglycemia
 - Encourage adequate hydration

Important notice: National Community Oncology Dispensing Association, Inc. (NCODA), has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional.



PQI Process continued:

- Prediabetic/diabetic patients:^{1,4}
 - Check HbA1c prior and consider consulting with an endocrinologist prior to treatment
 - Post-infusion blood glucose should be checked, and monitoring should occur
 - Post-dose blood glucose ≥ 500 mg/dL consider reduction to 45 mg with subsequent infusion
 - When a meal is consumed within 8 hours post-infusion ensure low carbohydrate diet
- Hypertension monitoring and management:
 - Check blood pressure at least 15 minutes prior infusion proceed if:
 - $BP \leq 150/90$ mmHg
 - If anti-hypertensives were required, consider reducing to 45 mg
 - Discontinue if blood pressure remains uncontrolled despite anti-hypertensives
- Infection prevention and management:
 - Before initiating initiate prophylaxis for pneumocystis jirovecii pneumonia (PJP)
 - Monitor patients for signs and symptoms of infection and withhold for Grade 3 or higher
- Neutropenia
 - Reported: All Grade (32%), Grade 3 (10%), Grade 4 (15%)¹
 - Monitor blood counts at least weekly while under treatment
 - $ANC < 0.5 \times 10^3$ cells/mm³: hold and monitor until $ANC \geq 0.5 \times 10^3$ cells/mm³ then resume at previous dose
 - If $ANC 0.5 \times 10^3$ cells/mm³ or less recurs, then reduce to 45 mg
- Diarrhea management:
 - If diarrhea develops, encourage adequate hydration and counsel on eating several small meals a day while adhering to the BRAT diet
 - See **Oncolytic Induced Diarrhea PQI**
 - Consider use of over the counter (OTC) anti-diarrheal including loperamide
 - Grade 3 diarrhea, hold until diarrhea resolves to \leq Grade 1 and consider reduction to 45 mg⁴

Patient Centered Activities:

- Consider endocrinology consult in diabetic patients starting copanlisib
- Counsel all patients on signs and symptoms of hyperglycemia, encourage a low-carbohydrate diet and consider insulin dose adjustments in diabetic patients already on insulin 6-8 hours post infusion
- Check blood pressure at least 15 minutes prior to infusion and consider the use of anti-hypertensives if blood pressure $\geq 150/90$ mmHg on two or more blood pressure checks
- Ensure high-risk patients are on PJP prophylaxis
- Counsel patient on use of OTC anti-diarrheal if diarrhea occurs

Important notice: National Community Oncology Dispensing Association, Inc. (NCODA), has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional.



References:

1. Aliqopa (copanlisib) [prescribing information]. Whippany, NJ: Bayer Healthcare Pharmaceuticals Inc; February 2020.
2. Esposito A, Viale G, Curigliano G. Safety, tolerability, and management of toxic effects of phosphatidylinositol 3-Kinase inhibitor treatment in patients with cancer. *JAMA Oncol.* 2019;5(9):1347-1354.
3. Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition of copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol.* 2017;35(35):3898-3905.
4. Cheson B, O'Brien S, Ewer M, et al. Optimal management of adverse events from copanlisib in the treatment of patients with non-hodgkin lymphomas. *Clin Lymphoma Myeloma Leuk.* 2019;19(3):135-141.
5. Dreyling M, Santoro A, Mollica L, et al. Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study. *Am J Hematol.* 2020;1–10. <https://doi.org/10.1002/ajh.25711>.

Important notice: National Community Oncology Dispensing Association, Inc. (NCODA), has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional.