ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Low Molecular Weight Heparins

FINAL ENVIRONMENTAL SCAN REPORT

April 2016

Conflict of Interest Statement

No study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the review of low-molecular-weight heparins and fondaparinux.

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Study Team

Environmental Scan: Sandra Knowles

Executive Summary

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

In Canada, there are four low molecular weight heparins (LMWHs) available in Canada: enoxaparin, dalteparin, nadroparin and tinzaparin. Fondaparinux, a selective factor Xa inhibitor, is also available. Various dosage forms are available for each drug to help facilitate weight-based dosing. LMWHs are only available as brand-name products in Canada. Fondaparinux is available as brand-name and generic products in Canada.

All public drug plans in Canada provide coverage for low molecular weight heparins. Dalteparin, enoxaparin and tinzaparin are covered in all jurisdictions. Nadroparin is covered in nine of 12 jurisdictions and fondaparinux in four. Five jurisdictions (Alberta, Quebec, Nova Scotia, New Brunswick, NIHB) list LMWHs as General Benefit, often due to concerns of potential delay in obtaining approval in rural communities. In Ontario, all LMWHs and fondaparinux are available as Limited Use and/or available through the Exceptional Access Program for specific indications.

In the United States, all drug plans reviewed provide coverage for enoxaparin (generic) as a preferred drug; note that enoxaparin is only available in Canada as the brand-name product. Australia provides coverage through the public plan programs for enoxaparin, dalteparin and fondaparinux, whereas tinzaparin and nadroparin are not currently covered. In New Zealand, enoxaparin and dalteparin are covered under the public drug plan; tinzaparin is not covered and nadroparin and fondaparinux are not available in New Zealand.

Part B: Impact of different drug reimbursement schemes for low-molecular-weight heparins and fondaparinux

No relevant studies were identified that evaluated the impact of various drug reimbursement schemes (e.g., prior authorization, step therapy) for coverage of LMWH or fondaparinux on outcomes or adherence.

Part C: Rapid review of selected topics

Pharmacologic and pharmacokinetic differences among the LMWHs: All LMWHs are derived from unfractionated heparin; however they are produced by different processes and have distinct biochemical and pharmacological properties, as well as pharmacokinetic properties.

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Introduction

Low molecular weight heparins (LMWHs) are used for a variety of different conditions and offer advantages over traditional unfractionated heparin, including a more predictable pharmacokinetic profile and ease of use. There are several LMWHs available for clinical use in Canada: dalteparin, enoxaparin, nadroparin and tinzaparin. In addition, fondaparinux, an indirect factor-Xa inhibitor, is also available.

All LMWHs are derived from unfractionated heparin; however they are produced by different processes and have distinct biochemical and pharmacological properties.[1;2] LMWHs have more predictable pharmacokinetic properties than unfractionated heparin including a longer half-life and better bioavailability, and are administered in fixed doses without the need for dose adjustment based on laboratory monitoring.[3;4] The various LMWHs differ in their pharmacokinetic properties and anticoagulant profiles, and in their recommended dosing regimens.[5] Similar to LMWHs, fondaparinux has almost complete bioavailability after subcutaneous injection, a long-half-life and lack of variability in anticoagulant response.[5]

Low molecular-weight heparin (LMWH) and fondaparinux (among other choices that include vitamin K antagonists and direct oral anticoagulants) represent options for treatment and prophylaxis for patients with venous thromboembolism (VTE) in a broad range of surgical and medical patients, including patients undergoing hip/knee surgery, patients with cancer and pregnant patients.[6]

The objectives of this report are:

- Part A: To summarize coverage low molecular weight heparins (LMWHs) through public drug programs in Ontario and across Canada, as well as in select international jurisdictions
- Part B: To determine the impact of different reimbursement schemes for LMWHs on patient access, quality of life and/or utilization and costs
- Part C: To provide rapid reviews on selected topics

Note: Guidelines for the use of low molecular weight heparins and fondaparinux are reviewed and evaluated as part of the Systematic Review Team's report (www.odprn.ca).

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability of Low Molecular Weight Heparins in Canada

In Canada, there are four low molecular weight heparins (LMWHs) commercially available: dalteparin, enoxaparin, nadroparin, tinzaparin. In addition, fondaparinux, a synthetic heparin-like compound, is available. All of these agents are available as injectables in various different strengths. Only fondaparinux is available as a generic product. Exhibit 1 outlines the dosage forms and costs (based on wholesale costs) for LMWHs and fondaparinux.

Exhibit 1: Commercially available low-molecular weight heparin and fondaparinux products in Canada

Drug Name	Brand name	Manufacturer	Availability	Generic/ biosimilar available	Cost*	Date available in Canada**	Date listed on ODB formulary
Dalteparin	Fragmin	Pfizer	Solution 10,000 IU/1mL 25,000 IU/mL 2500 IU/mL Prefilled syringes 2500 IU 3500 IU 5000 IU 7500 IU 10000 IU 12500 IU 15000 IU 18000 IU	No	106.91	Dec 1995	Dec 1998
Enoxaparin	Lovenox	Sanofi-Aventis	Solution 100 mg/mL Prefilled syringes 30mg 40mg 60mg 80mg 90mg (high potency) 100mg 120mg (high potency) 150mg (high potency) 300mg	No	86.49	Dec 1993	Jan 2003
Nadroparin	Fraxiparine	Aspen Pharma	Prefilled syringes 2850 IU 3800 IU 5700 IU 9500 IU	No	91.29	Feb 1998	April 1999

Drug Name	Brand name	Manufacturer	Availability	Generic/ biosimilar available	Cost*	Date available in Canada**	Date listed on ODB formulary
			11400 IU (high potency) 15200 IU (high potency) 19000 IU (high potency)				
Tinzaparin	Innohep	Leo Pharma	Solution 10000 IU/mL 20000 IU/mL Prefilled syringes 2500 IU 3500 IU 4500 IU 8000 IU 10000 IU 12000 IU 14000 IU 16000 IU 18000 IU	No	88.38	July 1997	Dec 1998
Fondaparinux	Arixtra	Aspen Pharma	Prefilled syringes 2.5mg 5 mg 7.5 mg 10 mg	Yes	159.92	July 2002	April 2004
	Generic	Dr. Reddy's Laboratories			111.94	March 2014	July 2014

*Cost for the usual daily dose (for nadroparin for 75kg person) for prophylaxis of VTE post hip replacement for 10 days based on prices obtained from the Ontario Drug Benefit Formulary (Accessed: November 6, 2015)

**Date obtained from Health Canada Database (http://webprod5.hc-sc.gc.ca/dpd-bdpp/newSearch-nouvelleRecherche.do?lang=eng)

Summary

- There are four low molecular weight heparins (LMWHs) available in Canada: enoxaparin, dalteparin, nadroparin and tinzaparin. Fondaparinux, a selective factor Xa inhibitor, is also available. Various dosage forms are available for each drug to help facilitate weight-based dosing.
- LMWHs are only available as brand-name products in Canada. Fondaparinux is available as brand-name and generic products in Canada.

Common Drug Review

The Common Drug Review (CDR) is a single process for reviewing new drugs and providing listing recommendations to participating publicly funded federal, provincial and territorial drug benefit plans in Canada; it was established in September 2003. Since all four LMWHs and fondaparinux were available prior to 2003, no review was completed by the CDR.

Product listing in Ontario

All LMWHs and fondaparinux are funded in Ontario either as Limited Use on the Ontario Drug Benefit (ODB) formulary or through the Exceptional Access Program.

Limited Use (LU)

Limited use (LU) drugs are drugs that have been deemed to have value in certain circumstances, although they may not be appropriate for general listing in the Formulary. Dalteparin, enoxaparin, nadroparin, fondaparinux and tinzaparin are available as Limited Use for specified indications or scenarios.

Exhibit 2: Limited Use Codes for LMWHs

Code	LMWHs Covered	Clinical Criteria	Authorization Period
186	Dalteparin, enoxaparin, nadroparin, tinzaparin	For acute treatment of deep venous thrombosis (DVT), for a maximum of three weeks	1 year
187	Dalteparin, enoxaparin, nadroparin, tinzaparin	For DVT in pregnant or lactating females	1 year
188	Dalteparin, enoxaparin, nadroparin, tinzaparin	For DVT in patients whom treatment with warfarin is not tolerated, or contraindicated	1 year
189	Dalteparin, enoxaparin, nadroparin, tinzaparin	For DVT in patients who have failed treatment with warfarin	1 year
323	Enoxaparin, tinzaparin	For the acute treatment of pulmonary embolism,, maximum of three weeks	1 year
378	Fondaparinux	For the post-operative prophylaxis of venous thromboembolic events in patients undergoing orthopedic surgery of the lower limbs such as hip fracture, hip replacement or knee surgery: limited to 9 days of reimbursement	1 year

In addition, several of these agents are available under the Exceptional Access Program.

Exhibit 3: Exceptional Access Program Criteria for LMWHs

Drug[1]	Criteria	Approval Duration
Dalteparin, enoxaparin, tinzaparin	For peri-operative bridging for patients who require long-term warfarin therapy and must temporarily discontinue it before and after surgery, and who are at moderate- to high-risk for an embolic event while off warfarin	Up to a maximum of 10 days before the date of surgery plus up to 7 days after surgery
Dalteparin, enoxaparin, tinzaparin	For post-operative prophylaxis of DVT for patients who had hip or knee surgery, and cannot use warfarin	Up to a maximum of 30 days starting on the day of surgery
Dalteparin	For extended treatment of symptomatic acute venous thromboembolism (VTE) in patients with cancer, who cannot use warfarin	Up to 6 months

[1]Approved strengths: dalteparin 10,000 IU/mL, 25,000 IU/mL; enoxaparin 100mg/mL, 150 mg/mL; tinzaparin 10,000 IU/mL, 20,000 IU/mL

Committee to Evaluate Drugs:

The Committee to Evaluate Drugs (CED) is the Ministry of Health and Long-term care's independent expert advisory committee on drug-related issues. Dalteparin was first added to the formulary in 1996, fondaparinux in 2004, enoxaparin in 2003, tinzaparin in 1997, and nadroparin in 1999. These products have been subsequently reviewed by the CED on an "as needed" basis, and additional indications have been added to the Limited Use listing (e.g., tinzaparin: acute treatment of pulmonary embolism, 2000) or recommendations have been made to include the specified indications under EAP (dalteparin: extended treatment of symptomatic venous thromboembolism in patients with cancer, 2006).

Summary

- In Ontario, dalteparin, enoxaparin, nadroparin, tinzaparin and fondaparinux are listed as Limited Use and/or available through the Exceptional Access Program for specific indications.
- The approval duration in Ontario varies depending on the indication and ranges from 9 days (for fondaparinux) to one year (e.g., for treatment of DVT in pregnant or lactating females).

Public Plan Listings in Canada

Part 1: Listing Status

In order to determine the listing of LMWHs and fondaparinux across Canada, the relevant webpages of the provincial drug formularies were searched (See Appendix A). In Canada, dalteparin,

enoxaparin and tinzaparin are available in all provinces either as a full (general) benefit or requiring prior authorization. Nadroparin is available in nine of 12 jurisdictions. Fondaparinux is available either as a full (general) benefit or requiring special authorization in 4 jurisdictions. A summary of the various listings is available in Exhibit 4.

Restriction Criteria

Seven jurisdictions require special authorization prior to coverage of LMWH and/or fondaparinux. Clinical criteria include treatment and prophylaxis of venous thromboembolism (VTE). Most jurisdictions indicate duration approval for specific indications. Clinical criteria used for special authorization for LMWHs and fondaparinux coverage are listed in Appendix B.

Exhibit 4: Public plan listings in Canada for low molecular weight heparin products and fondaparinux

Drug	Brand/ generic name	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB / NU/ NW
Dalteparin	Fragmin	Res	FB	Res	Res	Pas/ Res	FB	FB	FB	Res	Res	Res	FB
Enoxaparin	Lovenox	Res	FB	Res	Res	Pas/ Res	FB	FB	FB	Res	Res	Res	FB
Nadroparin	Fraxiparine	Res	FB	Res	Res	Pas/ Res	FB	FB	No	No	No	Res	FB
Tinzaparin	Innohep	Res	FB	Res	Res	Pas/ Res	FB	FB	FB	Res	Res	Res	FB
Fondaparinux	Arixtra	No	FB	No	No	Pas/ Res	FB	No	No	No	No	Res	No
	Generic	No	FB	No	No	Pas/ Res	FB	No	No	No	No	Res	No

NO=not listed
RES=restricted listing
FB=unrestricted listing
Current as of April 16, 2016

Part 2: Telephone Interview with Public Drug Program Representatives

A representative from each public drug program invited to participate in a 30 minute telephone interview (see Appendix C) to gather further information about formulary listing of LMWHs and fondaparinux. Exhibit 5 summarizes the information obtained in the interviews.

Exhibit 5: Summary of interviews with representative from public drug program

Province	Listing	Information on listing
British Columbia	Dalteparin, enoxaparin, nadroparin, tinzaparin	Prior approval required for all agents. A designated form is completed and faxed, or request can be called in.
Saskatchewan	Dalteparin, enoxaparin, nadroparin, tinzaparin	Prior approval required for all agents. Designated health care professionals, including physicians and pharmacists, can call in requests. Real-time approval provided during business hours.
Manitoba	Dalteparin, enoxaparin, nadroparin, tinzaparin	Prior approval required for all agents. Approval provided within 24 hours. In December 2014, expanded criteria to include prevention of VTE in patients undergoing pelvic or abdominal surgery for cancer or inflammatory bowel disease.
New Brunswick	Dalteparin, enoxaparin, nadroparin, tinzaparin	All agents available as General Benefit (with quantity limit of 30 days). If require more than 30 days, then written request required. Due to potential delay in obtaining approval especially in rural communities, LMWHs are available as General Benefit.
Nova Scotia	Dalteparin, enoxaparin, nadroparin, tinzaparin	All agents available as General Benefit. Due to potential delay in obtaining approval especially in rural communities, LMWHs are available as General Benefit.
Prince Edward Island	Dalteparin, enoxaparin, tinzaparin	Prior approval required for all agents. LMWHs not covered for outpatient prescriptions until 2012.
NIHB	Dalteparin, enoxaparin, nadroparin, tinzaparin	All agents available as General Benefit. Due to potential delay in obtaining approval especially in rural communities, LMWHs are available as General Benefit.
Yukon	Dalteparin, enoxaparin, nadroparin, tinzaparin, fondaparinux	Prior approval required for all agents; phone requests accepted as well. Approval provided within 24 hours.

Summary.

- All public drug plans in Canada provide coverage for low molecular weight heparins. Dalteparin, enoxaparin and tinzaparin are covered in all jurisdictions. Nadroparin is covered in nine of 12 jurisdictions and fondaparinux in four.
- Five jurisdictions (Alberta, Quebec, Nova Scotia, New Brunswick, NIHB) list LMWHs as General Benefit, often due to concerns of potential delay in obtaining approval in rural communities.
- Clinical criteria for coverage vary among the jurisdictions, and include treatment of DVT/PE, prophylaxis in hip or knee replacement surgery, prophylaxis in pregnant patients, prophylaxis in high-risk surgery.

Selected International Jurisdictions

United States

As a measure to control ever-increasing costs associated with healthcare, the use of a preferred drug list ("formulary") has been implemented in some jurisdictions. For example a preferred drug list is a list of medications that the provider will cover the cost for without the need to request a prior authorization. The preferred drugs are usually medications that are available generically or are the result of price negotiations between the pharmaceutical company and the provider.

A tiered co-payment system is a combination of cost-sharing and a preferred drug list.[7] Three-tier structures commonly assign generic medications the lowest copay, formulary brand medications a somewhat higher copay, and non-formulary brand medications the highest copay. Three-tier copays provide consumers with more choice than in a closed formulary (where tier three drugs would not be covered at all) and attempt to reduce the number of prior authorizations that are needed for drug approval.[8] In a five-tier system, tier 1 includes preferred generic drugs, tier 2 non-preferred generic drugs, tier 3 preferred brand drugs, tier 4 non-preferred brand drugs and tier 5 specialty drugs (e.g., injectables) (see Appendix D and Exhibit 6 for examples of copayments with tiered formulary systems). Note that nadroparin and tinzaparin are NOT available commercially in the United States.

Exhibit 6: Listing of LMWHs and fondaparinux for select plans in the United States

	Enoxaparin Lovenox + generics	Dalteparin Fragmin	Fondaparinux Arixtra + generics
AETNA Non-Medicare Prescription Drug Plan (http://www.aetna.com/products/rxnonmedicare/data/2013/CV2013/lmwh.html)	Generic: preferred Lovenox: formulary excluded	Formulary excluded (non-preferred)	Generic: preferred Arixtra: formulary excluded
Blue Cross Blue Shield of South Carolina Preferred Drug List (www.southcarolinablues.com)	Preferred	Non-preferred	Non-preferred
Blue Cross Blue Shield of Texas Standard Preferred Drug List (www.bcbstx.com)	Generic: preferred Lovenox: non-preferred	Non-preferred	Non-preferred
Connecticut Medicaid Preferred Drug List (www.ctdssmap.com)	Non-preferred	Non-preferred	Non-preferred
Idaho Medicaid Preferred Drug List (www.healthandwelfare.idaho.gov)	Preferred (Lovenox vial and enoxaparin generic syringe) Non-preferred: enoxaparin generic vial	Preferred	Non-preferred
Illinois Medicaid Preferred Drug List (http://www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf)	Generic: preferred Lovenox: non-preferred	Preferred	Generic: preferred Arixtra: non-preferred
Kaiser Permanente Medicare Part D Comprehensive Formulary (5-tier system) (www.healthy.kaiserpermanente.org)	Generic: Tier 2 Lovenox: Tier 3	Tier 4	Generic: Tier 2 Arixtra: Tier 4
Kentucky Preferred Drug List (www.ubsidiz.magellan**medicaid**.com)	Generic: preferred Lovenox: non-preferred	Preferred	Generic: preferred Arixtra: non-preferred
Oregon Fee-for-Service Enforceable Physical Health Preferred Drug List (http://www.oregon.gov/oha/healthplan/pages/tools_prov/pdl.aspx)	Generic: Non-preferred Lovenox: preferred	Preferred	Non-preferred (generic + Arixtra)
Texas Medicaid Preferred Drug List (http://www.txvendordrug.com/pdl/)	Generic: preferred Lovenox: non-preferred	Preferred	Non-preferred (generic + Arixtra)
WellCare Comprehensive Formulary (Medicare Advantage Plans) (covers New York, Connecticut, Florida, Georgia, Hawaii and others) (5-tier system) (https://www.wellcare.com/medicare_formulary/new_york)	Generic: preferred Lovenox: non-preferred	Non-preferred	Generic: preferred Arixtra: non-preferred
Wellmark Prior authorization/Step therapy (http://www.wellmark.com/HealthAndWellness/DrugInformation/PharmacyHome.aspx)	Generic: preferred Lovenox: non-preferred	Preferred	Generic: preferred Arixtra: non-preferred

Other Countries

Australia: In Australia, enoxaparin and dalteparin are available as unrestricted benefits on the Pharmaceutical Benefits Scheme (PBS).[9] Fondaparinux is available as an "Authority required: streamlined". Authority required (streamlined) are restricted benefits that do not require prior approval from the Department of Human Services but require the recording of a streamlined authority code, similar to Limited Use in Ontario. Note that tinzaparin and nadroparin are not currently listed on the PBS.

Exhibit 7: Low molecular weight heparins and fondaparinux (Australia, publically funded)

Product	Brand name	Comments
Enoxaparin	Clexane	Various dosage forms are available as unrestricted benefits; some are restricted for patients on hemodialysis
Dalteparin	Fragmin	Various dosage forms are available as unrestricted benefits; some are restricted for patients on hemodialysis OR for patients with solid tumour(s) and requiring treatment for symptomatic venous thromboembolism
Fondaparinux	Arixtra	For the prevention of venous thromboembolism in patients undergoing major hip surgery or total knee replacement (Authority required: streamlined)

New Zealand[10]*:* In New Zealand, the Pharmaceutical Management Agency (PHARMAC) is the agency that decides which medicines, medical devices and related products are subsidized. Exhibit 8 outlines the funding of LMWHs and fondaparinux in New Zealand.

Exhibit 8: Low molecular weight heparins (New Zealand, publically funded)

Product	Criteria (Authority required)
Enoxaparin (SA1174), dalteparin (SA1270)	1. Pregnancy 2. Malignancy (treatment of VTE) 3. Venous thromboembolism other than pregnancy or malignancy a. Treatment prior to establishing therapeutic level of oral anticoagulant b. Prophylaxis and treatment in high-risk surgery c. Enable cessation/re-establishment of existing oral anticoagulant treatment pre/post surgery d. Prophylaxis/treatment in Acute Coronary Syndrome Association with cardioversion of atrial fibrillation

Summary

- In the United States, all drug plans reviewed provide coverage enoxaparin (generic) as a preferred drug. Note that enoxaparin is only available in Canada as the brand name product (Lovenox). Dalteparin and fondaparinux (generic) are also available as a preferred drug in 50% of drug plans reviews.
- Australia provides coverage through the public plan programs for enoxaparin, dalteparin and fondaparinux. Note that tinzaparin and nadroparin are not currently covered.
- In New Zealand, enoxaparin and dalteparin are covered under the public drug plan. Tinzaparin is not covered. Nadroparin and fondaparinux are not available in New Zealand.

Part B: Impact of different drug reimbursement schemes for low-molecular weight heparins and fondaparinux

Methods

A literature search was conducted in Pubmed using the terms: enoxaparin OR dalteparin OR tinzaparin OR nadroparin OR low molecular weight heparins) AND (healthcare accessibility OR health policy OR reimbursement incentive OR cost sharing OR deductibles and coinsurance OR insurance coverage OR health benefit plans employee or insurance pharmaceutical service or managed care programs). Bibliographies of identified articles were scanned for additional relevant articles.

Results

No relevant studies were identified that investigated the impact of various drug reimbursement schemes (e.g., prior authorization, step therapy) for coverage of LMWH or fondaparinux on outcomes or adherence.

One study determined the average patient cost for filling a prescription for extended duration enoxaparin prophylaxis for gynecologic malignancy in the US.[11] 326 patients with patient cost data were available for analysis. A total of 234 patients (72%) had private insurance prescription coverage and two patients qualified for the Lovenox Patient Assistance Program. Patient assistance programs are sponsored by pharmaceutical companies and provide free medications to patients who cannot afford to buy their medication. Prescription insurance prior authorization was required for 32 patients (10%). Regardless of coverage, results showed that at least 90% of patients filled their prescription. There is limited applicability of these results to the Canadian context, as the majority of patients in this study had private insurance. As well, this study did not assess whether paying for these medications out-of-pocket (i.e., the non-insured group) would result in decreased adherence overall.

Summary

- There is no information regarding the use of various reimbursement schemes for low molecular weight heparins and/or fondaparinux.

Part C: Rapid Review of Selected Topics

Pharmacologic and Pharmacokinetic Differences among the Low-molecular-weight heparins

LMWHs are a diverse group of chemically distinct compounds. All are derived from unfractionated heparin and produced by enzymatic depolymerization.[2] Due to differences in manufacturing processes, the available products differ in terms of their mean molecular weights and pharmacological properties. LMWHs also differ in their pharmacokinetic properties and anticoagulant profiles and in their recommended dosing regimens.

LMWHs have pharmacokinetic advantages over heparin. Following subcutaneous injection, the bioavailability of LMWHs is approximately 90% and LMWHs produce a more predictable anticoagulant response than heparin.[5] The elimination half-life of LMWHs is about 3-6 hours after subcutaneous injection, is dose independent and anti-Xa levels peak 3-5 hours after dosing. Coagulation monitoring is generally not recommended in most patient populations.

Exhibit 9: Pharmacologic and pharmacokinetic properties of low-molecular-weight heparins

	Dalteparin	Enoxaparin	Nadroparin	Tinzaparin
Brand Name	Lovenox	Fragmin	Fraxiparine	Innohep
Method of preparation	Nitrous acid depolymerization	Benzylation followed by alkaline depolymerization	Nitrous acid depolymerization	Enzymatic depolymerization with heparinase
Mean molecular weight (daltons)	4,500	6,000	4,300	6,500
Elimination half-life (hrs)	4.5	3 to 5	3.5	3.4
Bioavailability after SC administration (%)	90-92	87	89	87
Anti-Xa/anti-IIa ratio	3.8	2.7	3.5	2.8
Anti-Xa activity (IU/mg)	100	156	90	100

SC: subcutaneous

In addition to these differences in pharmacological and pharmacokinetic properties, each of the products has its own approved indications and dosage recommendations.

Summary: All LMWHs are derived from unfractionated heparin; however they are produced by different processes and have distinct biochemical and pharmacological properties.

Health Canada Warnings and Safety Information

- Health Canada issued an advisory in 2003 outlining clarification of dosing recommendations for dalteparin administered post-operatively for thromboprophylaxis in patients undergoing elective hip surgery.[12]
- Safety information on tinzaparin was issued by Health Canada in 2010 detailing the use of tinzaparin in elderly patients with renal impairment. Tinzaparin is not recommended in elderly patients over 70 years of age with renal impairment.[13]

Discussion

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability in Canada

- There are four low molecular weight heparins (LMWHs) available in Canada: enoxaparin, dalteparin, nadroparin and tinzaparin. Fondaparinux, a selective factor Xa inhibitor, is also available. Various dosage forms are available for each drug to help facilitate weight-based dosing.
- LMWHs are only available as brand-name products in Canada. Fondaparinux is available as brand-name and generic products in Canada.

Public Plan Listing in Ontario

- In Ontario, dalteparin, enoxaparin, nadroparin, tinzaparin and fondaparinux are listed as Limited Use and/or available through the Exceptional Access Program for specific indications.
- The approval duration in Ontario varies depending on the indication and ranges from 9 days (for fondaparinux) to one year (e.g., for treatment of DVT in pregnant or lactating females).

Public Plan Listing in Canada

- All public drug plans in Canada provide coverage for low molecular weight heparins. Dalteparin, enoxaparin and tinzaparin are covered in all jurisdictions. Nadroparin is covered in nine of 12 jurisdictions and fondaparinux in four.
- Five jurisdictions (Alberta, Quebec, Nova Scotia, New Brunswick, NIHB) list LMWHs as General Benefit, often due to concerns of potential delay in obtaining approval in rural communities.
- Clinical criteria for coverage vary among the jurisdictions, and include treatment of DVT/PE, prophylaxis in hip or knee replacement surgery, prophylaxis in pregnant patients, prophylaxis in high-risk surgery.

Selected International Jurisdictions

- In the United States, all drug plans reviewed provide coverage enoxaparin (generic) as a preferred drug. Note that enoxaparin is only available in Canada as the brand-name product. Dalteparin and fondaparinux (generic) are also available as a preferred drug in 50% of drug plans reviews.
- Australia provides coverage through the public plan programs for enoxaparin, dalteparin and fondaparinux. Note that tinzaparin and nadroparin are not currently covered.
- In New Zealand, enoxaparin and dalteparin are covered under the public drug plan. Tinzaparin is not covered. Nadroparin and fondaparinux are not available in New Zealand.

Part B: Impact of different drug reimbursement schemes for coverage of LMWHs and fondaparinux

- There is no information regarding the use of various reimbursement schemes for low molecular weight heparins and/or fondaparinux.

Part C: Rapid Reviews of Selected Topics

- *Pharmacologic and pharmacokinetic differences among the LMWHs:* All LMWHs are derived from unfractionated heparin; however they are produced by different processes and have distinct biochemical and pharmacological properties.

Health Equity

In Ontario, all low molecular weight heparins and fondaparinux are available on the ODB formulary as Limited Use or through the Exceptional Access Program for specific indications. There are certain indications (e.g., prophylaxis in patients with cancer, use in patients undergoing abdominal surgery) which are currently not funded.

Conclusion

In Ontario, all four LMWHs (i.e., dalteparin, enoxaparin, nadroparin, tinzaparin) and fondaparinux are listed as Limited Use and/or available through the Exceptional Access Program for specific indications. Across Canada, all public drug plans in Canada provide coverage for low molecular weight heparins. Five jurisdictions (Alberta, Quebec, Nova Scotia, New Brunswick, NIHB) list LMWHs as General Benefit, often due to concerns of potential delay in obtaining approval in rural communities.

Despite the availability of LMWHs as a restricted medication (i.e., requiring special authorization) in many jurisdictions, there are no studies evaluating the use of different reimbursement schemes on adherence nor on outcome measures.

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Appendix A: Webpages for Provincial Drug Formularies

Province	Webpage for Drug Formulary
British Columbia	http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/Search.jsp
Alberta	https://idbl.ab.bluecross.ca/
Saskatchewan	http://formulary.drugplan.health.gov.sk.ca/
Manitoba	http://web6.gov.mb.ca/eFormulary/
Ontario	https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp
Quebec	http://www.ramq.gouv.qc.ca/en/regie/legal-publications/Pages/list-medications.aspx
New Brunswick	http://www.gnb.ca/0212/nbpdpformulary-e.asp
Nova Scotia	http://novascotia.ca/dhw/pharmacare/formulary.asp
Prince Edward Island	http://healthpei.ca/formulary
Newfoundland	http://www.health.gov.nl.ca/health/nlpdp/fmlsearch.asp
Yukon Territories	https://apps.gov.yk.ca/pls/apex40p/f?p=161:9000:4324580815029961:::::
NIHB (Non-insured Health Benefits) Program	http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fournir/pharma-prod/med-list/index-eng.php

Appendix B: Restriction Criteria for LMWHs and Fondaparinux

Drug	Criteria	Approval period
British Columbia		
Dalteparin, enoxaparin, nadroparin, tinzaparin	Treatment of venous thromboembolism: For the treatment of patients with acute deep vein thrombosis or pulmonary embolus who continue to receive care after leaving an acute care (hospital) setting. This treatment bridges the times gap to achieve therapeutic INR on oral anticoagulants OR Patients with treatment failure or oral anticoagulant therapy (recurrence of one or more deep vein thromboses or pulmonary emboli in patients with therapeutic INR on oral anticoagulants) OR Patients, associated with cancer, who have failed, or who are unable to tolerate, oral therapy with warfarin (applicable to dalteparin only). Prevention of venous thromboembolism: For prevention in patients following elective total knee replacement surgery OR Following elective total hip replacement surgery OR Following orthopedic surgery for major trauma OR With lupus anticoagulant syndrome, antiphospholipid syndrome or thrombophilia OR Before, during or after pregnancy OR Following abdominal or pelvic surgery for the management of malignant tumour (approved for dalteparin and enoxaparin prescriptions only) OR Following abdominal or pelvic surgery for the management of a malignant tumour (applicable to dalteparin and enoxaparin prescriptions only) and who are at high risk	Up to 10 days Up to 3 months, then reassessed Up to 6 months Up to 14 days Up to 35 days Up to 10 days Up to 3 months Up to 4 weeks post-partum Up to 10 days Up to 28 days for high risk patients

Drug	Criteria	Approval period
	(defined as those with previous history of VTE and/or anesthesia lasting longer than 2 hours and/or bed rest lasting 4 days or longer following surgery)	
Saskatchewan		
Dalteparin, enoxaparin, nadroparin, tinzaparin	1. For treatment of venous thromboembolism 2. For prophylaxis following total knee arthroplasty 3. For major orthopedic trauma 4. For long-term outpatient prophylaxis in patients who are pregnant 5. For long-term outpatient prophylaxis in patients who have a contraindication to, are intolerant to, or have failed, warfarin therapy 6. For long-term outpatient prophylaxis in patients who have lupus anticoagulant syndrome 7. Prophylaxis in patients undergoing total hip replacement or following hip fracture surgery 8. For treatment of pediatric patients where anticoagulant therapy is required and warfarin therapy cannot be administered (applicable to enoxaparin)	Up to 10 days Up to 35 days Up to10 days (may be reassessed) Up to 35 days
Manitoba		
Dalteparin, enoxaparin, nadroparin, tinzaparin	1. For prophylaxis of thromboembolic disorders (DVT) in patients undergoing orthopedic surgery of the hip or knee. 2. For treatment of deep venous thrombosis (DVT). 3. Peri-operatively if a high risk of thromboembolism exists (i.e. requiring anticoagulation where warfarin is withheld). 4. For treatment of recurrent DVT or pulmonary embolism occurring on therapeutic warfarin. 5. For antithrombotic therapy in infants < 1 year old. 6. For antithrombotic therapy during pregnancy (extend coverage for 2 weeks past due date). 7. For prophylaxis of thromboembolic disorders in spinal cord injuries 8. For the prevention of VTE in patients undergoing pelvic or abdominal surgery for cancer or inflammatory bowel disease	 Maximum 8-12 weeks Maximum 4 weeks
Prince Edward Island		
Dalteparin, enoxaparin, tinzaparin	1. For the acute treatment of DVT and/or PE 2. For prophylaxis in hip replacement and hip fracture surgery	Maximum 30 days Maximum 35 days

	3. For prophylaxis in knee replacement surgery 4. For prophylaxis in high risk surgery 5. For the extended treatment of recurrent symptomatic venous thromboembolism that has occurred while patients are on therapeutic doses of warfarin 6. For the treatment and secondary prevention of symptomatic venous thromboembolism or pulmonary embolism in patients with cancer	Maximum 10 days Maximum 10 days 6 months
Newfoundland		
Dalteparin, enoxaparin, tinzaparin	1. For treatment of acute venous thromboembolism 2. For extended treatment of acute VTE in patients who have treatment failure on therapeutic doses of warfarin 3. For prevention of VTE following total hip replacement surgery or hip fracture surgery 4. For prevention of VTE following total knee replacement surgery 5. For prophylaxis of VTE in patients with concomitant anticoagulation syndromes, or in patients who have failed to reach therapeutic INR while on oral anticoagulant therapy 6. For treatment of VTE in cancer patients (applicable to dalteparin) 7. For extended treatment in cancer patients with symptomatic VTE who have had a recurrent VTE on warfarin therapy (applicable to dalteparin) 8. For secondary prevention of symptomatic VTE in cancer patients who are on active chemotherapy with agents that interact with warfarin or in patients who have failed oral anticoagulants as evidenced by an extension or recurrent of DVT (applicable to dalteparin) 9. For the prophylaxis of venous thromboembolism post abdominal or pelvic surgery for management of a malignant tumour (applicable to enoxaparin) 10. For prophylaxis of VTE post abdominal or pelvic surgery for management of a malignant tumour in high risk patients (e.g., those with a history of VTE and/or anesthesia lasting >2 hours and/or bed rest lasting >4 days following surgery (applicable to enoxaparin)	Maximum 10 days Limited to 3 months Maximum 35 days Maximum 10 days Limited to 3 months Maximum 10 days Limited to 3 months Maximum 6 months Maximum 10 days Maximum 28 days
Yukon		
Dalteparin, enoxaparin, nadroparin, tinzaparin, fondaparinux	1. For treatment of approved chronic condition 2. For long-term outpatient prophylaxis in patients who are intolerant or have failed warfarin therapy	

Appendix C: Interview Questions

How long have you listed LMWHs and fondaparinux on your provincial formulary? How are they listed (e.g., restricted, general benefit)?
Why did you decide to list these agents this way?
What was the basis for this listing (e.g., quantity limits, general listing)?
Do you have any studies comparing usage/costs before and after implementation of this listing?
Why are certain LMWHs/fondaparinux NOT funded?
Do you restrict prescribing to certain specialties (or are certain specialties exempt from restrictions)?
Do you have any special restrictions regarding the use of LMWHs/fondaparinux?

Appendix D: Tiered cost-sharing options

Prescription Drug Plan	Tier 1 (generic)	Tier 2 (preferred brand)	Tier 3 (non-preferred brand)	Tier 4 (specialty)
Plan A	$5	$28	$55	25%
Plan B	$2	$20	$40	N/A
Plan C	$10	$25	50%	25%
Plan D	$4	$17	75%	25%

Adapted from:
http://www.cancer.org/treatment/findingandpayingfortreatment/managinginsuranceissues/medicare/medicarepartd/medicare-part-d-formularies-and-drug-coverage