Clinical Policy: Granisetron (Sancuso, Sustol)

Reference Number: CP.PMN.74
Effective Date: 11.01.16
Last Review Date: 08.23
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Granisetron (Sancuso®, Sustol®) is a serotonin (5-HT_3) receptor antagonist.

FDA Approved Indication(s)

Granisetron intravenous injection is indicated for:

- Prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin
- Prevention and treatment of postoperative nausea and vomiting (PONV) in adults

Granisetron tablet is indicated for the prevention of:

- Nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin
- Nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation

Sancuso is indicated for the prevention of nausea and vomiting in adults receiving moderately and/or highly emetogenic chemotherapy of up to 5 consecutive days duration.

Sustol is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MED) for anthracycline and cyclophosphamide (AC) combination chemotherapy regimens.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that granisetron, Sancuso, and Sustol are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Nausea and Vomiting Associated with Cancer Chemotherapy (must meet all)**:**

1. Prescribed for the prevention or treatment of chemotherapy-induced nausea/vomiting;
2. For Sancuso or Sustol: Age ≥ 18 years;
3. Member is scheduled to receive cancer chemotherapy (*see Appendix D*);

4. One of the following (a or b):
   a. Member must use generic granisetron, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;
5. Member meets one of the following (a or b):
   a. Failure of a formulary 5-HT_3 receptor antagonist (*ondansetron is preferred*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;
6. Dose does not exceed one of the following (a, b, c, or d):
   a. Intravenous injection: 10 mcg/kg;
   b. Tablet: 2 mg (2 tablets) per day;
   c. Sustol: 10 mg per 7 days;
   d. Sancuso: 1 patch per 7 days.

Approval duration: Projected course of chemotherapy up to 72 hours after completion of chemotherapy

B. Nausea and Vomiting Associated with Radiation Therapy (must meet all)**:**
1. Request is for granisetron tablet;
2. Prescribed for the prevention of radiation-induced nausea/vomiting;
3. Age ≥ 18 years;
4. Member is scheduled to receive radiation therapy;
5. Member meets one of the following (a or b):
   a. Failure of a formulary 5-HT_3 receptor antagonist (*ondansetron is preferred*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;
6. Dose does not exceed 2 mg (2 tablets) per day.

Approval duration: Projected course of radiation therapy up to 48 hours after completion of radiation therapy

C. Postoperative Nausea and Vomiting (must meet all):
1. Request is for granisetron IV injection;
2. Prescribed for the prevention or treatment of PONV;
3. Age ≥ 18 years;
4. Member is scheduled to undergo surgery;
5. Member meets one of the following (a or b):
   a. For prevention: Failure of a formulary 5-HT_3 receptor antagonist (*ondansetron is preferred*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. For treatment: Member did not receive a preoperative 5-HT_3 receptor antagonist (e.g., ondansetron);
6. Dose does not exceed 1 mg once.

Approval duration: One time approval (3 days)

D. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Nausea and Vomiting Associated with Chemotherapy or Radiation Therapy (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. One of the following (a or b):
   a. Member must use generic granisetron, unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E*);
4. Member meets one of the following (a or b):
   a. Member continues to receive cancer chemotherapy (*see Appendix D*);
   b. Member continues to receive radiation therapy;
5. If request is for a dose increase, new dose does not exceed one of the following (a, b, c, or d):
   a. Intravenous injection: 10 mcg/kg;
   b. Tablet: 2 mg (2 tablets) per day;
   c. Sustol: 10 mg per 7 days;
   d. Sancuso: 1 patch per 7 days.

Approval duration:
Chemotherapy-induced nausea/vomiting: Projected course of chemotherapy up to 72 hours after completion of chemotherapy
Radiation therapy-induced nausea/vomiting: Projected course of radiation therapy up to 48 hours after completion of radiation therapy

B. Postoperative Nausea and Vomiting
1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

5-HT_3: serotonin 5-hydroxytryptamine, type 3
ASCO: American Society of Clinical Oncology
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network
PONV: postoperative nausea and vomiting

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
5-HT$_3$ Serotonin Antagonists		
Akynzeo® (fosnetupitant/ palonosetron)	**Prevention of nausea and vomiting associated with highly emetogenic chemotherapy** 1 vial IV given 30 min prior to chemotherapy on day 1	1 vial/chemotherapy cycle
Akynzeo® (netupitant/ palonosetron)	**Prevention of nausea and vomiting associated with highly emetogenic chemotherapy** 1 capsule PO given 1 hour prior to initiation of chemotherapy on day 1 (in combination with dexamethasone) or 1 vial IV given 30 min prior to initiation of chemotherapy on day 1	1 capsule or vial/chemotherapy cycle
Anzemet® (dolasetron)	**Prevention of nausea and vomiting associated with chemotherapy** 100 mg PO within 1 hr prior to chemotherapy	100 mg/day
Aloxi® (palonosetron)	**Prevention of nausea and vomiting associated with chemotherapy** 0.25 mg IV given 30 min prior to chemotherapy **Prevention of PONV** 0.075 mg IV given immediately prior to anesthesia	Chemo-induced N/V prophylaxis: 0.25 mg/day PONV prophylaxis: 0.075 mg/day
ondansetron (Zofran®, Zofran® ODT, Zuplenz®)	**Prevention of nausea and vomiting associated with moderately emetogenic chemotherapy** <u>Age 12 years or older:</u> 8 mg PO given 30 min prior to chemotherapy, then repeat dose 8 hrs after initial dose, then 8 mg PO BID for 1 to 2 days after chemotherapy completion <u>Age 4 to 11 years</u>: 4 mg PO given 30 min prior to chemotherapy, then repeat dose 4 and 8 hrs after initial dose, then 8 mg PO TID for 1 to 2 days after chemotherapy completion **Prevention of nausea and vomiting associated with highly emetogenic chemotherapy** 24 mg PO given 30 min prior to start of single-day chemotherapy **Prevention of nausea and vomiting associated with emetogenic chemotherapy**	PO: 24 mg/day IV: 16 mg/dose (up to 3 doses/day)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	0.15 mg/kg/dose IV given 30 min prior to chemotherapy, then repeat dose 4 and 8 hrs after initial dose **Treatment of nausea and vomiting associated with chemotherapy*** 16 to 24 mg PO daily or 8 to 16 mg IV **Prevention of nausea and vomiting associated with radiation therapy** Total body irradiation: 8 mg PO given 1 to 2 hrs prior to each daily fraction of radiotherapy Single high-dose radiotherapy: 8 mg PO given 1 to 2 hrs prior to irradiation, then 8 mg PO Q8H for 1 to 2 days after completion of radiotherapy Daily fractionated radiotherapy: 8 mg PO given 1 to 2 hrs prior to irradiation, then 8 mg PO Q8H for each day of radiotherapy **Prevention of PONV** 16 mg PO given 1 hr prior to anesthesia or 4 mg IM/IV as a single dose given 30 min before end of anesthesia **Treatment of PONV*** 4 mg IV as a single dose	

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): hypersensitivity to granisetron or to any of its components, or to any of the other 5-HT3 receptor antagonists (Sustol), or to any of the components of the transdermal system (Sancuso)
- Boxed warning(s): none reported

Appendix D: American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) Recommendations in Oncology

- Minimal emetic risk chemotherapy: No routine prophylaxis is recommended.
- Low emetic risk chemotherapy: Recommended options include dexamethasone (recommended by both ASCO and NCCN) or metoclopramide, prochlorperazine, or a 5-HT_3 receptor antagonist (recommended by NCCN only). NK_1 receptor antagonists are not included in low risk antiemetic recommendations.

- Moderate emetic risk chemotherapy: 5-HT_3 receptor antagonists and dexamethasone may be used in combination and with or without NK_1 receptor antagonists. Olanzapine may also be used in combination with palonosetron and dexamethasone.
  - Examples of moderate emetic risk chemotherapy: bendamustine, carboplatin, clofarabine, cyclophosphamide < 1,500 mg/m^2, cytarabine > 200 mg/m^2, daunorubicin, doxorubicin < 60 mg/m^2, epirubicin ≤ 90 mg/m^2, idarubicin, ifosfamide, irinotecan, oxaliplatin
- High emetic risk chemotherapy: NK_1 receptor antagonists are recommended for use in combination with 5-HT_3 receptor antagonists and dexamethasone. Olanzapine may also be used in combination with 5-HT_3 receptor antagonists, dexamethasone, and/or NK_1 receptor antagonists.
  - Examples of high emetic risk chemotherapy: carmustine, cisplatin, cyclophosphamide > 1,500 mg/m^2, dacarbazine, mechlorethamine, streptozocin, fam-trastuzumab deruxtecan-nxki
- Breakthrough emesis: Per NCCN, an agent from a different drug class is recommended to be added to the current antiemetic regimen. Drug classes include atypical antipsychotics (olanzapine), benzodiazepines (lorazepam), cannabinoids (dronabinol, nabilone), phenothiazines (prochlorperazine, promethazine), 5-HT_3 receptor antagonists (dolasetron, ondansetron, granisetron), steroids (dexamethasone), or haloperidol, metoclopramide, scopolamine. An NK_1 receptor antagonist may be added to the prophylaxis regimen of the next chemotherapy cycle if not previously included.

Appendix E: States with Regulations against Redirections in Stage IV or Metastatic Cancer

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness.
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
LA	Yes	For stage 4 advanced, metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
MS	Yes	**Applies to HIM requests only** For advanced metastatic cancer and associated conditions
NV	Yes	Stage 3 and stage 4 cancer patients for a prescription drug to treat the cancer or any symptom thereof of the covered person
OH	Yes	**Applies to Commercial and HIM requests only** For stage 4 metastatic cancer and associated conditions
OK	Yes	**Applies to HIM requests only** For advanced metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes	For advanced metastatic cancer and associated conditions
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Granisetron tablet	Prevention of nausea and vomiting associated with chemotherapy	2 mg PO QD or 1 mg PO BID only on days chemotherapy is given	2 mg/day
	Prevention of nausea and vomiting associated with radiotherapy	2 mg PO QD given within 1 hr of radiation	2 mg/day
Granisetron injection	Prevention of Chemotherapy-Induced Nausea and Vomiting	10 mcg/kg IV within 30 minutes before initiation of chemotherapy, and only on the day(s) chemotherapy is given.	10 mcg/kg
	Prevention and treatment of postoperative nausea and vomiting	1 mg IV before induction of anesthesia or immediately before reversal of anesthesia	1 mg/operation
Granisetron (Sancuso)	Prevention of nausea and vomiting associated with cancer chemotherapy	Apply 1 patch to upper outer arm 24 to 48 hrs prior to chemotherapy; patch should be worn at minimum, 24 hours after chemotherapy is finished and for up to 7 days	1 patch/7 days
Granisetron (Sustol)	Prevention of nausea and vomiting associated with cancer chemotherapy	10 mg SC 30 minutes prior to the initiation of MED or AC combination chemotherapy on Day 1.	10 mg/7 days

VI. Product Availability

Drug Name	Availability
Granisetron	Tablet: 1 mg Injection: 1 mg/mL
Granisetron (Sancuso)	Transdermal system: 3.1 mg/24 hours
Granisetron (Sustol)	Extended-release pre-filled syringe: 10 mg/0.4 mL

VII. References

1. Granisetron tablet Prescribing Information. Montvale, NJ: Ascend Laboratories, LLC; March 2011. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=65d31bc7-c6a6-4515-8e3a-93e0754540b2. Accessed April 19, 2023.
2. Granisetron injection Prescribing Information. Lake Zurich, IL: Fresenius Kabi USA, LLC; July 2022. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=dddc8714-383f-4bc5-a468-ae89dbc802b4. Accessed April 19, 2023.

3. Sancuso Prescribing Information. Bedminster, NJ: Kyowa Kirin, Inc.; December 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/22198Orig1s019lbl.pdf. Accessed May 1, 2023.
4. Sustol Prescribing Information. San Diego, CA: Heron Therapeutics; August 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022445s000lbl.pdf. Accessed May 1, 2023.
5. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. Anesthesia & Analgesia: August 2020. 131 (2), 411-448.
6. Hesketh, PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Guideline Update. *J Clin Oncol*. 2020. 38:2,782-2,797. doi.org/10.1200/JCO.20.01296.
7. National Comprehensive Cancer Network. Antiemesis Version 1.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed May 1, 2023.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J3490	Unclassified drugs (Sancuso 3.1 mg/24 hr Patch)
J1627	Injection, granisetron extended release, 0.1 mg
J1626	Injection, granisetron hydrochloride, 100 mcg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.30.18	02.19
Added approval duration for radiation therapy to continued therapy section.	05.07.19	
1Q 2020 annual review: no significant changes; added HIM-Medical Benefit lines of business; references reviewed and updated.	11.01.19	02.20
1Q 2021 annual review: removed HIM-Medical Benefit line of business and removed NCCN dose language for I.A and I.C; references reviewed and updated.	11.13.20	02.21
Added allowance for bypassing redirection if state regulations do not allow step therapy in Stage IV or metastatic cancer settings with additional details in appendix E.	04.27.21	
Added Nevada to Appendix E.	08.03.21	
1Q 2022 annual review: added HIM line of business; removed Kytril as product is no longer in the market; added redirection to generic granisetron; updated HCPCS codes; references reviewed and updated.	10.04.21	02.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Template changes applied to other diagnoses/indications and continued therapy section.	10.10.22	
1Q 2023 annual review: PONV criteria set (previously removed as a result of Kytril discontinuation) was added back with additional age requirement as criteria would still apply for IV requests; added IV dose limits for chemotherapy-induced nausea/vomiting requests; modified to generalize beyond Stage IV or metastatic cancer to the following redirection bypass: "Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings"; references reviewed and updated.	10.04.22	02.23
3Q 2023 annual review: for prevention of nausea and vomiting associated with cancer chemotherapy added allowance for bypassing redirection if state regulations do not allow step therapy in certain oncology settings; references reviewed and updated; updated Appendix E to include Oklahoma.	04.19.23	08.23
Updated Appendix E to include Mississippi.	06.05.24	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan

retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.