Clinical Policy: Pediatric Benzodiazepine Use in Chemotherapy Induced Nausea and Vomiting (CINV)

Reference Number: GA.PMN.07
Effective Date: 08/01/16
Last Review Date: 7/2024
Line of Business: Medicaid

Revision Log

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

Description

The intent of the criteria is to ensure that patients follow selection elements established by Centene® medical policy for the use of benzodiazepine use in pediatric chemotherapy induced nausea and vomiting (CINV).

FDA Approved Indication(s)

Most benzodiazepines are indicated for anxiety and panic disorders.

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 pediatric benzodiazepine use in chemotherapy induced nausea and vomiting is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Prevention and/or Treatment of Acute and Delayed CINV due to Moderately to Highly Emetogenic Intravenous Chemotherapy (must meet all)**:**

1. Prescribed by an oncologist or hematologist;
2. Must be used in combination with a 5-HT3 antagonist plus a steroid, and/or Neurokinin-1 antagonist (NK1-RA) and/or olanzapine, unless contraindicated/intolerant to one of the mentioned antiemetic classes;
3. Lorazepam is preferred agent and the dose does not exceed 0.5mg-1mg by mouth every 4 to 6 hours as needed.

Approval duration: up to 5 days supply per treatment cycle, maximum 6 months total for initial approval

B. Prevention and/or Treatment of Acute and Delayed CINV due to Low Emetogenic Intravenous Chemotherapy (must meet all)**:**

1. Prescribed by an oncologist or hematologist;
2. Must be used in combination with 5-HT3 antagonist, steroid, metoclopramide, or prochlorperazine unless member has failure/contraindication/intolerance to one of the mentioned antiemetic classes;

3. Lorazepam is preferred agent and the dose does not exceed 0.5mg-1mg by mouth every 4 to 6 hours as needed.

Approval duration: up to 5 days supply per treatment cycle, maximum 6 months total for initial approval

C. Prevention and/or Treatment of Acute and Delayed CINV due to Moderate to Highly Emetogenic Oral Chemotherapy (must meet all)**:**

1. Prescribed by an oncologist or hematologist;
2. Used in combination with 5-HT3 antagonist, unless member has failure/contraindication/intolerance to 5-HT3 antagonist;
3. Lorazepam is preferred agent and the dose not exceed 0.5mg-1mg by mouth every 4 to 6 hours as needed.

Approval duration: up to 5 days supply per treatment cycle, maximum 6 months total for initial approval

D. Prevention and/or Treatment of Acute and Delayed CINV due to Low to Minimal Emetogenic Oral Chemotherapy (must meet all)**:**

1. Prescribed by an oncologist or hematologist;
2. Must be used in combination with metoclopramide, prochlorperazine, or 5-HT3 antagonist unless contraindicated/intolerant to all of the mentioned antiemetic classes (combination dopamine blockade should not be approved);
3. Lorazepam is preferred agent and the dose does not exceed 0.5mg-1mg by mouth every 4 to 6 hours as needed.

Approval duration: up to 5 days supply per treatment cycle, maximum 6 months total for initial approval

E. Breakthrough Treatment of Any Types of CINV (must meet all)**:**

1. Prescribed by an oncologist or hematologist;
2. Lorazepam will be added to an escalated anti-emetic regimen .
3. Lorazepam is preferred agent and the dose does not exceed 0.5mg-1mg by mouth every 4 to 6 hours as needed.

Approval duration: up to 5 day supply per treatment cycle, maximum 6 months total for initial approval

F. Prevention and/or Treatment of Anticipatory CINV (must meet all)**:**

1. Prescribed by an oncologist or hematologist;
2. Member is on optimal antiemetic therapy during every cycle of treatment;
3. Request is for Lorazepam and the dose does not exceed:
   a. Lorazepam 0.025 to 0.05mg/kg/dose (maximum: 4mg/dose) by mouth once beginning the night before chemotherapy treatment and once the next day prior to administration of chemotherapy of each cycle.

Approval duration: up to 5 days supply per treatment cycle, maximum 6 months total for initial approval

II. Continued Therapy

A. All Indications in Section I:

1. Must submit updated clinical notes regarding response to therapy along with current dated chemotherapy treatment plan

Approval duration: up to 5 day supply per treatment cycle, maximum 6 months total for additional approvals

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

Not applicable.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CINV: chemotherapy induced nausea and vomiting
FDA: Food and Drug Administration
HEC: Highly emetogenic chemotherapy
LEC: Low emetogenic chemotherapy
MEC: Moderate emetogenic chemotherapy
NK1-RA: Neurokinin 1 Receptor Antagonist
5-HT3 Antagonist: Serotonin Antagonist

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: General Information

Chemotherapy induced nausea and vomiting (CINV) can negatively impact a patient's quality of life, resulting in lack of compliance with subsequent chemotherapy regimens. Metabolic imbalances and nutritional deficiencies, poor patient functional and mental status, anorexia, and esophageal tears are among complications of CINV. The incidence of CINV can vary based on chemotherapeutic agents used, dosages prescribed, patient demographics (i.e., age, sex, etc.), prior history of chemotherapy, and alcohol use. About 90% of patients receiving highly emetogenic chemotherapy will have episodes of vomiting with only about 30% of these patients having episodes if appropriate prophylactic antiemetic therapies are in place. In general younger patients are more likely to experience nausea as compared to older patients. CINV is usually classified in five categories. One category is *Acute CINV*, which is defined as occurring within minutes to hours after chemotherapy, usually resolving within first 24 hours. Next is *Delayed CINV*, which occurs more than 24 hours after chemotherapy. Third is *Anticipatory CINV*, which occurs before patient's next treatment of chemotherapy. In this type of CINV, patients usually have a history of negative experience with chemotherapy treatment and younger patients are generally more susceptible due to more aggressive

chemotherapy regimens being utilized. *Breakthrough CINV* is episodes of vomiting occurring despite prophylactic treatment and/or requires rescue antiemetic drugs. Lastly, *Refractory CINV* is when vomiting occurs during additional chemotherapy cycles when prophylaxis and rescue has failed during early treatment cycles.

Appendix D: Emetogenic Potential of Intravenous Antineoplastic Agents

High Emetic Risk	Doxorubicin/epirubicin + cyclophosphamide Carmustine > 250 mg/m^2 Cisplatin Cyclophosphamide > 1,500 mg/m^2 Dacarbazine	Doxorubicin ≥ 60 mg/m^2 Epirubicin > 90 mg/m^2 Ifosfamide ≥ 2 g/m^2 per dose Mechlorethamine Streptozocin
Moderate Emetic Risk	Aldesleukin > 12-15 million IU/m^2 Amifostine > 300 mg/m^2 Arsenic Trioxide Azacitidine Bendamustine Busulfan Carboplatin* Carmustine* ≤ 250 mg/m^2 Clofarabine Cyclophosphamide ≤ 1500 mg/m^2 Cytarabine > 200 mg/m^2 Dactinomycin* Daunorubicin*	Dinutuximab Doxorubicin* < 60 mg/m^2 Epirubicin* ≤ 90 mg/m^2 Idarubicin Ifosfamide* < 2 g/m2 per dose Interferon alfa ≥ 10 million IU/m^2 Irinotecan* Melphalan Methotrexate* ≥ 250 mg/m^2 Oxaliplatin Temozolomide Trabectedin
Low Emetic Risk	Ado-trastuzumab emtansine Amifostine ≤ 300 mg/m^2 Aldesleukin ≤ 12 million IU/m^2 Belinostat Blinatumomab Brentuximab vedotin Cabazitaxel Carfilzomib Cytarabine 100-200 mg/m^2 Docetaxel Doxorubicin (Liposomal) Eribulin Etoposide 5-FU Floxuridine Gemcitabine Interferon alfa 5-10 million IU/m^2	Irinotecan (liposomal) Ixabepilone Methotrexate 50-250 mg/m^2 Mitomycin Mitoxantrone Necitumumab Omacetaxine Paclitaxel Paclitaxel-albumin Pemetrexed Pentostatin Pralatrexate Romidepsin Talimogene laherparepvec Thiotepa Topotecan Ziv-aflibercept

Minimal Emetic Risk	Alemtuzumab Asparaginase Bevacizumab Bleomycin Bortezomib Cetuximab Cladribine (2-chlorodeoxyadenosine) Cytarabine < 100 mg/m^2 Daratumumab Decitabine Denileukin diftitox Dexrazoxane Elotuzumab Fludarabine Interferon alpha ≤ 5 million IU/m^2 Ipilimumab Methotrexate ≤ 50 mg/m^2 Nelarabine	Nivolumab Obinutuzumab Ofatumumab Panitumumab Pegaspargase Peginterferon Pembrolizumab Pertuzumab Ramucirumab Rituxumab Siltuximab Temsirolimus Trastuzumab Valrubicin Vinblastine Vincristine Vincristine (liposomal) Vinorelbine

Appendix E: Emetogenic Potential of Oral Antineoplastic Agents

Moderate-High Emetic Risk	Altretamine Busulfan (≥ 4 mg/d) Ceritinib Crizotinib Cyclophosphamide (≥ 100 mg/m^2/d) Estramustine Etoposide Lenvatinib	Lomustine (single day) Mitotane Olaparib Panobinostat Procarbazine Temozolomide (> 75 mg/m^2/d) Trifluridine/tipiracil
Minimal-Low Emetic Risk	Afatinib Alectinib Axitinib Bexarotene Bosutinib Busulfan (< 4 mg/d) Cabozantinib Capecitabine Chlorambucil Cobimetinib Cyclophosphamide (<100 mg/m^2/d) Dasatinib Dabrafenib Erlotinib	Melphalan Mercaptopurine Methotrexate Nilotinib Osimertinib Palbociclib Pazopanib Pomalidomide Ponatinib Regorafenib Ruxolitinib Sonidegib Sorafenib Sunitinib

	Everolimus Fludarabine Gefitinib Hydroxyurea Ibrutinib Idelalisib Imatinib Ixazomib Lapatinib Lenalidomide	Temozolomide (≤ 75 mg/m^2/d) Thalidomide Thioguanine Topotecan Trametinib Tretinoin Vandetanib Vemurafenib Vismodegib Vorinostat

Appendix E: Recommended Dosing Regimens

Drug Name	Dosing Regimen
5HT3 Antagonist	
Ondansetron (Zofran®)	• HEC: *5mg/m^2/dose (0.15mg/kg/dose) IV/PO pre-therapy x 1 and then q8h* • MEC: *5mg/m^2/dose (0.15mg/kg/dose; max 8mg/dose) IV/PO pre-therapy x 1 and then q12h* • LEC: *10mg/m^2/dose (0.3mg/kg/dose; max 16mg/dose IV or 24mg PO) pre-therapy x 1*
Granisetron (Kytril®)	• HEC: *40mcg/kg/dose IV as a single daily dose* • MEC: *40mcg/kg/dose IV as a single daily dose or 40mcg/kg/dose po q12h* • LEC: *40mcg/kg/dose IV as a single daily dose or 40mcg/kg/dose po q12h*
Polanosetron (Aloxi®)	1 month to <17 years: *0.02mg/kg/dose (max 1.5mg) IV once pre-therapy* ≥17years: *0.5mg/dose PO once pre-therapy*
Neurokonin-1 Antagonist	
Arepitant (Emend®)	Day 1: *3mg/kg/dose (max: 125mg) PO x 1* Day 2 and 3: *2mg/kg/dose (max: 80mg) once daily*
Corticosteroids	
Dexamethasone	• HEC: *6mg/m^2/dose IV/PO q 6h* • MEC: *≤0.6m^2: 2mg/dose IV/PO q12h* *>0.6m^2: 4mg/dose IV/PO q12h* *If given with arepitant, reduce dexamethasone dose by half*

V. Dosage and Administration

Refer to the respective package inserts for dosage and administration.

VI. Product Availability

Refer to the respective package inserts for product availability.

VII. References

1. National Comprehensive Cancer Network. Antiemesis (Version 2.2022-March 23, 2022).
2. Gold Standard, Inc. Lorazepam Monograph. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed: July 12, 2022.
3. Guidelines on Chemotherapy-induced Nauseas and Vomiting in Pediatric Cancer Patients. COG Supportive Care Endorsed Guidelines. Version July 22, 2021.
4. Rasheed A and Bakhshi S. Antiemetic Regiment with Olanzapine in Pediatric Patients Receiving Highly Emetogenic Chemotherapy. Ind J Med Paediatr Oncol 2021;42:366–369.
5. Lee S, Kim S, Oh M, et. Al. Efficacy of Olanzapine for High and Moderate Emetogenic Chemotherapy in Children. *Children 2020, 7, 140.*
6. Moothedath, A, Meena J, Gupta A, et. Al. Efficacy and Safety of Olanzapine in Children Receiving Highly Emetogenic Chemotherapy, Journal of Pediatric Hematology/Oncology: January 28, 2022 - Volume - Issue - doi: 10.1097/MPH.0000000000002408

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	08.01.16	08.16
4Q 2017 annual review: updated references; updated each indication for use for more clarity on use of intravenous versus oral formulations of chemotherapy criteria; updated criteria and alprazolam dosing for anticipatory CINV; removed haloperidol from low-minimal CINV due to oral chemotherapy; added combination dopamine blockade should not be used.	12.01.17	12.17
2Q 2018 annual review: no significant changes	04.01.18	04.18
4Q 2018 annual review: no significant changes	12.01.18	12.18
Changed current Georgia policy templates to corporate standard templates for drug coverage criteria to meet corporate compliance. Changes/revisions included; new formatting, font size, use of standard policy language for each section of policy, and rearranged order of certain steps in criteria and sections.	2/21/19	
Annual review. Updated fonts.	3/19	4/19
Annual review. Changed NK1-RA use age from 12 to 6 in section A of initial criteria. Added NK1-RA as an option for therapy in section B of initial criteria. Added table for dosing antiemetic regimens. Deleted alprazolam from Prevention and/or Treatment of Anticipatory CINV section due to increase prevalence of rebound anxiety compared to lorazepam. Updated abbreviations appendix. Added	4/2020	4/2020

Reviews, Revisions, and Approvals	Date	P&T Approval Date
preferencing for a trial of olanzapine in breakthrough vomiting. Removed the category "Minimal" from IV chemotherapy antiemetic criteria as prophylaxis is not recommended. Updated dosing for lorazepam in Anticipatory vomiting section. Updated references.		
Annual review. Changed Centene logo to PSHP logo.	4/2021	4/2021
Updated initial and continuation approval duration to reflect number of chemotherapy treatment cycles with maximum 6 months of therapy per authorization.	7/2021	7/2021
3Q 2022 annual review. Changed high and moderate required treatment options to 5-HT3 antagonist plus steroid with/without NK1-RA or olanzapine for Prevention and/or Treatment of Acute and Delayed CINV for emetogenic Intravenous Chemotherapy. Combined criteria for high and moderate emetogenic intravenous chemotherapy due to having same treatment options/requirements. Added 5-HT3 antagonist as a treatment option requirement to Prevention and/or Treatment of Acute and Delayed CINV due to Low to Minimal Emetogenic Oral Chemotherapy criteria. Removed olanzapine as a requirement for Breakthrough Treatment of Any Types of CINV criteria. Changed Lorazepam dosing to not exceed 0.5mg-1mg for all indications except for anticipatory nausea and vomiting. Changed Lorazepam dosing to 0.025 to 0.05 mg/kg/dose, max 4mg/dose for anticipatory nausea and vomiting. References reviewed and updated.	7/2022	7/2022
3Q 2023 annual review. No changes made.	7/2023	7/2023
3Q 2024 annual review. No changes made.	7/2024	7/2024

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.

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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.

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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.

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