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Section:	Prescription Drugs	**Effective Date:**	April 1, 2024
Subsection:	Gastrointestinal Agents	**Original Policy Date:**	April 20, 2018
Subject:	5-HT3 Antagonists	**Page:**	1 of 6

Last Review Date: March 8, 2024

5-HT3 Antagonists

Description

Aloxi injection (palonosetron) / Anzemet* tablets (dolasetron) / Granisetron injection, Kytril tablets, Sancuso patch, Sustol injection (granisetron) / Ondansetron 24mg tablets, Zofran, Zuplenz oral film* (ondansetron)

* Prior authorization for the brand formulation applies only to formulary exceptions due to being a non-covered medication.

Background
Selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonists are antinauseant and anti-emetic agents with little or no affinity for other serotonin receptors, making them very useful in the treatment of nausea and vomiting. Often, these agents are used in the treatment of nausea and vomiting associated with chemotherapy in the treatment of cancer, as many of these 5-HT3 receptors are located centrally in the chemoreceptor trigger zone. 5-HT3 receptors are also located peripherally on vagal nerve terminals as well as on enteric neurons in the GI tract. When activated, they stimulate GI secretions and vagal afferent discharge, which induces vomiting. 5-HT3 antagonists block this from occurring (1).

Regulatory Status
FDA-approved indications:

- Aloxi, Anzemet, Granisetron, Kytril, Sancuso, Sustol, Zofran, and Zuplenz are serotonin-3 (5-HT3) receptor antagonists indicated for the prevention and treatment of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy or post-operative nausea and vomiting (2 -10).

- Ondansetron 24mg tablets are indicated for the prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy (11).

Off-label use of ondansetron for the treatment of nausea and vomiting of pregnancy during the first trimester did not increase the risk of specific birth defects (12).

Related policies
Barhemsys, Cannabinoids, NK1 antagonists

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

5-HT3 receptor antagonists may be considered **medically necessary** if the conditions indicated below are met.

5-HT3 receptor antagonists may be considered **investigational** for all other indications.

Prior-Approval Requirements

Prior authorization is not required if prescribed by an oncologist and/or the member has paid pharmacy claims for an oncology medication(s) in the past 6 months for a diagnosis of cancer.

Diagnoses

All 5-HT3 Antagonists (except for ondansetron 24mg tablets)

Patient must have **ONE** the following:

1. Prevention of nausea and/or vomiting due to radiation or cancer chemotherapy
2. Treatment of nausea and or vomiting due to radiation or cancer chemotherapy
3. Post-operative nausea and/or vomiting
    a. Operation was within the last month
4. **Zofran and Zuplenz only**: Nausea and/or vomiting of pregnancy (NVP)
    a. Patient has had an inadequate treatment response, intolerance, or contraindication to another treatment such as vitamin B6 or doxylamine

Ondansetron 24mg tablets only

Age 18 years of age or older

Diagnosis

Patient must have the following:

1. Prevention of nausea and/or vomiting due to radiation or cancer chemotherapy

Prior – Approval *Renewal* Requirements

Same as above

Policy Guidelines

Pre - PA Allowance

Quantity

Medication	Quantity Limit
Kytril (granisetron) 1 mg	6 tablets per 90 days
Sancuso (granisetron) patches	6 patches per 90 days
Zofran (ondansetron) 4 mg	36 units per 90 days
Zofran (ondansetron) 8 mg	
Zofran ODT (ondansetron) 4 mg	
Zofran ODT (ondansetron) 8 mg	
Zofran suspension (4 mg/5 mL)	180 mL per 90 days

Prior - Approval Limits

Quantity

Medication	Quantity Limit per 30 days	Quantity Limit per 90 days
Aloxi (palonosetron) 0.25mg/5mL	20 mLs per 30 days **OR**	60 mLs per 90 days **OR**
Palonosetron 0.25mg/2mL		
Granisetron 0.1mg/mL	4 mLs per 30 days **OR**	12 mLs per 90 days **OR**
Granisetron 1mg/mL single use vials		

Granisetron 4mg/4mL multiuse vial		
Kytril (granisetron) 1mg	6 tablets per 30 days **OR**	12 tablets per 90 days **OR**
Sancuso (granisetron) patches	6 patches per 30 days **OR**	12 patches per 90 days **OR**
Sustol ER Injection (granisetron) 10 mg/0.4mL	4 syringes per 30 days **OR**	12 syringes per 90 days **OR**
Ondansetron 24mg tablets	Not approved for use post-op	6 tablets per 90 days **OR**
Zofran (ondansetron) 4mg/2mL	20 mLs per 30 days **OR**	60 mLs per 90 days **OR**
Zofran (ondansetron) 40mg/20mL multiuse vial		
Zofran (ondansetron) 4mg	90 units per 30 days **OR**	240 units per 90 days **OR**
Zofran (ondansetron) 8mg		
Zofran ODT (ondansetron) 4mg		
Zofran ODT (ondansetron) 8mg		
Zofran suspension (ondansetron) 4mg/5mL	360 mLs per 30 days	1,250 mLs per 90 days

Medication with <u>approved Formulary Exception only</u>	**Quantity Limit per 30 days**	**Quantity Limit per 90 days**
Anzemet (dolasetron) 50mg, 100mg	4 tablets per 30 days	10 tablets per 90 days
Zuplenz oral film (ondansetron) 4mg, 8mg	90 units per 30 days	240 units per 90 days

Duration 1 month for post-operative nausea and/or vomiting
9 months for nausea and/or vomiting of pregnancy (NVP)
12 months for all other diagnoses

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonists are antinauseant, and anti-emetic agents with little or no affinity for other serotonin receptor, making them very useful in the treatment of nausea and vomiting. Often, these agents are used in the treatment of nausea and vomiting associated with chemotherapy in the treatment of cancer (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of 5-HT3 antagonists while maintaining optimal therapeutic outcomes.

References

1. Drug Facts and Comparisons. Wolters Kluwer. https://fco.factsandcomparisons.com/lco/action/home.
2. Aloxi [package insert]. Woodcliff Lake, NJ: Eisai Inc.; December 2015.
3. Anzemet [package insert]. Parsippany, NJ: Validus Pharmaceuticals LLC; June 2021.
4. Granisetron injection [package insert]. Schaumburg, IL: Sagent Pharmaceuticals; February 2016.
5. Kytril [package insert]. Nutley, NJ: Roche Laboratories Inc.; March 2010.
6. Sancuso [package insert]. Bedminster, NJ: Kyowa Kirin, Inc.; December 2022.
7. Sustol [package insert]. San Diego, CA: Heron Therapeutics; June 2023.
8. Zofran injectable [package insert]. Research Triangle Park, NC: GlaxoSmithKline; March 2017.
9. Zofran oral [package insert]. East Hanover: NJ: Novartis Pharmaceuticals Corporation: October 2017.
10. Zuplenz [package insert]. Raleigh, NC: Fortovia Therapeutics Inc.; June 2019.
11. Ondansetron [package insert]. Bachupally, India: Dr. Reddy's Laboratories Limited; May 2021.
12. Parker, S.E., et al. Ondansetron for Treatment of Nausea and Vomiting of Pregnancy and the Risk of Specific Birth Defects. Obstetrics & Gynecology: August 2018. Volume 132, Issue 2, p 385-394.

Policy History

Date	Action
April 2018	Addition to PA
June 2018	Annual review
February 2019	Addition of statement to Anzemet: *Prior authorization for the brand formulation applies only to formulary exceptions due to being a non-covered medication
March 2019	Annual review and reference update

July 2019	Added requirement that operation was within the last month for post-operative nausea and/or vomiting. Changed approval duration for post-operative nausea and/or vomiting to 1 month
September 2019	Annual review
December 2019	Annual review. Moved Zuplenz to MFE with PA only
March 2020	Annual review and reference update
December 2020	Annual review. Added indication for Zofran and Zuplenz: nausea and/or vomiting of pregnancy per SME
March 2021	Annual review and reference update
June 2021	Annual review
October 2021	Addition of ondansetron 24mg tablets to policy
December 2021	Annual review
March 2022	Annual review
March 2023	Annual review. Changed policy number to 5.50.015
June 2023	Annual review
March 2024	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 8, 2024 and is effective on April 1, 2024.