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Specialty Pharmacy & Infusion Solutions

CLINICAL GUIDELINES FOR OUTPATIENT SUBCUTANEOUS ADMINISTRATION OF TRASTUZUMAB AND HYALURONIDASE-OYSK (HERCEPTIN HYLECTA)

Section: Nursing
Compliance: ACHC Infusion Pharmacy
ACHC Standards: N/A
URAC Standards: N/A
TJC Standards: N/A
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I. POLICY

Trastuzumab and hyaluronidase-oysk is a subcutaneous combination product for the treatment of HER2-overexpressing breast cancer. It is composed of trastuzumab, a HER2/neu receptor antagonist, and hyaluronidase, an endoglycosidase. Trastuzumab inhibits proliferation of tumor cells that overexpress the HER2 proto-oncogene. Hyaluronidase is the enzyme responsible for breaking down hyaluronan in the extracellular matrix of extracellular tissue. By depolymerizing hyaluronan, hyaluronidase increases subcutaneous permeability; therefore, allowing increased systemic absorption of trastuzumab. It is indicated as an adjuvant therapy in combination with breast cancer regimens or as a single agent following multi-modal, anthracycline-based therapy. It is similarly used in the treatment of metastatic breast cancer. The following outlines the procedures for servicing patients in need of outpatient Trastuzumab and hyaluronidase-oysk home injections.

II. PATIENT ACCEPTANCE CRITERIA

A. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon dispensing pharmacy's admission criteria.
    1. Prescriber preferences
    2. Allergy profile
    3. Age ≥18 years
    4. Ability to secure contracted nursing for subsequent injections

B. Other relevant social and/or medical history including but not limited to:
    1. Pregnancy status

2. Assessment of left ventricular ejection fraction (LVEF)
3. Baseline cardiac evaluation
4. Hepatitis B virus screening with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), total Ig or IgG, and antibody to hepatitis B surface antigen (anti-HBs) prior to beginning systemic anticancer therapy.

C. Physician orders must include:
    1. Drug and dose
    2. Route of administration
    3. Frequency of administration
    4. Emergency medications per protocol
    5. Orders for pre-medications

D. Dispensing pharmacy treatment protocol for hypersensitivity or anaphylaxis reactions with IM epinephrine will be instituted unless a more comprehensive patient-specific orders are provided by physician.

III. PHARMACOLOGY OVERVIEW

A. Indications and dosing
    1. Dosing
        a. All indications are as follows:
            i. Trastuzumab 600 mg/hyaluronidase 10,000 units subcutaneously every three weeks.
    2. Duration
        a. Adjuvant breast cancer: 52 weeks, or until disease recurrence, whichever occurs first (not recommended for use beyond 1 year)
        b. Metastatic breast cancer: Until progression of disease
    3. Dose adjustments
        a. There are no dosage adjustments for renal or hepatic failure provided in the manufacturer's labeling
        b. Delayed or missed dosing
            i. If one dose is missed, it is recommended to administer the next 600 mg/10,000 units dose (i.e., the missed dose) as soon as possible.
            ii. The interval between subsequent Trastuzumab + Hyaluronidase-oysk doses should not be less than three weeks.
        c. Dose Adjustments based on Left Ventricular Ejection Fraction:
            i. Withhold Trastuzumab and hyaluronidase-oysk for ≥16% absolute decrease in left ventricular ejection fraction (LVEF) from pre-treatment values or LVEF below institutional limits of normal and ≥10% absolute decrease in LVEF from pretreatment values.
            ii. Trastuzumab and hyaluronidase-oysk may be resumed if, within 4−8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤15%.

iii. Permanently discontinue Trastuzumab and hyaluronidase-oysk for a persistent (>8 weeks) LVEF decline or for suspension of Trastuzumab and hyaluronidase-oysk dosing on more than 3 occasions for cardiomyopathy.

B. Contraindications
    1. None

C. Precautions
    1. Cardiomyopathy
        a. Trastuzumab and hyaluronidase-oysk can cause left ventricular cardiac dysfunction, including arrhythmias, hypertension, asymptomatic decline in LVEF, cardiac failure. Assess left ventricular ejection fraction (LVEF) prior to initiation of Trastuzumab and hyaluronidase-oysk and at regular intervals during treatment.
    2. Embryo-Fetal Toxicity
        a. Fetal harm (pulmonary hypoplasia, skeletal abnormalities, neonatal death) is associated when administered in pregnant women. Verify pregnancy status of female patients for initiation of treatment. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of Trastuzumab and hyaluronidase-oysk.
    3. Pulmonary Toxicity
        a. Fatal pulmonary toxicity may result. Other toxicities include dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, pulmonary insufficiency, and hypoxia. Consider baseline pulmonary function and concomitant disease states prior to treatment. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.
    4. Exacerbation of Chemotherapy-Induced Neutropenia
        a. Randomized controlled trials have shown increased risk of febrile neutropenia in patients receiving trastuzumab and chemotherapy compared with chemotherapy alone.
    5. Hypersensitivity
        a. Severe administration-related reactions, including hypersensitivity and anaphylaxis have occurred. Monitor patients for these reactions, especially during the first administration, and discontinue therapy in patients who experience severe reactions. For patients experiencing reversible Grade 1 or 2 hypersensitivity reactions, consider pre-medication with an analgesic, antipyretic, or an antihistamine prior to re-administration of trastuzumab and hyaluronidase-oysk.

D. Adverse Reactions
    1. Adjuvant breast cancer (≥10%): Fatigue, arthralgia, diarrhea, injection site reactions, upper respiratory tract infections, rash, myalgia, nausea, headache, edema, flushing, pyrexia, cough, pain in extremities.

2. Metastatic breast cancer (≥10%): Fever, chills, headache, infection, congestive heart failure, insomnia, cough, rash.

E. Drug Interactions
   1. Anesthetics
      a. The hyaluronidase component can increase incidences of systemic reactions to anesthetics via increased diffusion.
         i. Benzocaine
         ii. Bupivacaine
         iii. Butacaine
         iv. Chloroprocaine
         v. Dibucaine
         vi. Etidocaine
         vii. Lidocaine
         viii. Mepivacaine
         ix. Prilocaine
         x. Procaine
         xi. Proparacaine
         xii. Propoxycaine
         xiii. Ropivacaine
         xiv. Tetracaine
   2. Anthracyclines
      a. Increased risk of cardiomyopathy; avoid concomitant use with trastuzumab and use within 7 months of trastuzumab discontinuation.
         i. Daunorubicin
         ii. Doxorubicin
         iii. Epirubicin
         iv. Idarubicin
         v. Pirarubicin
         vi. Valrubicin
   3. Phenylephrine (systemic)
      a. Hyaluronidase may enhance the vasoconstriction effect of Phenylephrine.

F. Pharmacokinetics

PK parameters of Trastuzumab following Subcutaneous Administration of HERCEPTIN HYLECTA*

Absorption	
Absolute Bioavailability	0.77 (13)
First-order absorption rate, ka (day^{-1})	0.4 (2.92)†
T_{max} (day)	3 (1-14)‡
Distribution	
Volume of Central Compartment (L)	2.9 (19.1)
Elimination	
Linear Elimination Clearance (L/day)	0.11 (30)
Non-linear Elimination V_{max} (mg/day)	11.9 (19.9)†
Non-linear Elimination K_m (mg/L)	33.9 (38.6)†

* Parameters represented as geometric mean (%CV) unless otherwise specified
† Residual standard error
‡ Median (range)

IV. ADMINISTRATIVE GUIDELINES

A. The injection site should be alternated between the left and right thighs, delivered at least 2.5 cm from the previous site, and into healthy, unmarked skin.

B. The dose should be administered over 2 to 5 minutes, and other subcutaneous medications should be injected at different sites.

C. Must be administered by a healthcare professional.

V. NURSING PROCEDURE

A. Supplies
   1. Alcohol swabs
   2. Gloves
   3. Vial of Trastuzumab and hyaluronidase-oysk
   4. 10mL syringe
   5. Transfer needle
   6. Hypodermic needle
   7. Sharps container

B. How Supplied
   1. Trastuzumab and hyaluronidase-oysk injection for subcutaneous use supplied as a sterile, preservative-free, colorless to yellowish, clear to opalescent solution Trastuzumab and hyaluronidase-oysk 600 mg/10,000 units in 5mL in a single-dose vial.

C. Storage and Handling
   1. Store Trastuzumab and hyaluronidase-oysk vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

D. Administration
   1. Explain the reason for visit and use of Trastuzumab and hyaluronidase-oysk. Dose must be administered by a healthcare professional.
   2. Don gloves
   3. Remove Trastuzumab and hyaluronidase-oysk from fridge prior to use and allow to warm to room temperature before administration.
   4. The medication should be visually inspected for particulate matter and discoloration prior to use.
      a. The solution is available in a single use vial as a solution ready for injection (no dilution necessary).
   5. Prepare the dose in a syringe under aseptic conditions.
      a. After withdrawing appropriate dose of solution (5 mL) from the vial, replace the cap on the transfer needle attached to the syringe.

b. Immediately prior to administration, attach the hypodermic injection needle to the dose syringe for injection and inject subcutaneously over 2-5 minutes. Do not attach until time of administration to avoid clogging.
c. To minimize discomfort:
    i. Slow injection will promote effects of hyaluronidase
    ii. Inject at a 90-degree angle; if the syringe is at a 45-degree angle, ensure the bevel is pointed upward.
d. *Additional administration tips. Refer to manufacturer guide for most up to date information:*
    i. Consider asking the patient to wear loose clothing to facilitate access to the thigh area (i.e., skirt or loose shorts)
    ii. Ask the patient to sit back in a reclining chair or bed
    iii. Arrange your chair at the right level so your feet are flat on the floor, and you are able to sit up straight without twisting, bending, or reaching to administer the injection. You will be in position for at least 2 minutes.

6. The nurse is to remain with the patient for at least 30 minutes following medication administration to monitor vital signs and response to therapy.

VI. CLINICAL MONITORING

A. Cardiac Monitoring
    1. Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:
        i. Baseline LVEF measurement prior to initiation of Trastuzumab and hyaluronidase-oysk
        ii. LVEF measurements every 3 months during and upon completion of Trastuzumab and hyaluronidase-oysk
        iii. Repeat LVEF measurement at 4-week intervals if Trastuzumab and hyaluronidase-oysk is withheld for significant left ventricular cardiac dysfunction
        iv. LVEF measurements every 6 months for at least 2 years following completion of Trastuzumab and hyaluronidase-oysk

B. Monitor closely for signs/symptoms of hypersensitivity (particularly during the first dose) and/or pulmonary toxicity for at least 30 minutes following administration.

C. Patients should be aware of the signs and symptoms of a hypersensitivity reaction and symptoms that necessitate contacting their physician (weight gain >5 pounds in 24 hours, dizziness, loss of consciousness).

Please refer to the package insert for the most up to date guidance on this medication.

REFERENCES

HERCEPTIN HYLECTA (trastuzumab and hyaluronidase-oysk). South San Francisco CA; Genentech, Inc. 2019

Trastuzumab/hyaluronidase-oysk. In-Depth Answers. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health; 2022. Accessed Aug 25, 2022. https://www.micromedexsolutions.com