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: 4/2021 Revision Log
Line of Business: Medicaid

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 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, steroid, and Neurokinin-1 antagonist (NK1-RA) or member has failure/contraindication/intolerance to one of the mentioned antiemetic classes (if member is <6 years old, Neurokinin-1 antagonist is not needed);
3. Lorazepam is preferred agent and the dose does not exceed 0.5mg-2mg by mouth every 4 to 6 hours as needed.

Approval duration: up to 5 days

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

1. Prescribed by an oncologist or hematologist;
2. Must be used in combination with a 5-HT3 antagonist, steroid or NK1-RA, 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-2mg by mouth every 4 to 6 hours as needed.

Approval duration: up to 5 days

C. Prevention and/or Treatment of Acute and Delayed CINV due to Low t 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-2mg by mouth every 4 to 6 hours as needed.

Approval duration: up to 5 days

D. 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-2mg by mouth every 4 to 6 hours as needed.

Approval duration: up to 5 days.

E. 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, or prochlorperazine unless member has failure/contraindication/intolerance 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-2mg by mouth every 4 to 6 hours as needed.

Approval duration: up to 5 days

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

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

Approval duration: up to 5 days

G. 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 0.04 to 0.08mg/kg/dose (maximum: 2mg/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

II. Continued Therapy

A. All Indications in Section I:

1. Re-authorization for additional days must be reviewed by the plan on a case by case basis

Approval duration: Not applicable

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 $\geq$ 60 mg/m^2 Epirubicin > 90 mg/m^2 Ifosfamide $\geq$ 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* $\leq$ 250 mg/m^2 Clofarabine Cyclophosphamide $\leq$ 1500 mg/m^2 Cytarabine > 200 mg/m^2 Dactinomycin* Daunorubicin*	Dinutuximab Doxorubicin* < 60 mg/m^2 Epirubicin* $\leq$ 90 mg/m^2 Idarubicin Ifosfamide* < 2 g/m2 per dose Interferon alfa $\geq$ 10 million IU/m^2 Irinotecan* Melphalan Methotrexate* $\geq$ 250 mg/m^2 Oxaliplatin Temozolomide Trabectedin
Low Emetic Risk	Ado-trastuzumab emtansine Amifostine $\leq$ 300 mg/m^2 Aldesleukin $\leq$ 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	Irinotecan (liposomal) Ixabepilone Methotrexate 50-250 mg/m^2 Mitomycin Mitoxantrone Necitumumab Omacetaxine Paclitaxel Paclitaxel-albumin Pemetrexed Pentostatin Pralatrexate Romidepsin Talimogene laherparepvec

	Gemcitabine Interferon alfa 5-10 million IU/m^2	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)	Melphalan Mercaptopurine Methotrexate Nilotinib Osimertinib Palbociclib Pazopanib Pomalidomide Ponatinib Regorafenib Ruxolitinib Sonidegib

	Dasatinib Dabrafenib Erlotinib Everolimus Fludarabine Gefitinib Hydroxyurea Ibrutinib Idelalisib Imatinib Ixazomib Lapatinib Lenalidomide	Sorafenib Sunitinib 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 1.2013). Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#antiemesis. Accessed August 22, 2016.
2. National Guideline Clearinghouse (NGC). Guideline summary: Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. In: National Guideline Clearinghouse (NGC). Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2012 Sep 24. Available at: https://www.guideline.gov. Accessed August 26, 2016.
3. National Guideline Clearinghouse (NGC). Guideline summary: Guideline for the prevention and treatment of anticipatory nausea and vomiting due to chemotherapy in pediatric cancer patients. In: National Guideline Clearinghouse (NGC). Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2014 Apr 23. Available at: https://www.guideline.gov. Accessed August 26, 2016.
4. National Comprehensive Cancer Network. Antiemesis (Version 2.2017). Available at: https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed December 01, 2017.
5. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. Available at: http://cp.gsm.com.
6. National Comprehensive Cancer Network. Antiemesis (Version 1.2020-February 19, 2020). Available at: https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed March 30, 2020.
7. Guidelines on Chemotherapy-induced Nauseas and Vomiting in Pediatric Cancer Patients. COG Supportive Care Endorsed Guidelines. Version February 28, 2018. Available at: https://www.childrensoncologygroup.org/downloads/COG_SC_CINV_Guidelines_Document_Feb_2018.pdf. Accessed March 30, 2020.

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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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 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.	4/2020	4/2020
Annual review. Changed Centene logo to PSHP logo.	4/2021	4/2021

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.

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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.