Clinical Policy: Dalteparin (Fragmin)

Reference Number: ERX.SPA.207
Effective Date: 01.11.17
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

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).

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 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 in pediatric patients 1 month of age and older.

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

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 or fondaparinux, unless (a, b, or c):
   a. Enoxaparin or fondaparinux are contraindicated;
   b. History of clinically significant adverse effects to enoxaparin or fondaparinux;
   c. The requested use is FDA labeled for dalteparin but not for enoxaparin or fondaparinux (i.e., VTE treatment in patients with cancer, treatment of symptomatic VTE in pediatrics).

Approval duration:
Medicaid – 6 months
Commercial – Length of Benefit

**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: Antepartum (to estimated delivery date); postpartum (6 months)

C. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Thrombosis/Thromboembolism (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
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
Commercial – Length of Benefit

B. Anticoagulation in Pregnancy: Ante- and Postpartum (off-label) (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. See Section II.A for continued anticoagulation therapy beyond 6 months postpartum.

Approval duration: Antepartum (to estimated delivery date); postpartum (6 months)

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 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
STEMI: ST-elevated myocardial infarction
PE: pulmonary embolism
VTE: venous thromboembolism

Appendix B: Therapeutic Alternatives

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.
fondaparinux (Arixtra®) – Adults	<u>DVT prophylaxis following hip fracture, hip replacement, and knee replacement surgery and abdominal surgery</u> 2.5 mg SC per day <u>Acute DVT/PE treatment</u> SC based on body weight: < 50 kg: 5 mg per day 50 to 100 kg: 7.5 mg per day > 100 kg: 10 mg per day	DVT prophylaxis: 2.5 mg/day Acute treatment: 10 mg/day

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):
    - as monotherapy
    - for 5 - 10 days given concurrently with warfarin until transition to warfarin monotherapy, prior to switching to edoxaban, prior to switching to dabigatran for patients who refuse or have compelling reasons to avoid long-term low-molecular weight heparin
  - Anticoagulation for cancer patients following therapeutic anticoagulation failure with: heparin sodium, fondaparinux, warfarin sodium, apixaban, dabigatran, edoxaban, or rivaroxaban
  - Venous thromboembolism prophylaxis for adult patients with no contraindication to anticoagulation
    - for inpatient medical and/or surgical patients with cancer or those for whom a clinical suspicion of cancer exists
    - for inpatient surgical patients with cancer or those for whom a clinical suspicion of cancer exists as preoperative dosing for high-risk surgery (eg, abdominal/pelvic)
    - for outpatient surgical patients with cancer for up to 4 weeks following high-risk surgery (e.g., abdominal/pelvic)
  - Outpatient venous thromboembolism prophylaxis for adult multiple myeloma patients treated with immunomodulatory drug (IMiDs) and assessed as high risk (SAVED score ≥ 2 points or IMPEDE VTE score > 3 points) with no contraindication to anticoagulation

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 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.	

Indication	Dosing Regimen	Maximum Dose
DVT prophylaxis in medical patients	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: 4 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.	

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

VII. References

1. Fragmin Prescribing Information. New York, NY: Pfizer, Inc.; June 2020. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=2293. Accessed November 03, 2020.
2. Executive summary: Antithrombotic therapy and prevention of thrombosis: CHEST guidelines and expert panel reports. Available at http://www.chestnet.org/Guidelines-and-Resources/CHEST-Guideline-Topic-Areas/Pulmonary-Vascular. Accessed November 3, 2020 *The CHEST guideline series presents recommendations for the prevention, diagnosis, and treatment of thrombosis, addressing a comprehensive list of clinical conditions, including medical, surgery, orthopedic surgery, atrial fibrillation, stroke, cardiovascular disease, pregnancy, and neonates and children*.
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 November 7, 2020.
5. National Comprehensive Cancer Network. Cancer-Associated Venous Thromboembolic Disease Version 3.2021. Available at: http://www.nccn.org. Accessed November 23, 2021.
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. 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.
8. 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q18 annual review: Section I.A., Venous Thrombosis, is changed to "Thrombosis and Thromboembolism" so as not to restrict to venous thrombi. Section I.A criteria are edited to encompass CHEST guidelines for neonates and children (seen primarily under implantable devices), and the criteria is collapsed to maximize consistency across the Lovenox, Fragmin and Arixtra policies. Per specialist recommendation an additional indication is added for short-term prophylaxis to or from oral anticoagulation.	11.22.17	02.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Duration changed to length of benefit. Continuation criteria added for pregnancy. References updated.		
1Q 2019 annual review: no significant changes; references reviewed and updated.	11.13.18	02.19
RT4: no significant changes; updated FDA approved indication section to reflect pediatric indication expansion for treatment of symptomatic VTE.	06.03.19	
1Q 2020 annual review: no significant changes; added Medicaid line of business with 6 month approval durations for thrombosis/thromboembolism; dosage table updated; references reviewed and updated.	11.01.19	02.20
1Q 2021 annual review: no significant changes; added Appendix D; references reviewed and updated.	11.01.20	02.21
1Q 2022 annual review: no significant changes; added fondaparinux as a formulary alternative for thrombosis/thromboembolism; references reviewed and updated.	11.23.21	02.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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