Clinical Policy Title:	**dalteparin**
Policy Number:	RxA.139
Drug(s) Applied:	Fragmin®
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All Line of Business

Background

Fragmin® is a low molecular weight heparin (LMWH) indicated for:

- Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction.
- For prophylaxis of deep vein thrombosis (DVT):
  - 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.
- 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.
- 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.

Dosing Information

Drug Name	Indication Adults	Dosing Regimen	Maximum Dose
dalteparin (Fragmin®)	Unstable angina and non-Q-wave MI	120 IU/kg SC every 12 hours (with aspirin)	Varies
dalteparin (Fragmin®)	DVT prophylaxis in abdominal surgery	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	Varies
dalteparin (Fragmin®)	DVT prophylaxis in hip replacement surgery	**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,	Varies

		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	
dalteparin (Fragmin®)	DVT prophylaxis in medical patients	5,000 IU SC once daily	Varies
dalteparin (Fragmin®)	Extended treatment of VTE in adult patients with cancer	Month 1: 200 IU/kg SC once daily Months 2 – 6: 150 IU/kg SC once daily	Varies
dalteparin (Fragmin®)	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.	Varies
Do not use as intramuscular injection. Fragmin® should not be mixed with other injections or infusions.			

Dosage Forms

- 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 (25,000 IU/mL)

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

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;
      ii. Unstable angina or myocardial infarction;
      iii. Atrial fibrillation or prosthetic heart valve;
      iv. Major surgery - orthopedic and 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 labelled for dalteparin but not for enoxaparin (i.e., VTE treatment in patients with cancer, treatment of symptomatic VTE in pediatrics)

Approval Duration
Commercial: 6 months
Medicaid: 6 months
**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. High risk thrombophilia - including but not limited to Factor V Leiden homozygosity, prothrombin gene G20210A mutation homozygosity, heterozygosity for factor V Leiden and prothrombin G20210A mutation, antithrombin deficiency, history of recurrent thrombosis, and mechanical heart values;
   j. 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
Commercial: Antepartum (to estimated delivery date); postpartum (6 months)
Medicaid: Antepartum (to estimated delivery date); postpartum (6 months)

II. Continued Therapy Approval

A. Thrombosis/Thromboembolism (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
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);
   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

Commercial: 6 months
Medicaid: 6 months
**LMWHs include enoxaparin and dalteparin.*

B. Anticoagulation in Pregnancy: Ante- and Postpartum (off-label) (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. See Section II.A for continued anticoagulation therapy beyond 6 months postpartum.

Approval Duration:
Commercial: Antepartum (to estimated delivery date); postpartum (6 months)
Medicaid: Antepartum (to estimated delivery date); postpartum (6 months)

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
DVT: Deep vein thrombosis
LMWH: Low molecular weight heparin
PE: Pulmonary embolism
STEMI: ST-elevated myocardial infarction
VTE: Venous thromboembolism (typically refers to DVT or PE)

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

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):
  - Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins (LMWH) or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
    - Use of indwelling epidural catheters.
    - Concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drug (NSAIDs), platelet inhibitors, other anticoagulants.
    - A history of traumatic or repeated epidural or spinal punctures.
    - A history of spinal deformity or spinal surgery.
    - Optimal timing between the administration of Fragmin® and neuraxial procedures is not known.
  - Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.
  - Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

APPENDIX D: General Information

- Hemorrhage: Use caution in conditions with increased risk of hemorrhage.
- Thrombocytopenia: Monitor thrombocytopenia of any degree closely.
- Benzyl Alcohol Preservative: Do not use multiple-dose formulations in neonates and infants as they contain benzyl alcohol.
- Laboratory Tests: Periodic blood counts recommended.

References

1. Fragmin® Prescribing Information. New York, NY: Pfizer, Inc.; December 05, 2021. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020287Orig1s076lbl.pdf. Accessed February 4, 2021.
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 February 4, 2021.*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 February 4, 2021.
5. Cancer-associated venous thromboembolic disease (Version 2.2018). National Comprehensive Cancer Network Clinical Practice Guidelines. Available at nccn.org. Accessed February 4, 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.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established	01/2020	02/07/2020
Reviewed criteria	04/2020	
Policy was reviewed: 1. Clinical policy title table was updated. 2. Drug(s) applied was updated. 3. Line of Business Policy Applies to was update to all lines of business. 4. Dosing information was updated for indication and included: Do not use as intramuscular injection. Fragmin® should not be mixed with other injections or infusions. 5. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 6. Appendix B: "Therapeutic alternatives verbiage was updated to below are suggested therapeutic alternatives based on clinical guidance...." 7. Appendix D added. 8. References were reviewed and updated. 9. Dosage form updated to include: Multiple dose vial: 95,000 IU/3.8 mL (25,000 IU/mL). 10. Updated Boxed Warning to include: Monitor patients	02/05/2021	03/09/2021

frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis. 11. Updated section I for Anticoagulation in Pregnancy: Ante- and Postpartum (off-label) to include: High risk thrombophilia - including but not limited to Factor V Leiden homozygosity, prothrombin gene G20210A mutation homozygosity, heterozygosity for factor V Leiden and prothrombin G20210A mutation, antithrombin deficiency, history of recurrent thrombosis, and mechanical heart values.		