Clinical Policy: Dalteparin (Fragmin)
Reference Number: ERX.SPA.207
Effective Date: 01.11.17
Last Review Date: 02.19

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):
  o In patients undergoing hip replacement surgery;
  o In patients undergoing abdominal surgery who are at risk for thromboembolic complications;
  o 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;
          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 labeled for dalteparin but not for enoxaparin (i.e., VTE treatment in patients with cancer, treatment of symptomatic VTE in pediatrics).

Approval duration: 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);
   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: Length of Benefit

*LMWHs include enoxaparin and dalteparin.

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
STEMI: ST-elevated myocardial infarction
PE: pulmonary embolism
VTE: venous thromboembolism

Appendix B: Therapeutic Alternatives

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
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<tbody>
<tr>
<td>enoxaparin (Lovenox®) - Adults</td>
<td>DVT prophylaxis in abdominal surgery 40 mg SC once daily</td>
<td>Dose as specified; duration may vary.</td>
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<td>DVT prophylaxis in knee replacement surgery 30 mg SC every 12 hours</td>
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<td></td>
<td>DVT prophylaxis in hip replacement surgery 30 mg SC every 12 hours or 40 mg SC once daily</td>
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<td></td>
<td>DVT prophylaxis in medical patients 40 mg SC once daily</td>
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<tr>
<td></td>
<td>Inpatient treatment or acute DVT with or without PE 1 mg/kg SC every 12 hours or 1.5 mg/kg SC once daily</td>
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</tr>
<tr>
<td></td>
<td>Outpatient treatment of acute DVT without PE 1 mg/kg SC every 12 hours</td>
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<tr>
<td></td>
<td>Unstable angina and non-Q wave MI 1 mg/kg SC every 12 hours (with aspirin)</td>
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<td></td>
<td>Acute STEMI in patient &lt; 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)</td>
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<tr>
<td></td>
<td>Acute STEMI in patient ≥ 75 years of age 0.75 mg/kg SC every 12 hours (no bolus) (with aspirin)</td>
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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):
  o Active major bleeding
  o History of heparin induced thrombocytopenia or heparin-induced thrombocytopenia with thrombosis
  o Hypersensitivity to dalteparin sodium (e.g., pruritis, rash, anaphylactic reactions)
  o In patients undergoing epidural/neuraxial anesthesia, do not administer Fragmin
  o As a treatment for unstable angina and non-Q-wave MI
  o For prolonged VTE prophylaxis
  o Hypersensitivity to heparin or pork products
- Boxed warning(s): spinal/epidural hematomas
V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina and non-Q-wave MI</td>
<td>120 IU/kg SC every 12 hours (with aspirin)</td>
<td>Varies</td>
</tr>
<tr>
<td>DVT prophylaxis in abdominal surgery</td>
<td>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</td>
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<tr>
<td>DVT prophylaxis in hip replacement surgery</td>
<td>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</td>
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<tr>
<td>DVT prophylaxis in medical patients</td>
<td>5,000 IU SC once daily</td>
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<tr>
<td>Extended treatment of VTE in patients with cancer</td>
<td>Month 1: 200 IU/kg SC once daily Months 2 – 6: 150 IU/kg SC once daily</td>
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<tr>
<td>Treatment of VTE in pediatric patients</td>
<td>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.</td>
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</tbody>
</table>

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

Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>Policy created.</td>
<td>12.01.16</td>
<td>01.17</td>
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<tr>
<td>4Q17 Annual Review</td>
<td>09.28.17</td>
<td>11.17</td>
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<tr>
<td>Converted to new template.</td>
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<td>Updated approval durations from 3/6 months to 6/12 months;</td>
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<tr>
<td>Section I.A. Criteria are edited to follow CHEST 2016 guidelines in addition to labeled indications. Major additions include 1) prophylaxis: hip fracture/knee replacement, major orthopedic, general, cardiac, thoracic surgery, craniotomy; traumatic injury; critical illness; restricted mobility due to intracerebral hemorrhage; a-fib; prosthetic heart valve; 2) treatment: SVT; CVST; splanchnic thrombosis without cancer; nonbacterial thrombotic endocarditis. Warfarin bridging criteria are moved to renewal criteria. Removed from section I.B. Required risk factors associated with Cesarean. Added preferencing for enoxaparin. Section II. Criteria are edited to follow CHEST 2016 guidelines. Major additions include 1) recurrent venous thrombosis on a non-low molecular weight heparin, 2) any other indication in section I.A. where bridging to warfarin is inappropriate or member has a contraindication to warfarin and extended (indefinite) anticoagulation therapy is required.</td>
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<td>1Q18 annual review:</td>
<td>11.22.17</td>
<td>02.18</td>
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<tr>
<td>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. Duration changed to length of benefit. Continuation criteria added for pregnancy. References updated.</td>
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<tr>
<td>1Q 2019 annual review: no significant changes; references reviewed and updated.</td>
<td>11.13.18</td>
<td>02.19</td>
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<tr>
<td>RT4: no significant changes; updated FDA approved indication section to reflect pediatric indication expansion for treatment of symptomatic VTE.</td>
<td>06.03.19</td>
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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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