Clinical Policy: Dalteparin (Fragmin)

Reference Number: CP.PHAR.225
Effective Date: 05.01.16
Last Review Date: 02.25
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
Dalteparin (Fragmin®) is a low molecular weight heparin (LMWH).

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***For Health Insurance Marketplace (HIM),** if request is through pharmacy benefit, Fragmin 95,000 units/3.8 mL is non-formulary and should not be approved using these criteria; refer to the formulary exception policy, HIM.PA.103.*

FDA Approved Indication(s)
Fragmin is indicated:

- For prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy;
- For prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):
  - In patients undergoing hip replacement surgery;
  - In patients undergoing abdominal surgery who are at risk for thromboembolic complications;
  - In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness;
- For extended treatment of symptomatic venous thromboembolism (VTE: proximal DVT and/or PE), to reduce the recurrence of VTE in adult patients with cancer. In these patients, the Fragmin therapy begins with the initial VTE treatment and continues for six months;
- For treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence of VTE in pediatric patients from birth (gestational age at least 35 weeks).

Limitation(s) of use: Fragmin is not indicated for the acute treatment of VTE.

Policy/Criteria
Provider must submit documentation (including 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 Fragmin is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria
A. Thrombosis/Thromboembolism* (must meet all):
1. Any of the following indications (a, b, or c):

a. Thrombosis or thromboembolism prevention associated with any of the following conditions:
   i. Cancer (*see Appendix D*);
   ii. Unstable angina or myocardial infarction;
   iii. Atrial fibrillation or prosthetic heart valve;
   iv. Major surgery - orthopedic or non-orthopedic;
   v. Critical illness related to ICU admissions or events;
   vi. Restricted mobility associated with acute illnesses or conditions;
   vii. Implanted devices-vascular (e.g., central venous access device, umbilical venous catheter, devices/fistulas related to hemodialysis, ventricular assist devices);
b. Thrombosis or thromboembolism treatment;
c. Short-term prophylaxis for transition to or from oral anticoagulation;

2. Failure of a trial of enoxaparin unless (a, b, or c):
   a. Enoxaparin is contraindicated;
   b. History of clinically significant adverse effects to enoxaparin;
   c. The requested use is FDA labeled for dalteparin but not for enoxaparin (i.e., VTE treatment in patients with cancer, treatment of symptomatic VTE in pediatrics).

Approval duration:
Medicaid – 6 months
HIM – 6 months (*refer to HIM.PA.103 for Fragmin 95,000 units/3.8 mL)*
Commercial – 6 months or to the member's renewal date, whichever is longer

**Includes off-label use for adults and pediatrics.*

B. Anticoagulation in Pregnancy: Ante- and Postpartum (off-label) (must meet all)**:**

1. Any of the following indications:
   a. Acute venous thrombosis during current pregnancy;
   b. Prior venous thrombosis;
   c. Receiving long-term therapy with a vitamin K antagonist (e.g., warfarin);
   d. Prosthetic heart valve;
   e. Inherited thrombophilia;
   f. Antiphospholipid antibody syndrome;
   g. Development of severe ovarian hyperstimulation syndrome post assisted reproduction;
   h. Cesarean section – current pregnancy and request is for the postpartum period.
   i. Any other indication not listed here that is listed in section I.A.;
2. Member is pregnant or < 6 months postpartum;
3. Failure of a trial of enoxaparin, unless contraindicated or clinically significant adverse effects are experienced.

Approval duration:
HIM – Antepartum (to estimated delivery date); postpartum (6 months) (*refer to HIM.PA.103 for Fragmin 95,000 units/3.8 mL)*
Medicaid/Commercial – Antepartum (to estimated delivery date); postpartum (6 months)

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.

II. Continued Therapy

A. **Thrombosis/Thromboembolism** (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. Continued use is limited to any of the following indications (a, b, or c):
      a. Venous thrombosis prophylaxis or treatment in the presence of cancer;
      b. Past history of failed anticoagulation therapy (clot development) on a non-LMWH* (e.g., failed therapy on heparin, fondaparinux, warfarin, apixaban, dabigatran, edoxaban, rivaroxaban);
         **LMWHs include enoxaparin and dalteparin*
      c. Any other indication in section I.A where bridging to warfarin is inappropriate or member has a contraindication to warfarin and extended (indefinite duration) anticoagulation therapy is required.

   Approval duration:
   Medicaid – 6 months
   HIM - 6 months *(refer to HIM.PA.103 for Fragmin 95,000 units/3.8 mL)*
   Commercial – 6 months or to the member's renewal date, whichever is longer

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B. **Anticoagulation in Pregnancy: Ante- and Postpartum (off-label)** (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. See Section II.A for continued anticoagulation therapy beyond 6 months postpartum.

Approval duration:
HIM – Antepartum (to estimated delivery date); postpartum (6 months) (*refer to HIM.PA.103 for Fragmin 95,000 units/3.8 mL)*
Medicaid/Commercial – Antepartum (to estimated delivery date); postpartum (6 months)

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

DVT: deep vein thrombosis
LMWH: low molecular weight heparin
NCCN: National Comprehensive Cancer Network
PE: pulmonary embolism
STEMI: ST-elevated myocardial infarction
VTE: venous thromboembolism (typically refers to DVT or PE)

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
enoxaparin (Lovenox®)	*Adults:* DVT prophylaxis in abdominal surgery 40 mg SC once daily DVT prophylaxis in knee replacement surgery 30 mg SC every 12 hours DVT prophylaxis in hip replacement surgery 30 mg SC every 12 hours or 40 mg SC once daily DVT prophylaxis in medical patients 40 mg SC once daily Inpatient treatment or acute DVT with or without PE 1 mg/kg SC every 12 hours or 1.5 mg/kg SC once daily Outpatient treatment of acute DVT without PI 1 mg/kg SC every 12 hours Unstable angina and non-Q wave MI 1 mg/kg SC every 12 hours (with aspirin) Acute STEMI in patient < 75 years of age 30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC every 12 hours (with aspirin) Acute STEMI in patient ≥ 75 years of age 0.75 mg/kg SC every 12 hours (no bolus) (with aspirin)	Dose as specified; duration may vary.

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.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Active major bleeding
  - History of heparin induced thrombocytopenia or heparin induced thrombocytopenia with thrombosis
  - Hypersensitivity to dalteparin sodium (e.g., pruritis, rash, anaphylactic reactions)
  - In patients undergoing epidural/neuraxial anesthesia, do not administer Fragmin
  - As a treatment for unstable angina and non-Q-wave MI
  - For prolonged VTE prophylaxis
  - Hypersensitivity to heparin or pork products
- Boxed warning(s): spinal/epidural hematomas

Appendix D: General Information

- Per National Comprehensive Cancer Network (NCCN) guidelines for cancer-associated venous thromboembolic disease, dalteparin is recommended for:
  - Anticoagulation for management of acute superficial vein thrombosis, anticoagulation for acute DVT, acute catheter-related DVT, and/or acute pulmonary embolism, management of acute splanchnic vein thrombosis, or consider for management of chronic splanchnic vein thrombosis in cancer patients with no contraindication to anticoagulation (preferred for patients with gastric or gastroesophageal lesions):
    - administered as monotherapy
    - administered for at least 5 days given concurrently with warfarin until transition to warfarin monotherapy, prior to switching to edoxaban, prior to switching to dabigatran if preferred regimens not appropriate or unavailable
  - Anticoagulation for cancer patients following progression or new thrombosis on therapeutic anticoagulation with: heparin sodium, fondaparinux, warfarin sodium, apixaban, dabigatran, edoxaban, or rivaroxaban
  - Venous thromboembolism prophylaxis:
    - For adults with cancer (excluding basal/squamous cell skin cancer) or those for whom a clinical suspicion of cancer exists who are admitted for medical or surgical hospitalizations and no contraindication to anticoagulation
    - For adults with cancer (excluding basal/squamous cell skin cancer) or those for whom a clinical suspicion of cancer exists who are admitted for surgical hospitalizations and requires preoperative dosing for high-risk surgery (e.g. abdominal/pelvic surgery) and no contraindication to anticoagulation
    - For adults with advanced unresectable and metastatic pancreatic cancer receiving/starting systemic therapy for their cancer that are ambulatory with post-medical oncology discharge and assessed as intermediate or high risk for VTE based on Khorana score ≥ 2
    - For adults with cancer who are at risk in the ambulatory setting after discharge for up to 4 weeks postoperative following high-risk surgery (e.g. abdominal/pelvic)

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Unstable angina and non-Q-wave MI	Adults: 120 IU/kg SC every 12 hours (with aspirin)	Varies
DVT prophylaxis in abdominal surgery	Adults: 2,500 IU SC once daily or 5,000 IU SC once daily or 2,500 IU SC followed by 2,500 IU SC 12 hours later and then 5,000 IU SC once daily	
DVT prophylaxis in hip replacement surgery	Adults: Postoperative start – 2,500 IU SC 4 to 8 hours after surgery, then 5,000 IU SC once daily or Preoperative start – day of surgery 2,500 IU SC 2 hours before surgery followed by 2,500 IU SC 4 to 8 hours after surgery, then 5,000 IU SC once daily	

Indication	Dosing Regimen	Maximum Dose
	Preoperative start – evening before surgery 5,000 IU SC followed by 5,000 IU SC 4 to 8 hours after surgery, then 5,000 IU once daily.	
DVT prophylaxis in medical	Adults: 5,000 IU SC once daily	
Extended treatment of VTE in patients with cancer	Adults: Month 1: 200 IU/kg SC once daily Months 2 – 6: 150 IU/kg SC once daily	
Treatment of VTE in pediatric patients	Starting dose by age: Birth (gestational age at least 35 weeks) to less than 2 years: 150 IU/kg SC BID 2 years to less than 8 years: 125 IU/kg SC BID 8 years to less than 17 years: 100 IU/kg SC BID Whenever possible, administer benzyl alcohol-free formulations (prefilled syringes) in pediatric patients. The 10,000 units/4 mL (2,500 units/mL) single-dose vials are preservative-free. For treatment of neonates, use this vial presentation.	

VI. Product Availability

- Single-dose prefilled syringe: 2,500 IU/0.2 mL, 5,000 IU/0.2 mL, 7,500 IU/0.3 mL, 12,500 IU/0.5 mL, 15,000 IU/0.6 mL, 18,000 IU/0.72 mL
- Single-dose graduated syringe: 10,000 IU/mL
- Multiple-dose vial: 95,000 IU/3.8 mL
- Single-dose vial: 10,000 IU/4 mL

VII. References

1. Fragmin Prescribing Information. New York, NY: Pfizer, Inc.; October 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020287s080lbl.pdf. Accessed October 29, 2024.
2. Executive summary: Antithrombotic therapy and prevention of thrombosis: CHEST guidelines and expert panel reports. Available at: https://www.chestnet.org/guidelines-and-topic-collections/guidelines/pulmonary-vascular. Accessed October 29, 2024.
3. Thromboembolism in pregnancy. Practice Bulletin No. 196. American College of Obstetrics and Gynecologists. *Obstet Gynecol.* July 2018; 132: e1-17.
4. Dalteparin. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at nccn.org. Accessed October 29, 2024.

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6. Kearon C, Akl EA, Omelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016;149:315-352.
7. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guidelines and Expert Panel Report. Chest 2021 Dec; 160 (6): e545- e608.
8. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020 Oct 13;4(19):4693-38.
9. Mehta LS, Warnes CA, Bradley E, et al. Cardiovascular considerations in caring for pregnant patients – a scientific statement from the American Heart Association. Circulation. June 2020;141:e884–e903. DOI: 10.1161/CIR.0000000000000772.
10. Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline. Chest. 2022 Nov;162(5):e207-e243. doi: 10.1016/j.chest.2022.07.025.

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
J1645	Injection, dalteparin sodium, per 2500 IU

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	11.01.20	02.21
1Q 2022 annual review: no significant changes; added language redirecting to HIM.PA.103 if the request is for Fragmin 95,000 units/3.8 mL; references reviewed and updated.	11.23.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.05.22	
1Q 2023 annual review: no significant changes; RT4: added newly approved 10,000 IU/4 mL (2,500 IU/mL) dosage strength; updated appendix D with current NCCN compendium language; references reviewed and updated.	11.21.22	02.23
1Q 2024 annual review: updated appendix D with current NCCN compendium language; references reviewed and updated.	10.31.23	02.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2025 annual review: RT4: added newly approved pediatric extension for pediatric patients from birth (gestational age at least 35 weeks) for treatment of symptomatic venous thromboembolism; updated Appendix D with current NCCN compendium language; references reviewed and updated.	10.18.24	02.25

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.