MEMORIAL HERMANN HEALTH SYSTEM
MEMORIAL HERMANN HEALTH PLAN HOLDINGS, LLC
POLICY

POLICY TITLE:	MHHP MEDM-MA OFF-008 Off-Label Drugs
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POLICY PURPOSE:

This policy establishes the criteria for coverage of off-label indications for medical drugs, ensuring that treatments align with clinical evidence and regulatory guidance while maintaining patient access to necessary care. The criteria are applied in addition to any applicable National Coverage Determination (NCD), Local Coverage Determination (LCD).

DEFINITIONS:

Brand Name Drug: The first version of a particular medication to be developed or a medication that is sold under a pharmaceutical manufacturer's own registered trade name or trademark. The original manufacturer is granted a patent, which allows it to be the only company to make and sell the new drug for a certain number of years.

Centers for Medicare & Medicaid Services (CMS): MS is the federal agency that provides health coverage to more than 160 million through Medicare, Medicaid, the Children's Health Insurance Program, and the Health Insurance Marketplace. CMS works in partnership with the entire health care community to improve quality, equity and outcomes in the health care system.

CMS Recognized Compendia: The Centers for Medicare and Medicaid Services (CMS) recognizes several compendia for determining if a drug or biological is medically accepted for off-label use. The CMS uses these compendia to determine if a drug or biological is medically accepted for off-label use in anti-cancer chemotherapeutic regimens.

Food and Drug Administration (**FDA):** An agency of the United States federal government responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter medications, vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices, cosmetics,

and veterinary products. The FDA's main goal is to ensure that these products are safe and effective for their intended use, and that their labeling and marketing are truthful and not misleading.

Generic Drugs: Prescription Drugs that have been determined by the Food and Drug Administration (FDA) to be equivalent to Brand Name Drugs but are not made or sold under a registered trade name or trademark. Generic Drugs have the same active ingredients, meet the same FDA requirements for safety, purity, and potency and must be dispensed in the same dosage form (e.g., tablet, capsule, cream) as the Brand Name Drug.

Off Label Drug: The prescription and administration of a medication for a purpose, dosage, or patient population that is not approved by the regulatory agency Food and Drug Administration (FDA).

SCOPE:

This policy applies to Memorial Hermann Medicare plans.

POLICY STATEMENT

The Policy for Off-Label Drug Policy governs the approval and utilization of medications used for:

- off- label indications or
- other indications or
- for purposes other than those specified in its approved labeling or
- for treatment regimens and patient groups not mentioned in the label approved by the U.S. Food and Drug Administration (FDA).

This policy shall not be interpreted to require coverage for any drug or biological agent when the FDA has determined its use to be contraindicated. Memorial Hermann Health Plan will evaluate each request for unlabeled use of any drug on a case-by-case basis. This policy should only be applied when there is no CMS coverage guidance or Memorial Hermann Health Plan internal coverage drug- specific criteria (i.e. InterQual) or policy addressing the requested off-label use of an FDA- approved drug.

Note: This policy does not apply to Clinical Trial Phases for Investigational New Drugs.

Initial Authorization Criteria

Initial Authorization Criteria
Product: All Off-Label Requested Products
Approval Length: 6 Month(s)
Guideline Type: Prior Authorization
Approval Criteria

1. Requested drug has been approved as safe and effective by the U.S. Food and Drug Administration (FDA) for at least ONE indication.

AND

2. The requested indication has sufficient strength of evidence (see below) supported by one of the following:
    a. The requested indication is supported in the drug labeling (manufacturer's prescribing
    b. information) or the product's dossier, **OR**
    c. The requested indication is supported by one of the Medicare approved compendia:
        i. The American Hospital Formulary Service Drug Information (AHFS-DI),
        ii. DRUGDEX System by Micromedex,
        iii. National Comprehensive Cancer Network (NCCN) Compendium,
        iv. Elsevier Gold Standard's Clinical Pharmacology; **OR**
    d. The provider submits at least two high-quality peer-reviewed clinical studies demonstrating safety, efficacy and clinical benefit (journals listed below "Journals Accepted for Reference" for what is acceptable) for the requested indication.

AND

3. One of the following:
    a. Documentation member has tried and failed, or has a contraindication to, the FDA labeled alternatives for the member's diagnosis.

OR

    b. Documentation member has tried and failed, or has a contraindication to, the treatment guideline recommended formulary alternatives which are standard of care, and which are of equal or greater efficacy compared to the requested agent for the member's diagnosis.

AND

4. The requested drug, dose, frequency, and duration for treatment of the member's diagnosis and age is NOT identified as unsupported by compendia of current literature (e.g., AHFS, Micromedex, NCCN, current medical standard and accepted guidelines, etc.)

AND

5. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the

prescriber within the documentation submitted for review AND the requested drug is not contraindicated by the FDA for the off-label use prescribed.

AND

6. Prescriber attests to baseline and ongoing safety monitoring per FDA label for the requested drug.

AND

7. Provider must submit member's medical records and other relevant documentation as deemed necessary by Memorial Hermann Health Plan to determine if an off-label use is reasonable and necessary for treatment of a member's condition or disease.
   NOTE: It is the responsibility of the prescribing physician to submit to Memorial Hermann Health Plan the documentation supporting the proposed off label use or uses, as requested. Otherwise, the request may be denied due to inadequate or incomplete information.

AND

8. The requested drug is being prescribed by an appropriate specialist for the indication requested.

AND

9. The requested drug dose does not exceed quantity limits or other safety limits.

Additional Notes:
Initial authorization: up to 6 months; duration of therapy needs to be supported by evidence provided to support utilization.
Age Restrictions: Not to exceed limits in compendia or articles provided.
Site of Care: Infusions must occur in an outpatient infusion center unless medically necessary (e.g., high risk of infusion reactions requiring inpatient monitoring).

Reauthorization Criteria

Reauthorization Criteria
Product: All Off-Label Requested Products
Approval Length: Through the end of Plan Year
Guideline Type: Prior Authorization
Approval Criteria

1. The request is not for continuation of therapy of medications for off-label uses for new Memorial Hermann Health Plan members: Initial criteria must be met.

AND

2. One of the following:
   a. Adherence to therapy at least 75% of the time as verified by the prescriber or member medication fill (or claim) history.

OR

   b. Adherence less than 75% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation.

AND

3. Prescriber attests to or the clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity.

AND

4. Documentation of a positive clinical response to therapy (e.g., improvement in laboratory parameters or disease state response or other clinical evidence of positive benefit) with submitted medical records (such as office chart notes, lab results or other clinical information).

AND

5. Prescriber attests to ongoing safety monitoring per FDA label for the requested drug.

AND

6. The requested dose does not exceed quantity limits or other safety limits.

Additional Notes:
Reauthorization: Up to end of the plan year (12 months maximum). Duration of therapy needs to be supported by evidence provided to support utilization. Age Restrictions: Not to exceed limits in approved compendia listed above or articles provided
Site of Care: Infusions must occur in an outpatient infusion center unless medically necessary (e.g., high risk of infusion reactions requiring inpatient monitoring).

Quantity Limit Criteria

Quantity Limit Criteria
Product: All Off-Label Requested Products
Approval Length: Through the end of Plan Year
Guideline Type: Quantity Limit
Approval Criteria 1. One of the following: a. Quantity limit override requests must involve an FDA-approved indication **OR** b. Quantity limit override requests involving off-label indications must meet off-label guideline requirements (initial criteria for new starts or reauthorization criteria for continuation of therapy)

AND

2. One of the following:
    a. The higher dose or quantity is supported in the drug labeling (dosage and administration section of the manufacturer's prescribing information);

    OR

    b. The higher dose or quantity is supported by one of the Medicare approved compendia:
        i. The American Hospital Formulary Service Drug Information (AHFS-DI),
        ii. DRUGDEX System by Micromedex,
        iii. National Comprehensive Cancer Network (NCCN) Compendium,
        iv. Elsevier Gold Standard's Clinical Pharmacology.

Additional Notes: Higher dosing may be accepted if the provider supplies medical references or literature that is peer-reviewed showing support for the safety and efficacy of the drug at the dose requested.

Site of Care: Infusions must occur in an outpatient infusion center unless it is medically necessary to administer in other places of service (e.g., high risk of infusion reactions requiring inpatient monitoring).

Categories of Evidence

Memorial Hermann Health Plan accepts the following levels of evidence from compendia:

1. Elsevier Gold Standard's Clinical Pharmacology: The narrative text is supportive of the requested off-label use and noted as a 'Strong Recommendation.' Recommendations noted as 'Equivocal/Weak' are not considered supportive of an off-label indication.
2. American Hospital Formulary Service-Drug Information (AHFS-DI): The narrative text in AHFS-DI is supportive of the requested off-label use.
   NOTE: The "dagger" symbol is used to indicate off-label drug use by the American Hospital Formulary Service Drug Information® (AHFS®, Bethesda, MD). If AHFS indicates an off-label use but qualifies that statement with "but additional study is needed" or "further study is needed to evaluate safety and efficacy", the qualifying language does not support an off- label indication as medically necessary.
3. Wolters Kluwer Clinical Drug Information Lexi-Drugs Compendium: Recommendations noted as 'Equivocal or Against Proposed off label use' are not considered supportive of an off- label indication.
4. National Comprehensive Cancer Network Compendium (NCCN):

MHI recognizes Category 1 and 2 A approvals. Category 2b may be reviewed on a case-by-case basis by the medical director for appropriate support.

5. Micromedex DrugDex: MHI recognizes Class I and IIa strength of recommendation. Class IIb may be reviewed on a case-by-case basis by the medical director for appropriate support.

NOTE: The complete absence of narrative text on a use or a requested indication is considered neither supportive nor non-supportive.

Journals Accepted for Reference

Off-label use of drugs or regimens may also be considered medically accepted if supported as safe and effective according to peer-reviewed articles eligible for coverage from one of the following journals:

- American Journal of Hematology
- Annals of Pharmacotherapy
- Blood (ASH Journal)
- Clinical Cancer Research (AACR Journal)
- Clinical Pharmacology & Therapeutics
- JAMA Oncology
- Journal of Clinical Oncology (JCO)
- Journal of Immunotherapy
- Journal of the American Medical Association (JAMA)
- Nature Reviews Drug Discovery
- New England Journal of Medicine (NEJM)
- The Lancet

The articles submitted should meet the following requirements to be accepted:

1. Journals should be published **within the last 5 years** to ensure up-to-date clinical validity. If there are no recent studies that exist within 5 years, systematic reviews older than 5 years may still be accepted if – they remain gold standard for a specific off-label use and/or they have been cited in recent guidelines or compendia (ex. NCCN, ASCO, ACR).

2. Phase III randomized, placebo-controlled studies with subject size sufficient to determine statistical validity [Published studies required] or an adequate number of well-designed studies with sufficient numbers of subjects in relation to the incidence or prevalence of the disease

    NOTE: *Peer-Review Medical Literature: Off-label uses that are supported by clinical research peer-reviewed medical literature that may appear in scientific, medical, and pharmaceutical

publications in which original manuscripts are published, only after having been critically reviewed for scientific accuracy, validity, and reliability by unbiased, independent experts prior to publication. Memorial Hermann Health Plan considers any drug being studied in a phase I or phase II clinical trial or use that is based solely on evidence from a phase I or phase II clinical trial, investigational. All submitted studies must be published Phase III randomized, placebo-controlled studies with subject size sufficient to determine statistical validity.

3. Published in the regular editions of the journals that publish original manuscripts only after the manuscripts have been critically reviewed by unbiased independent experts for
scientific accuracy, validity, and reliability.

   NOTE: If ANY of the below are met, evidence is considered insufficient. Articles submitted must not be in the form of:

   - A special supplement or publication and not to include publications privately funded by parties (i.e., manufacturers of the product) with a vested interest in the recommendations and provides full disclosure of any conflict of interest or biases for all authors, contributors, or editors associated with the journal or organization
   - In-house publications by pharmaceutical manufacturing companies or abstracts (including meeting abstracts) are not considered peer review medical literature
   - Retrospective studies, opinion statements, *case reports, letters to the editor, abstracts of a publication, reports of Phase I or Phase II trials are not sufficient.
     *In general, case reports are considered uncontrolled, are based on anecdotal information, and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.

REFERENCES

Centers for Medicare & Medicaid Services. Baltimore, MD. Available at: https://www.cms.gov/

DrugDex® System (database online). Greenwood Village, CO: Thomson Micromedex. Available at: http://www.micromedexsolutions.com.

Facts and Comparisons® (database online). St. Louis, MO: Wolters Kluwer Health, Inc. Available at: http://www.factsandcomparisons.com.

National Comprehensive Cancer Network®. NCCN Drugs & Biologic Compendium™ (database online). Available at: http://www.nccn.org.

U.S. Food and Drug Administration (FDA). Off-label and investigational use of marketed drugs, biologics, and medical devices. Available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm.