ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Drug Class Review: Low-Molecular-Weight Heparins and Fondaparinux

FINAL CONSOLIDATED REPORT

April 2016

Ontario Drug Policy Research Network

The Ontario Drug Policy Research Network (ODPRN) is funded to conduct drug class reviews as part of an initiative to modernize the public drug formulary in Ontario. As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP), Ministry of Health and Long-Term Care to select key priority areas and topics for formulary modernization, then conducts independent drug class reviews and disseminates the results of each of these reviews directly to the OPDP to facilitate informed decision making on public drug funding policies. The drug class reviews may lead to recommendations such as expansion of access to drugs on the formulary, revision or restriction of access to drugs, no change to current listing status and/or education of clinicians regarding appropriate prescribing.

Conflict of Interest Statement

Muhammad Mamdani was a member of an advisory board for Hoffman La Roche, Pfizer, Novartis, GlaxoSmithKline and Eli Lilly Canada.
Paul Oh was a member of an advisory board for Amgen, Astra Zeneca, Janssen, Novartis, Pfizer, Roche and Sanofi.
Tara Gomes, Muhammad Mamdani and David Juurlink received grant funding from the Ministry of Health and Long-term Care.
Marc Carrier received research funding from Leo Pharma, BMS and consulting fees from Pfizer, Leo Pharma and Bayer.
Scott Walker received an educational grant from Sanofi Aventis.
No other 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 drug class review for low-molecular-weight heparins.

Acknowledgments

This review was funded by grants from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund. The work was also supported by The Keenan Research Centre of St. Michael's Hospital (SMH), the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario MOHLTC and by the Canadian Institute for Health Information (CIHI). Datasets provided by ICES were linked using unique encoded identifiers and analyzed at ICES. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources and supporting organizations. No endorsement by SMH, ICES, CIHI, or the Ontario MOHLTC is intended or should be inferred.

Study Team

- Formulary Modernization Team: Paul Oh, Sandra Knowles
- Qualitative Team: Alekhya Mascarenhas, Radha Sayal, Sobia Khan and Julia Moore from the Knowledge Translation Program at the Li Ka Shing Knowledge Institute
- Systematic Review Team: George A. Wells, Amy Johnston, Shu-ching Hsieh, Shannon Kelly, Annie Bai, Becky Skidmore
- Pharmacoepidemiology Team**:** Diana Martins, Wayne Khuu, Mina Tadrous, Samantha Singh, Marc Carrier, David Juurlink, Mike Paterson, Muhammad Mamdani, Tara Gomes
- Pharmacoeconomics Team: Doug Coyle, Karen Lee, Mirhad Lončar, Kathryn Coyle
- Research Team, Clinical Experts: Marc Carrier
- Research Team, Representative from Committee to Evaluate Drugs: Scott Walker
- Patient Representative: Rose Shannon

Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

List of abbreviations	
AB	Alberta
BC	British Columbia
CDR	Common Drug Review
CIHI	Canadian Institute for Health Information
DOAC	Direct-acting oral anticoagulant
DVT	Deep vein thrombosis
EAP	Exceptional Access Program
GB	General benefit
HFS	Hip fracture surgery
HIT	Heparin-induced thrombocytopenia
ICER	Incremental cost-effectiveness ratio
ICES	Institute for Clinical Evaluative Sciences
LDUH	Low dose unfractionated heparin
LMWH	Low molecular weight heparin
LU	LU
MB	Manitoba
MOHLTC	Ministry of Health and Long-Term Care
NB	New Brunswick
NIHB	Non-insured Health Benefits
NL	Newfoundland
NS	Nova Scotia
NU	Nunavut
NW	Northwest Territories
ODB	Ontario Drug Benefit
ODPRN	Ontario Drug Policy Research Network
ON	Ontario
OPDP	Ontario Public Drug Programs
PE	Pulmonary embolism
PEI	Prince Edward Island
Q4	Fourth quarter
QALY	Quality adjusted life years
QC	Quebec
SK	Saskatchewan
SMH	St. Michael's Hospital
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
TX	Treatment
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
YK	Yukon Territories

Executive Summary

Low-molecular-weight heparins (LMWH) and fondaparinux are anticoagulants used in the treatment and prevention of venous thromboembolism. In Canada, there are four LMWHs commercially available: dalteparin, enoxaparin, nadroparin, tinzaparin. In addition, fondaparinux, a synthetic heparin-like compound, is available. All of these agents are available as injectable formulations in various strengths. Only fondaparinux is currently available as a generic product.

In Ontario, all LMWHs and fondaparinux are funded through the Ontario Public Drug Programs (OPDP) either as Limited Use (LU) on the Ontario Drug Benefit (ODB) formulary or through the Exceptional Access Program (EAP); the OPDP only funds medications that are administered on an outpatient basis. There are six LU codes for various indications [i.e., acute treatment of deep venous thrombosis (DVT), treatment of DVT in pregnant or lactating females, DVT treatment in patients whom treatment with warfarin is not tolerated or contraindicated or for patients who failed warfarin, acute treatment of pulmonary embolism, post-operative prophylaxis of lower limb surgery (for fondaparinux)]. In addition, there are three EAP clinical criteria for funding for dalteparin, enoxaparin and tinzaparin: for perioperative bridging for patients who require long-term warfarin therapy, for post-operative prophylaxis of DVT in patients with hip or knee surgery and cannot use warfarin, and for extended treatment of venous thromboembolism (VTE) in patients with cancer who cannot use warfarin (dalteparin only).

Although there are a variety of clinical indications that are currently funded for these drugs in Ontario, clinicians have requested that additional indications be considered for inclusion on the ODB formulary, in particular prophylaxis in patients undergoing non-orthopaedic surgery and prophylaxis in cancer patients. As well, because these products are listed as LU for some indications and EAP for others, there is a potential for inappropriate use of the LU codes to gain access to this class of medications for other indications. As part of the formulary modernization review, an evaluation of LMWH and fondaparinux use in outpatients was undertaken, in order to evaluate the current program for coverage of these agents and to provide policy recommendations for these products to the OPDP.

Key Considerations for Reimbursement Options

Clinical recommendations

- In our review of 28 guidelines, LMWHs and/or fondaparinux were recommended for use in a variety of different indications including prophylaxis (e.g., post-operative prophylaxis for patients undergoing surgery of the lower limbs and in non-orthopedic surgical patients, peri-operative bridging for patients on warfarin) and treatment of VTE (e.g., treatment of DVT in non-cancer patients and in patients with cancer, treatment of DVT in pregnant and/or lactating females).
- No guideline developed recommendations for post-operative prophylaxis of DVT for patients with hip or knee surgery who cannot use warfarin.
- Routine primary thromboprophylaxis for prevention of VTE is not recommended in cancer patients with no additional risk factors.

Safety

- LMWHs are associated with a number of serious adverse effects including bleeding events, thrombocytopenia and osteopenia. Other adverse effects include hyperkalemia, injection site reactions and allergic reactions.
- Although the risk of heparin-induced thrombocytopenia (HIT) is lower with LMWHs than with unfractionated heparin, in patients with a history of HIT, LMWHs are contraindicated. In contrast fondaparinux can be used as an option in patients with HIT.
- LMWH is associated with a lower risk of osteoporosis than unfractionated heparin.

Accessibility

- All LMWHs and fondaparinux are available through the Ontario Drug Benefit Program, either as a LU benefit on the ODB formulary or through the Exceptional Access Program. The EAP's telephone request service (TRS) also considers coverage of LMWHs in specific situations. The TRS provides a one-business day turnaround time for LMWH requests meeting criteria.
- Despite some indications being listed on EAP, physicians in our qualitative analysis did not find that the EAP process prevented access for their eligible patients. However, many clinicians are unfamiliar with accessibility of LMWH through EAP, and are only aware of the LU listing for these drugs.
- From our analyses of utilization data, current LU codes appear to be used inappropriately in some patients in order to obtain LMWH coverage for unlisted indications.

Pharmacoeconomics

- There was suggestion of increasing use of LMWHs for treatment of patients with cancer-associated thrombosis. Therefore, the comparative cost-effectiveness of LMWH in the treatment and secondary prevention of venous thromboembolism in patients with cancer was assessed. The availability of well-conducted independent economic analyses from the Canadian perspective is currently lacking in the published literature. Due to time constraints, other indications for LMWHs were not evaluated from a pharmacoeconomic perspective in our review.
- A de novo economic model was developed to assess the cost-effectiveness of LMWH medications compared with warfarin in the secondary prevention of cancer-related VTE. In patients with cancer diagnosed with a VTE, long term prophylaxis with LMWH was not cost-effective in comparison with warfarin prophylaxis based on a commonly used threshold of $50,000 per quality-adjusted life year (QALY) gained.
    - Long-term (6-month) prophylaxis against recurrent VTE with LMWH results in slightly greater QALYs compared with warfarin; however, the costs associated with LMWH are significantly greater than warfarin. The incremental cost effectiveness ratio (ICER) for LMWH versus warfarin is $1.6 million per QALY gained.

Reimbursement Options: Final Recommendations

Final recommendations for the LMWH drug class review are based on results of the review, input from stakeholders and feedback from the ODPRN Citizen's Panel. Considerations for the final recommendation include:

- Clinical recommendations:
  - LMWHs are recommended for use in a large number of different indications including acute treatment and prophylaxis. Most indications require initiation of LMWH therapy immediately upon diagnosis; the diagnosis is made in an acute care setting.

- Accessibility:
  - LMWHs are available as LU and EAP; however, many clinicians are unfamiliar with accessibility of LMWH through EAP and are only aware of LU listing.
  - LU codes were found to be used inappropriately; LU codes 186 and 188 were used most frequently regardless of the medical indication. The liberal interpretation of these specific LU codes highlights the need for more explicit wording.
  - The EAP process is considered by many physicians to be cumbersome. Despite the availability of the telephone request service, many specialists with a busy clinical practice often do not have time to call during office hours, which then may result in at least a one-day delay for approval. Additionally, for patients in a hospital setting who require LMWH on discharge, the clinicians reported that the availability of the TRS only on weekdays may result in a delay in discharge of the patient over the weekend. Due to the urgency of LMWH initiation, delays in accessing EAP approval may result in deleterious outcomes for patients.

- Cost-effectiveness:
  - Secondary prophylaxis with LMWH in cancer patients (currently funded under EAP) was not found to be cost-effective in comparison with warfarin prophylaxis at current listing prices based on a commonly used threshold of $50,000 per quality-adjusted life year (QALY) gained; the ICER for LMWH versus warfarin was greater than $1 million per QALY gained.
  - Despite the lack of cost-effectiveness of this option, guidelines recommend LMWH over vitamin K antagonists for this indication, due to superior efficacy of LMWH compared to vitamin K antagonists.
  - Since cost-effectiveness of LMWHs for other indications was not determined in our review, it is unknown whether LMWHs would be cost-effective for these indications.

- Stakeholder perspective:
  - Overall, stakeholders were strongly in favour of streamlined LU codes. They also stated that this would allow for improved tracking of publically funded prescriptions versus a general benefit listing.
  - For the extended treatment of cancer-associated thrombosis, clinicians and

patient representatives noted that use of warfarin is often challenging due to the multiple drug interactions and intensive monitoring which is often inconvenient and burdensome for patients undergoing cancer treatment.

- Other considerations:
  - Approximately $33.6 million was spent on LMWHs by the OPDP in 2014. Coverage was provided to over 24,580 users in the community setting.
  - Over 3,200 requests for LMWH were evaluated by the OPDP in fiscal 2014/15; moving current EAP indications to LU would eliminate the use of EAP for accessing LMWHs.

It is recommended that LMWHs and fondaparinux be listed as LU for most indications using revised streamlined LU codes; access of LMWHs through EAP would only be required for uncommon situations (e.g., pregnant patient with a history of heparin-induced thrombocytopenia who requires anticoagulation with fondaparinux).

Limited Use for LMWH and fondaparinux

- Acute treatment of VTE in non-cancer patients
- Acute treatment and secondary prophylaxis for VTE in patients with cancer
- Treatment and prophylaxis of VTE in pregnant or lactating females
- Post-operative prophylaxis of VTE for patients undergoing surgery of lower limbs
- Post-operative prophylaxis of VTE for patients undergoing non-orthopaedic surgery and who are at high risk of thromboembolic complications
- Peri-operative bridging for patients who require long-term warfarin therapy

Other considerations:

1. *LMWH use in pediatrics:* In our review of LMWHs, we focused our review on the adult population and did not examine the use in pediatrics. However, the pediatric population is unique, and additional review of LMWHs in pediatrics is warranted.
2. *Price negotiations for LMWHs:* In our cost-effectiveness model for extended treatment of VTE in patients with cancer, LMWH was not shown to be cost-effective at currently listed prices. However, with a reduction in price of approximately 91%, LMWHs would become a cost-effective option.
3. *EAP for fondaparinux for patients with cancer-associated thrombosis and heparin-induced thrombocytopenia (HIT) or in pregnant females with history of HIT:* Although fondaparinux has not been studied in patients with cancer-associated thrombosis, guidelines suggest that fondaparinux is an option for patients with a history of HIT in this population. Additionally, fondaparinux has been used during pregnancy in patients with history of HIT. Therefore, EAP for fondaparinux should be considered in patients with cancer-associated thrombosis with a history of HIT and pregnant patients with a history of HIT. Note that the availability on the ODB formulary of fondaparinux for other indications (e.g., acute treatment, post-operative prophylaxis) is via LU.

Table of Contents

List of Exhibits

Rationale for Review

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 injectable formulations in various strengths. Only fondaparinux is available as a generic product*. Note: In this report, the designation "LMWH" will include fondaparinux, unless otherwise noted.*

In Ontario, all LMWHs are funded in Ontario through the Ontario Public Drug Programs (OPDP) either as Limited Use (LU) on the Ontario Drug Benefit (ODB) formulary or through the Exceptional Access Program (EAP); the OPDP only funds medications that are administered on an out-patient basis. There are six LU codes for various indications [i.e., acute treatment of deep venous thrombosis (DVT), treatment of DVT in pregnant or lactating females, DVT treatment in patients whom treatment with warfarin is not tolerated or contraindicated or for patients who failed warfarin, acute treatment of pulmonary embolism, post-operative prophylaxis of lower limb surgery (for fondaparinux)]. In addition, there are three EAP clinical criteria for funding for dalteparin, enoxaparin and tinzaparin: for perioperative bridging for patients who require long-term warfarin therapy, for post-operative prophylaxis of DVT in patients with hip or knee surgery and cannot use warfarin, and for extended treatment of venous thromboembolism (VTE) in patients with cancer who cannot use warfarin (dalteparin only).

Although there are a variety of clinical indications that are currently funded for these drugs in Ontario, clinicians have requested that additional indications be considered for inclusion on the ODB formulary, in particular prophylaxis in patients undergoing non-orthopaedic surgery and prophylaxis in cancer patients. As well, because these products are listed as LU for some indications and EAP for others, there is a potential for inappropriate use of the LU codes to gain access to this class of medications for other indications. As part of the formulary modernization review, an evaluation of LMWHs was undertaken for use in outpatients, in order to evaluate the current program for coverage of these agents and to provide policy recommendations for these products in Ontario.

This report outlines the key findings for each of the components of the review. More detailed information for each of the reviews can be found on the ODPRN website: http://www.odprn.ca

Background Information

Low molecular weight heparins (LMWHs) are anticoagulants that are used for a variety of different conditions in both inpatient (e.g., prevention of DVT in medical inpatients, management of acute coronary syndrome) and outpatient settings. Furthermore, many patients are initiated on a LMWH in a hospital setting, but then continue with these medications as outpatients. 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 (not fondaparinux) 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]

Public plan reimbursement of LMWHs and fondaparinux

Canada

All public drug plans in Canada provide coverage for LMWHs. 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. Six provinces (British Columbia, Saskatchewan, Manitoba, Prince Edward Island, Newfoundland, Ontario) list LMWHs as a restricted benefit, requiring prior authorization for coverage. 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, secondary prophylaxis in cancer patients.

Exhibit 1: 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

Current as of February 22, 2016

NO=not listed; RES=restricted listing (e.g. Exceptional Access Program in Ontario); FB=unrestricted listing; PAS=passive listing (e.g., LU in Ontario)

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 LMWHs were available prior to 2003, no review was completed by the CDR.

Public Plan Reimbursement in Ontario

In Ontario, dalteparin, enoxaparin, nadroparin, tinzaparin and fondaparinux are listed as LU and/or are available through the Exceptional Access Program for specific indications. The EAP's telephone request service (TRS) also considers coverage of LMWHs in specific situations. The TRS provides a one-business day turnaround time for LMWH requests meeting criteria.

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, tinzaparin and fondaparinux are available as LU for specified indications or scenarios (Exhibit 2).

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 for other indications.

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 (initial approval duration; extension may be granted based on case-by-case review)

[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

Components of the Drug Class Review

The objective of the drug class review for LMWHs is to provide evidence-informed policy recommendations for these drugs in Ontario.

The treatment of LMWHs drug class review is comprised of:

- qualitative analyses of perspectives of prescribers and pharmacists
    - one-on-one semi-structured telephone interviews regarding specific experiences and perceptions relevant to funding policies for LMWHs
- environmental scans of:
    - national and international drug policies
    - considerations relating to health equity
- analysis of real-world drug utilization using:
    - administrative claims data from Ontario and across Canada (where available)
- systematic review and critical appraisal of evidence-based clinical practice guidelines
- cost-effectiveness analysis for the prevention of recurrent VTEs in cancer patients

Results from all of the above components were reviewed and consolidated into a set of policy recommendations.

Overview of Findings

Qualitative Research Team: Perspectives of Physicians and Pharmacists

Findings of the qualitative study represented common experiences and perceptions described across pharmacist and physician (primary care physicians, internists, oncologists, hematologist, emergency department physicians) groups. Eighteen semi-structured telephone interviews with physicians and pharmacists were conducted.

Influences and perceptions of LMWH prescription

- LMWH prescription is linked to various factors such as availability on hospital formularies, physician familiarity with LMWH dose calculations, the introduction of new oral anticoagulants and patient ease of use (prefilled syringes preferred over multidose vials).

> *"if I write brand B to my out-patient and that patient is admitted to hospital and there's no brand B and there's a huge kerfuffle about what actual dosing the patient should get when they're admitted to hospital because the hospital only has brand A – not brand B – it makes it kind of difficult to actually choose brand B as an out-patient in someone who, despite the fact that brand B may be a better choice – maybe the syringe size is more fitting, maybe they're paying for it themselves and it's cheaper than brand A"* –hematologist

Patient adherence to LMWH

- Participants described their impression that most patients are highly adherent to LMWH, despite the requirement for self-injection.
- Review of the literature also indicates high adherence rates to LMWH. In these studies, patients described how the process of self-injecting LMWH transferred a sense of responsibility to them, which in turn helped them adhere to the treatment course.

Accessibility to LMWH on the ODB formulary

- Many physician participants may be inappropriately applying LU codes to obtain LMWH coverage for a variety of reasons.
    - Physicians admitted that they use code 188 for a wide range of indications, either because they find it easier to remember one code, they interpret the criteria for this code more broadly or they believe applying the code is in the best interest of the health care system and of patients.
- Participants were divided in terms of their perceived need for LU criteria revision.
    - Some physician participants (especially those who use more broad interpretations of the LU codes) were satisfied with the criteria. Other participants felt that the criteria could be expanded to include indications for cancer VTE, and post-operative prophylaxis of VTE in patients undergoing orthopedic surgery for hip fractures.
- Physician participants said that their preference is to use the LU codes whenever

possible and they do not have experience using the Exceptional Access Program (EAP).

- Participants suggested some cost saving measures for the LU program.
    - In order to reduce wastage, limit the amount of drug which is dispensed at certain time intervals.
    - Training pharmacists to administer injections to patients who need nursing support.
    - Negotiating with manufacturers to have one LMWH adopted across the province, for both hospital and outpatient use

> *"To be honest, I don't see any reason why this type of medication should be under any limited access, because they're really not… there's no reason to abuse them…they also have a side effect profile that you don't want exposed patients that don't have a good indication for this type of treatment"* –oncologist

> "*At the present time I use the special access code saying that the patient doesn't tolerate [warfarin]. It's up to me to determine whether they tolerate [warfarin], or not. If it is frequent sampling, and poking them, giving the blood, they use antibiotics, or injections with drugs. Those are all good reasons for me to say they are not tolerating it, but of course I never even put the patient on [warfarin], but I will actually put that access code down, but I think that's kosher.*" –Hematologist

Pharmacoepidemiology Team

Various data sources were used to examine trends in national and provincial prescribing of LMWHs including IMS Geographic Prescription Monitor, Canadian Institute for Health Information National Prescription Drug Utilization Information System (CIHI-NPDUIS) and administrative databases in Ontario. Several limitations are associated with the analysis of the data including: data presented are based on prescriptions filled (unable to verify that the patient took the medication); IMS Geographic Prescription Monitor does not collect patient-level data.

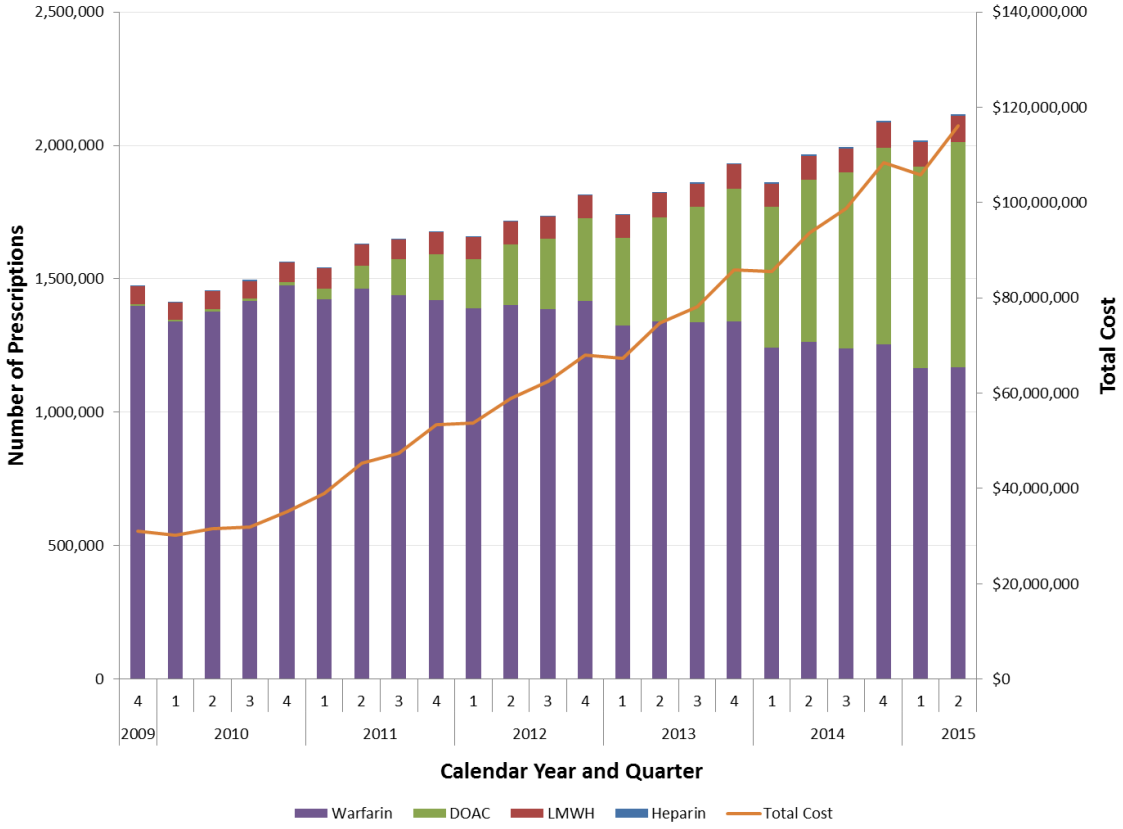
Current Utilization across Canada

Quarterly dispensing of prescriptions for anticoagulant medications in Canada has increased by 42.9% over the past 4 years (Exhibit 4). A total of $116.1 million was spent on all anticoagulant medications nationally in the second quarter (Q2) of 2015, an increase of 249% from Q4 2009 ($33.3 million). This increase was largely driven by the increased use and costs of direct-acting oral anticoagulants (DOACs), which comprised 40% of the total prescription market share (N=2.1 million prescriptions) but accounted for 65% of the total costs ($74.9 million of $116.1 million) in Q2 2015.

Low-molecular-weight heparin (LMWH) accounted for 4.5% (95,366 prescriptions) of all anticoagulant prescriptions in Canada in Q2 2015 and 26.9% ($31.2 million) of total costs. In the same time period, the number of prescriptions dispensed and costs for LMWH increased

by 30.6% and 65.8%, respectively (from 73,020 prescriptions dispensed at a cost of $18.8 million in Q4 2009 to 95,366 prescriptions dispensed at a cost of $31.2 million in Q2 2015). Among all LMWH medications dispensed nationally in Q2 2015, over half (53.3%) were for dalteparin, followed by enoxaparin (28.5%) and tinzaparin (17.2%).

Exhibit 4: Total number of prescriptions and total cost of anticoagulants dispensed to all individuals in Canada, by drug class and quarter



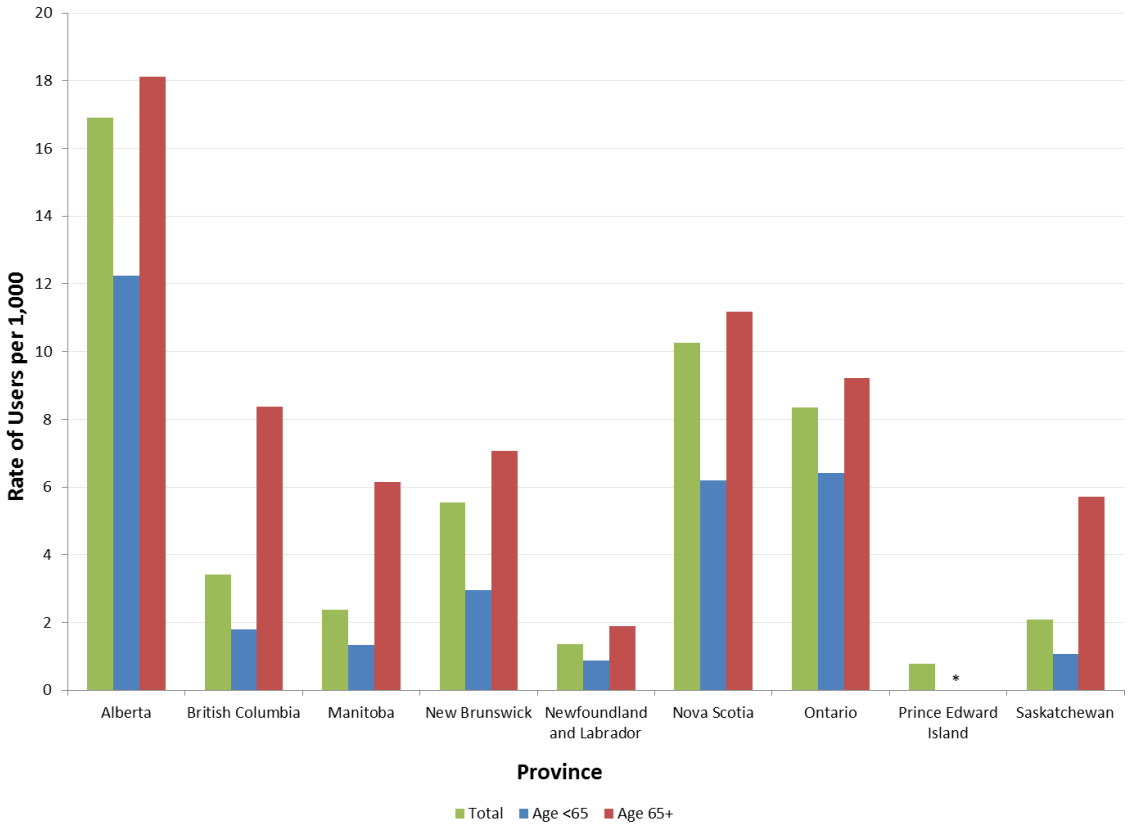
Data Source: IMS GPM

In 2014, approximately $61.2 million was spent on publicly-funded LMWH prescriptions in the studied provinces in Canada, with 63.8% of costs ($39.1 million) attributed to users aged 65 and older. Ontario had the highest overall costs ($33.7 million) compared to other studied provinces in Canada in 2014. Dalteparin was the most commonly dispensed publicly-funded LMWH medication in most provinces in 2014, except for New Brunswick and Newfoundland and Labrador where enoxaparin was most commonly dispensed and Saskatchewan where tinzaparin was most commonly dispensed.

There was a wide variation in the rate of prescriptions dispensed for publicly-funded LMWH medications between provinces in Canada. The rate of publicly-funded LMWH medication dispensed was lowest in Prince Edward Island (0.8 users per 1,000 active drug plan beneficiaries) and highest in Alberta (16.9 per 1,000 active drug plan beneficiaries) in 2014 among provinces compared (data not available for Quebec and the territories for this

comparison) (Exhibit 5). Ontario had the third highest rate of LMWH use (8.4 users per 1,000 active drug beneficiaries) in 2014.

Exhibit 5: Rate of publicly-funded LMWH medication users by province and age in Canada, in 2014

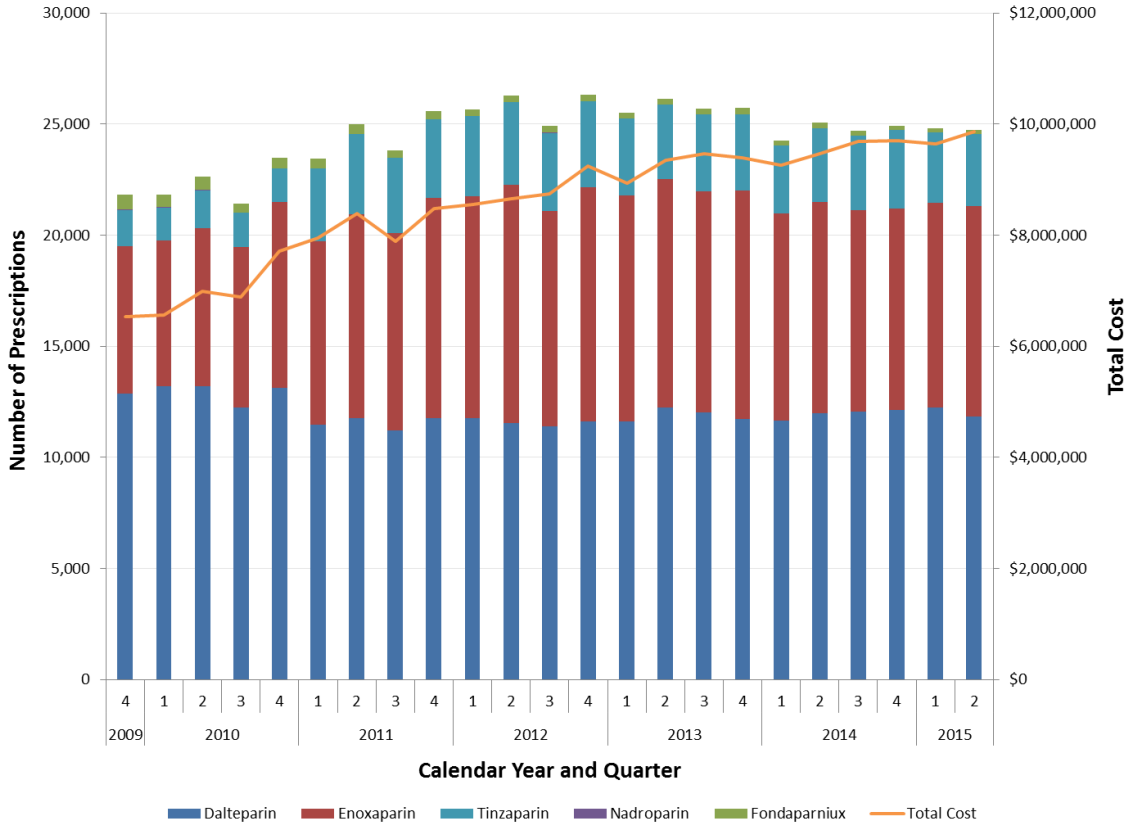


***In accordance with the CIHI privacy policy, in cases where the number of beneficiaries (*) is less than 5 (but greater than 0), this number, along with other associated data element, have been suppressed to ensure confidentiality. Data Source: CIHI NPDUIS and ICES.**

Use of LMWH in Ontario

Similar to national trends, the number of prescriptions dispensed for LMWH has increased 15.2% in Ontario, from 21,480 prescriptions dispensed in Q4 2009 to 24,747 prescriptions dispensed in Q2 2015. Costs have increased by 47.7% over the study period in Ontario, from $6.5 million in Q4 2009 to $9.9 million in Q2 2015. At the beginning of the study period in Q4-2009, dalteparin accounted for over half (58.9%; 12,866 of 21,840 prescriptions) of all LMWH prescriptions dispensed in Ontario. By the end of the study period (Q2-2015), this decreased to 47.8% (11,839 of 24,747 prescriptions).

Exhibit 6: Total number of prescriptions and cost of LMWH dispensed in Ontario, by drug and quarter



Data Source: IMS GPM[12]

Characteristics of Publically-funded LMWH Users and Patterns of Prescribing in Ontario

Ontario has seen a 142.9% increase in the number of publicly-funded users of LMWH over 10 years, from 10,121 users in 2004 to 24,584 users in 2014. Dalteparin has remained the LMWH with the most users but has seen a decrease in its market share from 62.2% (6,300 users) in 2004 to 43.9% (10,791 users) in 2014.

There were 127,333 new users of LMWHs in Ontario between 2002 and 2012. The majority of users (87.6%; N=111,507) were 65 years of age or older when they received their first prescription. Approximately three-quarters (75.2%; N=95,704) had been hospitalized at least once in the year prior to receiving their first LMWH prescription and 39% of users (N=49,631) had received a warfarin prescription in the 120 days prior to their first LMWH prescription. One-third of new-users (32%; N=40,690) received their initial prescription from a general practitioner.

Use of LU Codes for LMWH Prescription Claims in Ontario

LU (LU) codes 186 and 188, indicative of DVT, were used most frequently (48.9% and 29.2% of people treated with LMWH in FY 2014) regardless of the medical indication determined by physician diagnosis codes or hospitalization/emergency department information. The LU code that was most frequently used appropriately was code 187 (use in pregnancy/lactation); however, approximately 47% of pregnant/lactating women had LMWH coverage using a

different LU code. In patients with cancer (which does not have an associated LU code), LU code 188 (47.3%) and 186 (37.0%) were used most frequently.

The median time to discontinuation of LMWH across all indications was 30 days or less. The longest median time to discontinuation was found in users with cancer and DVT (30 days (IQR=7 to 149 days)) and pregnant or lactating users (30 days (IQR=12 to 101 days). Shorter periods of continuous use were found with other indications, with median time to discontinuation ranging from 8 to 16 days.

Systematic Review Team

Clinical recommendations

The objective of the systematic review was to provide a summary of recommendations for the use of LMWHs for the acute treatment and prevention of VTE across a variety of outpatient focused indications through the undertaking of a systematic review and critical appraisal of evidence-based clinical practice guidelines. Care should be taken when interpreting the individual recommendations that have been summarized as we were unable to rule out the influence of expert opinion and consensus processes in some of the guideline documents. For more detailed information about levels of confidence associated with each unique recommendation, please refer to the Systematic Review Unit's report (www.odprn.ca). For a summary of the recommendations, see Exhibits 7 and 8.

A total of 28 guidelines met the inclusion criteria for this review. Eleven (39%) guidelines were published in 2012 and twelve (43%) were published from 2013-2015. Fourteen (50%) guidelines were developed by groups located in the United States, while the remaining guidelines were developed by groups based exclusively in Europe (n=7) and Canada (n=6). Additionally, one guideline was developed by an international group of experts based throughout Europe and North America.

Cancer patients were the most represented patient group across included guidelines with 17 (61%) having provided at least one recommendation of relevance to this patient group. Ten of these guidelines were entirely devoted to the prevention and/or treatment of VTE in cancer patients. A further three guidelines were uniquely devoted to the prevention or treatment of VTE in pregnant women, and two guidelines were specifically focused on patients undergoing orthopedic surgery.

Exhibit 7: Prophylaxis using low-molecular weight heparins

	Recommendation	Reference
Post-operative prophylaxis of DVT for patients with hip or knee surgery who cannot use warfarin		
	No recommendations specific to this indication were identified.	None
Post-operative prophylaxis of VTE for patients undergoing surgery of the lower limbs		
Initiation of prophylaxis	For patients undergoing major orthopedic surgery (THA, TKA, or HFS), post-operative prophylaxis with LMWH to begin ≥12 hours after surgery **(strong recommendation based on moderate-quality evidence).**	[7]
	Patients undergoing elective hip surgery who receive thromboprophylaxis with fondaparinux should begin treatment between 6-8 hours after surgery **(high level of evidence from RCTs or systematic reviews).**	[8]
Preferred pharmacologic intervention	There is insufficient evidence to recommend one type of anticoagulant therapy over another for the prophylaxis of VTE in patients undergoing surgery of the lower limbs **(insufficient or conflicting evidence).**	[9]
	The use of LMWH over alternative prophylactic treatments (fondaparinux, DOACs, LDUH, adjusted-dose VKA, or aspirin) was recommended in patients undergoing total hip or knee arthroplasty **(weak recommendation based on low to moderate quality evidence).**	[7]
Duration of prophylaxis	For patients undergoing THA, TKA, or HFS, prophylaxis with LMWH, fondaparinux, DOACs, LDUH, adjusted-dose VKA, or aspirin is recommended for a 10-14 day period **(weak recommendation based on low to moderate quality evidence).**	[7]
	Prophylaxis should be provided for between 4-5 weeks after HFS **(high level of evidence from RCTs or systematic reviews).**	[8]
	For patients undergoing elective hip surgery, prophylaxis with LMWH should be continued for 4-6 weeks with LMWH or fondaparinux **(high level of evidence based on RCTs or systematic reviews (LMWH) and low level of evidence based on well-conducted observational studies).**	[8]
Prevention of VTE in non-orthopedic surgical patients		
Initiation of prophylaxis	Cancer patients undergoing surgery should start prophylaxis preoperatively from between 12-2 hours prior to surgery **(high level of evidence; further research unlikely to change confidence in effect estimate).**	[10-13]
Preferred pharmacologic	No guideline specifically recommended the use of one LMWH over another.	None
	Across surgical interventions for *non-cancer* patients, LMWH, fondaparinux, or UFH/LDUH are generally recommended in patients at moderate to high risk of VTE or those undergoing major surgical interventions	[8;11;14]

	Recommendation	Reference
intervention	**(high level of evidence based on RCTs).**	
	For patients at high risk for VTE undergoing general abdominal-pelvic surgery (not at high risk for bleeding), prophylaxis with low-dose aspirin or fondaparinux in patients for whom heparin is contraindicated or unavailable is recommended (**weak recommendation based on low or very-low quality evidence).**	[14]
	For patients undergoing *cancer* surgery, thromboprophylaxis with LMWH or UFH is generally recommended **(high level of evidence; further research unlikely to change confidence in effect estimate).** There is no current evidence to support the use of fondaparinux as an alternative to LMWH for cancer surgery **(low level of evidence; further research likely to impact confidence in effect estimate).**	[8;10-15]
Duration of prophylaxis	Depending on the type of surgical intervention and clinical scenario, the guidelines generally recommend that thromboprophylaxis continue for at least 1-4 weeks post-operatively **(level of evidence varies).**	[8;10-18]
Prevention of VTE in patients with cancer		
Initiation of prophylaxis	Cancer outpatients with no additional risk factors for VTE should not receive routine thromboprophylaxis for VTE, including cancer patients with indwelling catheters **(weak recommendation based on moderate-quality evidence).**	[11-13;16;16;18-22]
Preferred pharmacologic intervention	Prophylaxis with LMWH, VKAs, or low-dose aspirin is weakly recommended for patients undergoing chemotherapy **(low level of evidence)**. One 2015 guideline strongly recommended that LMWH should be used for higher-risk multiple myeloma patients **(sufficient evidence from published studies)**.	[10-13;15]
	For the prophylaxis of VTE in cancer outpatients, there is no preferred LMWH **(expert opinion).**	[12]
	There is insufficient evidence to recommend the use of DOACs for the prevention of VTE in cancer patients.	[12]
Duration of prophylaxis	Cancer patients receiving chemotherapy, radiotherapy, steroids and/or hormonal therapy should generally receive prophylaxis for between 4-6 months, depending on their clinical scenario **(strength of recommendation varies from directly relevant high-quality evidence to indirect evidence only).**	[11;15;18]
Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery		
Initiation and duration of bridging therapy	VKAs should be stopped as late as 5 days prior to surgery **(strong recommendation based on low or very-low quality evidence).**	[8;23]
	LMWHs (at preoperative dose) should be stopped approximately 24 hours prior to surgery **(weak recommendation based on low or very low quality evidence).**	[8;23]

	Recommendation	Reference
	VKAs should generally be resumed between 12-24 hours after surgery, but for high-bleeding risk surgery, VKAs should be resumed between 48-72 hours after surgery **(weak recommendation based on low or very-low quality evidence).**	8;23;24
Preferred pharmacologic intervention	No guidelines recommended the use of one LMWH over another	None
	LMWH should be used preferentially over UFH in high-risk patients and to enable outpatient bridging **(low (level of evidence based on well-conducted observational studies in applicable population).**	8

THA=total hip arthroplasty; TKA=total knee arthroplasty; HFS=hip fracture surgery; LMWH=low molecular weight heparin; VTE=venous thromboembolism; DOAC=direct-acting oral anticoagulant; LDUH: low density unfractionated heparin; UFH=unfractionated heparin; VKA=vitamin K antagonist (e.g., warfarin)

Exhibit 8: Treatment using low-molecular weight heparins

	Recommendation	References
Treatment of DVT in non-cancer patients		
Initiation of treatment	VTE treatment should be started with UFH, LMWH or fondaparinux for at least 5 days in non-cancer patients **(high level of evidence based on RCTs or systematic reviews)**; VKA therapy should be started on day 1-2 of treatment with LMWH or UFH **(weak recommendation based on low or very-low quality evidence).**	8;25-27
Preferred pharmacologic intervention	No guidelines recommend the use of a specific LMWH over another	None
	LMWHs are generally recommended for the outpatient treatment of DVT **(may be reasonable to perform based on evidence from RCTs).**	26;28
	LMWHs are recommended for initial treatment of DVT in non-cancer patients over UFH or fondaparinux **(high level of evidence for patient preference of LMWHs in addition to expert consensus).**	26
	LMWH or fondaparinux are recommended over IV UFH or SC UFH for the treatment of acute DVT of the leg or upper extremity DVT that involves the axillary or more proximal veins **(weak recommendation based on moderate-quality evidence for LMWH; weak recommendation based on low or very-low quality evidence for fondaparinux).**	28
	In patients with no cancer and acute DVT of leg, VKA therapy is weakly recommended over LMWH for long-term therapy **(low or very-low quality evidence).** A transition to warfarin or a switch to DOACs is recommended after 1 week of treatment of iliofemoral DVT with LMWH (**strong recommendation based on moderate-quality evidence).**	28;29

	Recommendation	References
Duration of treatment	LMWHs for 3-6 months as an alternative to VKA therapy **(high level of evidence based on RCTs or systematic reviews).**	8;27
	Treatment with anticoagulants for at least 3 months across a variety of clinical scenarios is recommended. The indefinite use of anticoagulant therapy is recommended in certain clinical scenarios (e.g., in patients with unknown risk factors) **(level of evidence varies).**	8;8;24-27;27-30
Treatment of symptomatic, acute VTE in patients with cancer		
Initiation of treatment	For the initial treatment of VTE in cancer patients, LMWH is strongly recommended over UFH for an initial 5-10 days (if no severe renal impairment) but fondaparinux can also be used in certain clinical scenarios **(level of evidence varies)**	10;12;13;17;22;27
	Monotherapy with LMWH is generally recommended instead of overlapping with warfarin for the initial 6 months of treatment **(strong recommendation based on high-quality evidence).**	22;27
Preferred pharmacologic intervention	No available evidence was available to recommend one LMWH over another	17
	The use of dalteparin was recommended for chronic treatment (>30 days) based on one randomized controlled trial in cancer patients as well as its FDA approval status **(lower-level evidence and expert consensus).**	27
	DOACs are not generally recommended for treatment of VTE in patients with cancer due to insufficient evidence **(insufficient evidence and immediate expert consensus).**	12;13;17;28
	LMWH is the preferred anticoagulant in patients with cancer over VKA therapy or DOACs. VKA therapy is recommended if LMWH is contraindicated **(strong evidence for the use of LMWH over VKA therapy; further evidence unlikely to change the direction of the effect estimate).**	10;12;13;16;17;20;22;24;28;28;29
Duration of treatment	For short-term therapy (10 days-3 months), LMWH is generally recommended over VKA therapy **(strong recommendation based on high-quality evidence).**	8;10;26;28
	If long-term therapy (>3 months) is indicated, LMWH, VKAs or DOACs can be used for 6 months, although DOACs are not recommended in all guidelines for treatment of VTE in cancer patients **(levels of evidence vary)**.	8;12;12;15;22
Treatment of DVT in patients in whom treatment with warfarin is not tolerated, or is contraindicated		
	Adult outpatients with VTE who are unable to take warfarin should be anticoagulated with subcutaneous heparin, but preferentially with LMWH **(generally should be performed based on evidence from RCTs).**	26
Treatment of DVT in patients who have failed treatment with warfarin		
	For patients with cancer, a switch to LMWH for a minimum of four weeks (at therapeutic dose) is recommended in patients who fail warfarin treatment (**intermediate level of evidence based on**	22

	Recommendation	References
	systematic reviews of cohort studies). If patients fail treatment with either warfarin *or* LMWH, these authors recommend a switch to either DOACs or fondaparinux **(recommendation based on evidence from case series studies).**	
Treatment of VTE in pregnant and/or lactating females		
Preferred pharmacologic intervention	LMWH is strongly recommended for the treatment of VTE in pregnant and/or lactating females over VKAs and UFH **(moderate-quality evidence)**. Fondaparinux, oral direct thrombin and Xa factor inhibitors are not recommended in breastfeeding women **(weak to strong recommendations based on low or very-low quality evidence).**	8;31-33
	No guideline specifically recommends the use of one LMWH over another	None
Duration of treatment	The recommended minimum treatment duration is 3 months **(weak recommendation based on low or very-low quality evidence).**	8;31;32
	LMWH should be discontinued at least 24 hr prior to induction/C-section and resumption of anticoagulation is recommended no sooner than 4-12 hours after delivery **(strong recommendation based on moderate-quality evidence).**	26;31;33
	Prophylaxis is weakly recommended for at least 6 weeks postpartum **(low level evidence from well-conducted observational studies).**	8;31;32

LMWH=low molecular weight heparin; VTE=venous thromboembolism; DOAC=direct oral anticoagulant; LDUH = low dose unfractionated heparin; UFH=unfractionated heparin; VKA=vitamin K antagonist (e.g., warfarin); FDA=Food Drug Administration; RCT = randomized controlled trial

Safety

A review of the literature was done to describe safety issues related to the use of LMWHs.

- LMWHs are associated with a number of adverse effects including bleeding events, thrombocytopenia and osteopenia. Other adverse effects include hyperkalemia, injection site reactions and allergic reactions.
- In contrast to unfractionated heparin and warfarin, there is no proven method for reversing the anticoagulant effects of LMWH although protamine sulfate neutralizes a variable portion of the anti-Xa activity of LMWH. [5] If bleeding occurs with fondaparinux, recombinant factor VIIa may be effective. [5]
- The frequency of heparin-induced thrombocytopenia (HIT) is threefold lower with LMWHs than with heparin. However, in patients with HIT antibodies, there is cross-reactivity with LMWH and these agents are contraindicated. [5] In contrast fondaparinux can be used as an option in patients with HIT.[34]
- LMWH is associated with a lower risk of osteoporosis than unfractionated heparin. [5] There are limited in vitro studies assessing the effects of fondaparinux on bone metabolism.[5]
- The Institute for Safe Medication Practices has classified LMWHs as “high-alert” drugs in the acute-care setting; a high-alert medication is a drug that has a heightened risk of causing significant patient harm when used in error.[35]

Pharmacoeconomics Team

Cost-Effectiveness Literature Review

A systematic review of the literature was conducted to summarize the current published evidence on the comparative cost-effectiveness of low-molecular weight heparins for the treatment or secondary prevention of deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients with cancer. Three published economic evaluations which addressed the research questions of the review were identified; two studies focused on the secondary prevention of cancer-related VTE[36;37], while one study assessed the comparative cost-effectiveness of therapies in the initial management (treatment) of DVT in cancer patients[38]. Two of three included studies cited financial support from the pharmaceutical industry, and results of these studies favoured the sponsor’s product. The paucity of well conducted independent analysis from the Canadian perspective precluded any inferences regarding the cost-effectiveness of LMWH medications in the treatment or secondary prevention of cancer-related VTE.

Of the three published economic evaluations identified in this review (two cost-effectiveness/cost-utility analyses and one cost-minimization analysis), two analyses were conducted in the United States and one in Canada. The two cost-effectiveness/cost-utility analyses differed in their approach to modeling costs and benefits associated with chosen treatment comparators: one study adopted a trial-based analysis based on the Canadian CLOT trial, while the other study used a decision-tree model. The cost-minimization analysis assumed equal efficacy between all modeled treatment and reported the findings in terms of cost savings. In addition to the receipt of industry funding, the main limitations among included studies relate to unsupported assumptions regarding the impact of LMWH on patients’ survival, or the approach to eliciting utility values from patient surrogates in the case

of the Canadian study. Moreover, the publication date of these economic analyses is unlikely to reflect the current clinical evidence base and cost data.

Given the shortcomings associated with the published literature, which limit the applicability and generalizability of the results, a de-novo economic model which incorporates relevant evidence form the Canadian context is required to assess the comparative cost-effectiveness of this drug class for treatment or secondary prevention of DVT or PE in patients with cancer.

De novo Economic Evaluation for the Prevention of Recurrent VTEs in Cancer Patients

A de novo decision analytic economic model was developed to assess the cost-effectiveness of LMWH versus warfarin for the prevention of recurrent VTEs in patients with cancer. The model structure was adapted from Aujesky et al. (2005).[36] Two analyses were conducted. In the first case, the model was populated with data from the CLOT clinical trial which compared a LMWH, dalteparin, with warfarin treatment over a 6-month period in patients diagnosed with cancer who had experienced a VTE. [39;40] Outcomes included the rate of recurrence of VTEs (DVTs or PEs), major bleeds, minor bleeds and mortality. In the second analysis, the model was adapted to allow the relative risk of events (DVTs, major bleeds, minor bleeds and death) with LMWH from a Cochrane meta-analysis to be applied to the probabilities of the warfarin arm of the CLOT trial to estimate the comparative cost-effectiveness of treatments.[40] Resource use was estimated based on the results of the CLOT clinical trial and costs were sourced from established Canadian references.[41-48] Utilities associated with each of the states within the model were derived from the literature.[49-51] Analysis was conducted from the perspective of the Ontario Ministry of Health with results presented as incremental cost per quality-adjusted life years (QALY) gained. The impact of alternative assumptions regarding parameter estimates and model structure were tested through deterministic sensitivity analyses. Detailed probabilistic sensitivity analysis was performed to assess decision uncertainty.

Long-term (6-month) prophylaxis against recurrent VTE with LMWH results in slightly greater QALYs compared with warfarin; however, the costs associated with LMWH are significantly greater than warfarin. The incremental cost effectiveness ratio (ICER) for LMWH versus warfarin is $1.7 million per QALY gained.

These results were found to be robust to alternative assumptions regarding input parameters for costs, resources, utilities and model structure with the ICER ranging from $175,000 to $2.4 million per QALY with LMWH versus warfarin.

In probabilistic sensitivity analyses, LMWH was found to be more effective than warfarin in approximately 70% of replications, but it was found to be more costly in 100% of replications. The probability that LMWH is cost effective at a willingness to pay per QALY value of both $50,000 and $100,000 was zero.

In patients with cancer diagnosed with a VTE, long-term prophylaxis with LMWH was not cost-effective as compared with warfarin prophylaxis. The ICER for LMWH versus warfarin was greater than $1 million per QALY.

Budget impact analysis in Ontario

The overall cost for LMWHs obtained through the OPDP program in 2014 was $33,660,440. Average costs for dalteparin and enoxaparin were calculated for each LU code. These average costs were used to calculate the total cost if access to only dalteparin or enoxaparin was available, where indicated for use (i.e., preferential listing). The total cost savings by using enoxaparin when possible is estimated to be $10,684,793 per year, a 32% savings (from $33,660,440 to $22,975,647). In contrast, switching to dalteparin is estimated to increase costs by $7,787,299 to $41,447,740. This analysis was meant to provide crude estimates of potential budget impact and results should be interpreted with caution as there may be variation in dosing, duration, and indications of use between the various LMWHs. If preferential therapy were an option to be formally considered, we would recommend more robust analysis that would control for these factors and include all LMWHs.

Due to a number of limitations, it is difficult to model the various options considered for reimbursement in our report. For example, analysis from the pharmacoepidemiology team indicates that the LU codes are currently not used appropriately. Therefore, expanded LU codes (i.e., Option 2) or General Benefit (i.e., Option 3) listing may only lead to small increases in utilization/cost.

Health Equity Issues

No major health equity issues were identified in this review. See Appendix A for Health Equity Considerations.

Accessibility of LMWHs and Fondaparinux

All LMWHs and fondaparinux are available through the ODB Program, either listed as a LU benefit or through the EAP. The EAP's TRS considers coverage of LMWHs in specific situations. The TRS provides a one-business day turnaround time for LMWH requests meeting criteria.

Despite some indications being listed on EAP, physicians in our qualitative analysis did not find that the EAP process prevented access for their eligible patients. However, many clinicians are unfamiliar with accessibility of LMWH through EAP, and are only aware of the LU listing for these drugs. From our analyses of utilization data, current LU codes appear to be used inappropriately in some patients in order to obtain LMWH coverage for unlisted indications.

Recommendations for Consideration

Key Considerations

<u>Clinical recommendations</u>

- In our review of 28 guidelines, LMWHs and/or fondaparinux were recommended for use in a variety of different indications including prophylaxis (e.g., post-operative prophylaxis for patients undergoing surgery of the lower limbs and in non-orthopedic surgical patients, peri-operative bridging for patients on warfarin) and treatment of VTE (e.g., treatment of DVT in non-cancer patients and in patients with cancer, treatment of DVT in patients in

whom treatment with warfarin is not tolerated, is contraindicated or who have failed treatment with warfarin, and treatment of DVT in pregnant and/or lactating females).
- No guideline developed recommendations for post-operative prophylaxis of DVT for patients with hip or knee surgery who cannot use warfarin.
- For most indications, no guideline specifically recommended the use of one LMWH over another.
- Routine thromboprophylaxis is not recommended in cancer patients with no additional risk factors for prevention of VTE.

Safety
- LMWHs are associated with a number of adverse effects including bleeding events, thrombocytopenia and osteopenia. Other adverse effects include hyperkalemia, injection site reactions and allergic reactions.
- The frequency of heparin-induced thrombocytopenia (HIT) is threefold lower with LMWHs than with heparin. However, in patients with HIT antibodies, there is cross-reactivity with LMWH and these agents are contraindicated. In contrast fondaparinux can be used as an option in patients with HIT.
- LMWH is associated with a lower risk of osteoporosis than unfractionated heparin. There are limited in vitro studies assessing the effects of fondaparinux on bone metabolism.

Accessibility
- All LMWHs and fondaparinux are available through the Ontario Drug Benefit Program, either as a LU benefit on the ODB formulary or through the Exceptional Access Program. The EAP's telephone request service (TRS) also considers coverage of LMWHs in specific situations. The TRS provides a one-business day turnaround time for LMWH requests meeting criteria.
- Despite some indications being listed on EAP, physicians in our qualitative analysis did not find that the EAP process prevented access for their eligible patients. However, many clinicians are unfamiliar with accessibility of LMWH through EAP, and are only aware of the LU listing for these drugs.
- From our analyses of utilization data, current LU codes appear to be used inappropriately in some patients in order to obtain LMWH coverage for unlisted indications.

Pharmacoeconomics
- *Cost effectiveness literature review:*
    - A systematic review of the literature was conducted to summarize the current published evidence on the comparative cost-effectiveness of low-molecular weight heparins for the treatment or secondary prevention of deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients with cancer.
    - Three published economic evaluations which addressed the research questions of the review were identified; two studies focused on the secondary prevention of cancer-related VTE, while one study assessed the comparative cost-effectiveness of therapies in the initial management (treatment) of DVT in cancer patients.
    - Limitations of these studies relate to unsupported assumptions regarding the impact of LMWH on patients' survival, the approach to eliciting utility values from patient surrogates, and receipt of industry funding. Moreover, the publication date

of these economic analyses is unlikely to reflect the current clinical evidence base and cost data.

- *De novo economic evaluation:*
  - An independent de novo economic model was developed to assess the cost effectiveness of LMWH medications compared with warfarin in the secondary prevention of cancer-related VTE.
  - A decision tree model was developed and adapted to allow incorporation of effectiveness data from two different sources, modeling the impact of treatment over a 6-month period.
  - Long-term (6-month) prophylaxis against recurrent VTE with LMWH results in slightly greater QALYs compared with warfarin; however, the costs associated with LMWH are significantly greater than warfarin.
  - In patients with cancer diagnosed with a VTE, long term prophylaxis with LMWH was not cost-effective in comparison with warfarin prophylaxis based on a commonly used threshold of $50,000 per quality-adjusted life year (QALY) gained. The incremental cost effectiveness ratio (ICER) for LMWH versus warfarin is greater than $1 million per QALY gained.

Reimbursement Options

Given that the guidelines reviewed recommended the use of LMWHs and/or fondaparinux for various indications and that criteria for LU codes often did not match actual patient indication, four main reimbursement options for LMWHs and fondaparinux are proposed (see Appendix B).

Option 1a (status quo): LU for LMWH and fondaparinux; Exceptional Access Program (EAP)

Details:

- No change to listing status and EAP availability of LMWH.

Rationale:

- No accessibility issues were identified in this review.
- Since secondary prophylaxis with LMWH in cancer patients (currently funded under EAP) was not cost-effective in comparison with warfarin prophylaxis based on a commonly used threshold of $50,000 per quality-adjusted life year (QALY) gained, it should remain as EAP.

Limitations:

- The current LU codes are not aligned with patient indication; there are clinicians who may be inappropriately applying LU codes to obtain LMWH coverage for patients.
- The prophylactic use of LMWHs for patients undergoing non-orthopedic surgery, recommended in various guidelines, is not considered in this option.
- No change in EAP requests is anticipated with this option (over 3200 requests were evaluated by the EAP in fiscal 2014/15).

Option 1b: Status quo + additional EAP indications (prophylaxis non-orthopaedic surgery + primary prophylaxis in cancer patients)

Details:

- This option includes the addition of LMWHs available as EAP for prophylaxis of patients undergoing non-orthopaedic surgery and outpatients with patients with active malignancy receiving chemotherapy at high risk of thrombosis (primary prophylaxis).

Rationale:

- Since routine prophylaxis in all outpatients with cancer is not recommended nor was the cost-effectiveness of this indication evaluated, using EAP to access LMWHs, rather than an LU code, is suggested.
- No cost-effectiveness analysis was available for the indication of prophylaxis in patients undergoing non-orthopaedic surgery; therefore, a more restrictive option (i.e., EAP) is recommended.
- No change in utilization (and thus cost) is anticipated with this option, as non-orthopaedic surgical patients and cancer patients are likely accessing LMWHs through the LU (code 188).

Limitations:

- The current LU codes are not aligned with patient indication; there are clinicians who may be inappropriately applying LU codes to obtain LMWH coverage for patients. This practice may continue with this option as LMWHs are accessible via LU and EAP.
- There may be an increase in EAP requests with this option.

Option 1c: Status quo + additional LU indication (prophylaxis non-orthopaedic surgery) + additional EAP indication (primary prophylaxis in cancer patients)

Details:

- This option includes the addition of LMWHs as LU listing for prophylaxis of patients undergoing non-orthopaedic surgery.
- With this option, an additional EAP indication is suggested for the use of LMWH in outpatients with patients with active malignancy receiving chemotherapy at high risk of thrombosis (primary prophylaxis).

Rationale:

- Since routine prophylaxis in all outpatients with cancer is not recommended nor was the cost-effectiveness of this indication evaluated, using EAP to access LMWHs, rather than an LU code, is suggested.
- No change in utilization (and thus cost) is anticipated with this option, as non-orthopaedic surgical patients and cancer patients are likely accessing LMWHs through the LU (code 188). However, there is a potential for expanded use of LMWHs if clinicians feel more comfortable prescribing for broader indications.

Limitations:

- The current LU codes are not aligned with patient indication; there are clinicians who may be inappropriately applying LU codes to obtain LMWH coverage for patients. This practice may continue with this option as LMWHs are accessible via LU and EAP.
- There may be an increase in EAP requests with this option.

Option 2a: LU for LMWH and fondaparinux

Details:

- This option includes the addition of LMWHs for prophylaxis of patients undergoing non-orthopaedic surgery as well as for use of LMWH in outpatients with patients with active malignancy receiving chemotherapy at high risk of thrombosis.
- All indications currently available through EAP are moved to LU (i.e., perioperative bridging, post-operative prophylaxis of DVT in patients unable to use warfarin, secondary prophylaxis ("extended treatment") in patients with cancer).

Rationale:

- There is potential for an increase in utilization with this option, as some clinicians may feel more comfortable prescribing LMWH more broadly if there is an official listing. However, it is difficult to determine whether there will be an increase in utilization/costs, or how much of an increase would occur. Note that our data indicate that non-orthopaedic surgical patients and cancer patients are likely already accessing LMWHs through the LU (code 188).
- This option would eliminate the use of EAP for accessing LMWH (over 3200 requests were evaluated by the EAP in fiscal 2014/15), thereby reducing the workload for the OPDP.

Limitations:

- Secondary prophylaxis with LMWH in cancer patients (currently funded under EAP) was not cost-effective in comparison with warfarin prophylaxis based on a commonly used threshold of $50,000 per quality-adjusted life year (QALY) gained; the incremental cost effectiveness ratio (ICER) for LMWH versus warfarin is greater than $1 million per QALY gained. However, despite the lack of cost-effectiveness of this option, guidelines recommend LMWH over vitamin K antagonists for this indication, due to improved efficacy of LMWH over vitamin K antagonists.[12;13;28]
- The indication of "primary prophylaxis for cancer patients" is not a Health Canada-approved indication for any of the LMWHs. Generally, only Health Canada-approved indications are considered for LU listing; therefore, this indication would not be appropriate for a LU listing.

Option 2b: LU for LMWH and fondaparinux (streamlined codes)

Details:

- This option amalgamates the current LU codes and EAP criteria as well as the additional indication for prophylaxis in non-orthopaedic surgical patients into six streamlined LU Codes based on patient population (See Appendix C and D).
    a. Acute treatment of VTE in non-cancer patients
    b. Acute treatment and secondary prophylaxis for VTE in patients with cancer
    c. Treatment and prophylaxis of VTE in pregnant or lactating females
    d. Post-operative prophylaxis of VTE for patients undergoing surgery of lower limbs
    e. Post-operative prophylaxis of VTE for patients undergoing non-orthopaedic surgery and who are at high risk of thromboembolic complications
    f. Peri-operative bridging for patients who require long-term warfarin therapy

Rationale:

- Simplifying the LU codes and eliminating the EAP criteria may help clinicians choose the appropriate code and better understand details of approved indications.
- Similar to option 2a, there is potential for an increase in utilization with this option, as some clinicians may feel more comfortable prescribing LMWH more broadly if there is an official listing. However, it is difficult to determine whether there will be an increase in utilization/costs, or how much of an increase would occur. Note that our data indicate that non-orthopaedic surgical patients and cancer patients are likely already accessing LMWHs through the LU (code 188).
- This option would eliminate the use of EAP for accessing LMWH (over 3200 requests were evaluated by the EAP in fiscal 2014/15), thereby reducing the workload for the OPDP.

Limitations:

- Secondary prophylaxis with LMWH in cancer patients (currently funded under EAP) was not cost-effective in comparison with warfarin prophylaxis based on a commonly used threshold of $50,000 per quality-adjusted life year (QALY) gained; the incremental cost effectiveness ratio (ICER) for LMWH versus warfarin is greater than $1 million per QALY gained. However, despite the lack of cost-effectiveness of this option, guidelines recommend LMWH over vitamin K antagonists for this indication, due to improved efficacy of LMWH over vitamin K antagonists.[12;13;28]

Option 3: General Benefit for all LMWH and fondaparinux

Details:

- All LMWHs and fondaparinux are listed as General Benefit.

Rationale:

- By listing all LMWHs and fondaparinux as General Benefit, all indications (either official Health Canada or “off-label”) for these medications would be covered.

- This option would eliminate the use of EAP for accessing LMWH (over 3200 requests were evaluated by the EAP in fiscal 2014/15), thereby reducing the workload for the OPDP.
- The current LU codes are not aligned with patient indication; there are clinicians who may be inappropriately applying LU codes to obtain LMWH coverage for patients. Listing LMWHs as General Benefit would eliminate the use of LU codes.
- This option is aligned with other jurisdictions in Canada (i.e., Alberta, Quebec, Nova Scotia, New Brunswick, NIHB).

Limitations:

- Secondary prophylaxis with LMWH in cancer patients (currently funded under EAP) was not cost-effective in comparison with warfarin prophylaxis based on a commonly used threshold of $50,000 per quality-adjusted life year (QALY) gained; the incremental cost effectiveness ratio (ICER) for LMWH versus warfarin is greater than $1 million per QALY gained. However, despite the lack of cost-effectiveness of this option, guidelines recommend LMWH over vitamin K antagonists for this indication, due to improved efficacy of LMWH over vitamin K antagonists.[12;13;28]
- Either no change in utilization or a potential increase in utilization is anticipated with this option. In Nova Scotia, LMWHs are available as General Benefit; however, the rate of utilization in Nova Scotia is similar to Ontario, suggesting no change in utilization if a General Benefit listing is considered in Ontario. In contrast, in Alberta where LMWHs are also available as a General Benefit, the rate of utilization is almost twice that of Ontario; based on this data, a potential two-fold increase in utilization and cost (approximate increase of $34 million) would be expected.
- With this option, an increase in the use of these LMWHs for non-approved indications may occur (either by indication or duration).

<u>Option 4: Preferential listing for enoxaparin (as General Benefit), EAP for dalteparin for treatment of VTE in cancer patients, EAP for all other drugs</u>

Details:

- Enoxaparin listed as General Benefit for all indications
- Fondaparinux, tinzaparin, nadroparin, dalteparin available through EAP for patients unable to use enoxaparin (e.g., contraindication, allergy) or for specific indications (e.g., dalteparin for treatment of VTE in cancer patients)

Rationale:

- For most indications based on guideline recommendations, there is no preference to the use of one LMWH over another.
- Enoxaparin is less costly than dalteparin. Therefore, a decrease in costs of 32% ($10.7 million) may be realized for this drug class with this reimbursement option.
- In Ontario, enoxaparin is used by over 41% of all users of LMWH.
- This option would eliminate the use of EAP for accessing enoxaparin, thereby reducing the workload for the OPDP.
- Listing enoxaparin as General Benefit would eliminate the use of LU codes. The current LU codes are not aligned with patient indication; there are clinicians who may be inappropriately applying LU codes to obtain LMWH coverage for patients.

Limitations:

- Dalteparin is currently the most commonly used LMWH in Ontario, accounting for almost 50% of prescriptions. This option would result in a major change in practice (i.e., use of enoxaparin as preferred LMWH).
- The choice of LMWH in outpatient settings is often dictated by the LMWH that the patient was on during their hospital stay; most hospitals in Ontario only have one LMWH on their formulary. With this reimbursement option, potential medication errors may result since many patients would need to be switched to enoxaparin on discharge.
- Secondary prophylaxis with LMWH in cancer patients (currently funded under EAP) was not cost-effective in comparison with warfarin prophylaxis based on a commonly used threshold of $50,000 per quality-adjusted life year (QALY) gained; with this option, dalteparin for secondary prophylaxis is available through EAP.
- With this option, an increase in the use of enoxaparin for non-approved Health Canada indications may occur (either by indication or duration), as it would be available as General Benefit.

Stakeholder Review

Findings from the stakeholder review contributed to selection of final policy recommendations, and include feedback solicited from an open call for review, comments received during a workshop for stakeholders, as well as results from the ODPRN Citizen's Panel. See www.odprn.ca for summary of stakeholder's comments and responses from ODPRN.

Findings from the ODPRN Citizens' Panel

Citizens' Panel (CP) members considered each of the policy options on factors related to acceptability, accessibility and affordability, and ranked options from most to least preferable from a societal viewpoint. Overall, panel members had similar thoughts to interview participants; option 2b was chosen as the most acceptable option (Exhibit 9).

Exhibit 9: Overall pre-survey aspect rankings for policy options

	Mean Ranking (*SD*) (1 = Most Acceptable, 7 = Least Acceptable)
Option 1a (status quo)	5.8 (1.8)
Option 1b: addition of indications to EAP	5.2 (0.8)
Option 1c: addition of indications to both EAP and LU	4.4 (1.8)
Option 2a: LU for current LU/EAP criteria	3.6 (1.8)
Option 2b: streamlined LU codes	2.2 (0.8)
Option 3: General Benefit	3.6 (2.3)
Option 4: Preferential listing for enoxaparin	3.2 (2.7)

Final Policy Recommendations

Final recommendations for the LMWH drug class review are based on results of our entire review (pharmacist and prescriber perspectives, clinical recommendations, utilization data in Ontario and across Canada, cost-effectiveness analysis), input from stakeholders and feedback from the ODPRN Citizen's Panel. Considerations for the final recommendation include:

- Clinical recommendations:
  - LMWHs are recommended for use in a large number of different indications including acute treatment and prophylaxis. Most indications require initiation of

LMWH therapy immediately upon diagnosis; the diagnosis is often made in an acute care setting.

- Accessibility:
  - LMWHs are available as LU and EAP; however, many clinicians are unfamiliar with accessibility of LMWH through EAP and are only aware of LU listing.
  - LU codes were found to be used inappropriately; LU codes 186 and 188 were used most frequently regardless of the medical indication. The liberal interpretation of these specific LU codes highlights the need for more explicit wording.
  - The EAP process is considered by many physicians to be cumbersome. Despite the availability of the telephone request service, many specialists with a busy clinical practice often do not have time to call during office hours, which then may result in at least a one-day delay for approval. Additionally, for patients in a hospital setting who require the LMWH on discharge, the clinicians reported that the availability of the TRS only on weekdays may result in a delay in discharge of the patient over the weekend. Due to the urgency of LMWH initiation, delays in accessing EAP approval may result in deleterious outcomes for patients.
- Cost-effectiveness:
  - Secondary prophylaxis with LMWH in cancer patients (currently funded under EAP) was not found to be cost-effective in comparison with warfarin prophylaxis at current listing prices based on a commonly used threshold of $50,000 per quality-adjusted life year (QALY) gained; the ICER for LMWH versus warfarin was greater than $1 million per QALY gained.
  - Despite the lack of cost-effectiveness of this option, guidelines recommend LMWH over vitamin K antagonists for this indication, due to superior efficacy of LMWH compared to vitamin K antagonists.
  - Since cost-effectiveness of LMWHs for other indications was not determined in our review, it is unknown whether LMWHs would be cost-effective for these indications.
- Stakeholder perspective:
  - Overall, stakeholders were strongly in favour of streamlined LU codes. They also stated that this would allow for improved tracking of publically funded prescriptions versus general benefit listing.
  - For the extended treatment of cancer-associated thrombosis, clinicians and patient representatives noted that use of warfarin is often challenging due to the multiple drug interactions and intensive monitoring which is often inconvenient and burdensome for patients undergoing cancer treatment.
- Other considerations:
  - Approximately $33.6 million was spent on LMWHs by the OPDP in 2014. Coverage was provided to over 24,580 users in the community setting.
  - Over 3,200 requests for LMWH were evaluated by the OPDP in fiscal 2014/15; moving current EAP indications to LU would eliminate the use of EAP for accessing LMWHs.

It is recommended that LMWHs and fondaparinux be listed as LU for most indications using revised streamlined LU codes; access of LMWHs through EAP would only be required for uncommon situations (e.g., pregnant patient with a history of heparin-induced thrombocytopenia who requires anticoagulation with fondaparinux).

Limited Use for LMWH and fondaparinux

- Acute treatment of VTE in non-cancer patients
- Acute treatment and secondary prophylaxis for VTE in patients with cancer
- Treatment and prophylaxis of VTE in pregnant or lactating females
- Post-operative prophylaxis of VTE for patients undergoing surgery of lower limbs
- Post-operative prophylaxis of VTE for patients undergoing non-orthopaedic surgery and who are at high risk of thromboembolic complications
- Peri-operative bridging for patients who require long-term warfarin therapy

Other considerations:

1. *LMWH use in pediatrics:* In our review of LMWHs, we focused our review on the adult population and did not review the use in pediatrics. However, the pediatric population is unique, and additional review of LMWHs in pediatrics is warranted.
2. *Price negotiations for LMWHs:* In our cost-effectiveness model for extended treatment of VTE in patients with cancer, LMWH was not shown to be cost-effective at currently listed prices. However, with a reduction in price of approximately 91%, LMWHs would become a cost-effective option.
3. *EAP for fondaparinux for patients with cancer-associated thrombosis and heparin-induced thrombocytopenia (HIT) or in pregnant females with history of HIT:* Although fondaparinux has not been studied in patients with cancer-associated thrombosis, guidelines suggest that fondaparinux is an option for patients with a history of HIT in this population. Additionally, fondaparinux has been used during pregnancy in patients with history of HIT. Therefore, EAP for fondaparinux should be considered in patients with cancer-associated thrombosis with a history of HIT and pregnant patients with a history of HIT. Note that the availability on the ODB formulary of fondaparinux for other indications (e.g., acute treatment, post-operative prophylaxis) is via LU.

Reference List

(1) Hirsh J, Raschke R. Heparin and low-molecular-weight heparin. *Chest* 2004; 126:188s-203s.

(2) Merli G, Groce J. Pharmacological and clinical differences between low-molecular-weight heparins: implications for prescribing practice and therapeutic interchange. *P&T* 2010; 35:95-105.

(3) Aguilar OM, Kleiman NS. Low molecular weight heparins. *Expert Opin Pharmacother* 2000; 1(6):1091-1103.

(4) Weitz J. Low-molecular-weight heparins. *N Engl J Med* 1997; 337:688-698.

(5) Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl):e24S-e43S.

(6) Thaler J, Pabinger I, Ay C. Anticoagulant treatment of deep vein thrombosis and pulmonary embolism: the present state of the art. *Fron Cardiovas Med* 2015; 2:1-7.

(7) Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl):e278S-e325S.

(8) Nicolaides AN, Fareed J, Kakkar AK, Comerota AJ, Goldhaber SZ, Hull R et al. Prevention and treatment of venous thromboembolism--International Consensus Statement. *Int Angiol* 2013; 32(2):111-260.

(9) American Academy of Orthopaedic Surgeons (AAOS). American Academy of Orthopaedic Surgeons clinical practice guideline on preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. http://www.aaos.org/research/guidelines/VTE/VTE_summary_of_recs.pdf . 2011.

(10) Farge D, Debourdeau P, Beckers M, Baglin C, Bauersachs RM, Brenner B et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *J Thromb Haemost* 2013; 11(1):56-70.

(11) Siragusa S, Armani U, Carpenedo M, Falanga A, Fulfaro F, Imberti D et al. Prevention of venous thromboembolism in patients with cancer: guidelines of the Italian Society for Haemostasis and Thrombosis (SISET)(1). *Thromb Res* 2012; 129(5):e171-e176.

(12) Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014. *J Clin Oncol* 2015; 33(6):654-656.

(13) Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013; 31(17):2189-2204.

(14) Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl):e227S-e277S.

(15) Mandala M, Falanga A, Roila F. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2011; 22 Suppl 6:vi85-vi92.

(16) Watson HG, Keeling DM, Laffan M, Tait RC, Makris M. Guideline on aspects of cancer-related venous thrombosis. *Br J Haematol* 2015; 170(5):640-648.

(17) Easaw JC, Shea-Budgell MA, Wu CM, Czaykowski PM, Kassis J, Kuehl B et al. Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: treatment. *Curr Oncol* 2015; 22(2):144-155.

(18) Easaw JC, Shea-Budgell MA, Wu CM, Czaykowski PM, Kassis J, Kuehl B et al. Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 1: prophylaxis. *Curr Oncol* 2015; 22(2):133-143.

(19) Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl):e195S-e226S.

(20) Debourdeau P, Farge D, Beckers M, Baglin C, Bauersachs RM, Brenner B et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. *J Thromb Haemost* 2013; 11(1):71-80.

(21) Tait C, Baglin T, Watson H, Laffan M, Makris M, Perry D et al. Guidelines on the investigation and management of venous thrombosis at unusual sites. *Br J Haematol* 2012; 159(1):28-38.

(22) Carrier M, Lazo-Langner A, Shivakumar S, Tagalakis V, Gross PL, Blais N et al. Clinical challenges in patients with cancer-associated thrombosis: Canadian expert consensus recommendations. *Curr Oncol* 2015; 22(1):49-59.

(23) Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl):e326S-e350S.

(24) Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C et al. Guidelines on oral anticoagulation with warfarin - fourth edition. *Br J Haematol* 2011; 154(3):311-324.

(25) Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl):e152S-e184S.

(26) Greenberg G, Venous Thromboembolism Guideline Team. Venous thromboembolism. http://www.med.umich.edu/1info/FHP/practiceguides/vte/vte/pdf . 2016.

(27) Streiff MB, Bockenstedt PL, Cataland SR, Chesney C, Eby C, Fanikos J et al. Venous thromboembolic disease. *J Natl Compr Canc Netw* 2011; 9(7):714-777.

(28) Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl):e419S-e494S.

(29) Liu D, Peterson E, Dooner J, Baerlocher M, Zypchen L, Gagnon J et al. Diagnosis and management of iliofemoral deep vein thrombosis: clinical practice guideline. *CMAJ* 2015; 187(17):1288-1296.

(30) Nguyen G, Bernstein C, Bitton A, et al. Concsensus statements on the risk, prevention and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. *Gastroenterology* 2014; 146:835-848.

(31) Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl):e691S-e736S.

(32) Chan WS, Rey E, Kent NE, Chan WS, Kent NE, Rey E et al. Venous thromboembolism and antithrombotic therapy in pregnancy. *J Obstet Gynaecol Can* 2014; 36(6):527-553.

(33) James A. Practice bulletin no. 123: thromboembolism in pregnancy. *Obstet Gynecol* 2011; 118(3):718-729.

(34) Blackmer A, Oertel M, Valgus J. Fondaparinux and the management of heparin-induced thrombocytopenia: the journey continues. *Ann Pharmacotherapy* 2009; 43:1636-1646.

(35) Institute for Safe Medication Practices (ISMP). ISMP list of high-alert medications in acute care settings. https://www.ismp.org/tools/highalertmedications.pdf . 2014.

(36) Aujesky D, Smith KJ, Cornuz J, Roberts MS. Cost-effectiveness of low-molecular-weight heparin for secondary prophylaxis of cancer-related venous thromboembolism. *Thrombosis and Haemostasis* 2005; 93(3):592-599.

(37) Dranitsaris G, Vincent M, Crowther M. Dalteparin versus warfarin for the prevention of recurrent venous thromboembolic events in cancer patients: A pharmacoeconomic analysis. *PharmacoEconomics* 2006; 24(6):593-607.

(38) Avritscher EBC, Cantor SB, Shih Y-C, Escalante CP, Rivera E, Elting LS. Cost-minimization analysis of low-molecular-weight heparin (dalteparin) compared to unfractionated heparin for inpatient treatment of cancer patients with deep venous thrombosis. *Supportive Care in Cancer* 2004; 12(7):531-536.

(39) Lee AY, Levine MN FAU - Baker R, Baker RI FAU - Bowden C, Bowden CF, Kakkar AK FAU - Prins M, Prins MF et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *New England Journal of Medicine* 2003; 349(2):146-153.

(40) Akl EA, Kahale L, Barba M, Neumann I, Labedi N, Terrenato I et al. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. *Cochrane Database Syst Rev* 2014; 7(CD006650).

(41) Canadian Institute for Health Information (CIHI). Patient Cost Estimator. https://www cihi ca/en/spending-and-health-workforce/spending/patient-cost-estimator [2016 [cited 2016 Jan. 12]; Available from: URL:https://www.cihi.ca/en/spending-and-health-workforce/spending/patient-cost-estimator

(42) Schedule of benefits for physician services under the Health Insurance Act. 2015. Ontario Ministry of Health and Long-Term Care. 1-12-2016.

(43) Boucher M, Rodger M, Johnson JA, Tierney M. Shifting from inpatient to outpatient treatment of deep vein thrombosis in a tertiary care center: a cost-minimization analysis. *Pharmacotherapy* 2003; 23(3):301-309.

(44) Goeree R, Blackhouse G, Petrovic R, Salama S. Cost of stroke in Canada: a 1-year prospective study. *Journal of Medical Economics* 2005; 8(1-4):147-167.

(45) Ontario Drug Benefit Formulary/Comparative Drug Index: Edition 42. 2015. Ontario Ministry of Health and Long-Term Care. 1-11-2016.

(46) Welcome Home Care. How much does homecare cost in Ontario? http://www welcomehomecare ca/cost-of-home-care/ [2016 [cited 2016 Jan. 13]; Available from: URL:http://www.welcomehomecare.ca/cost-of-home-care/

(47) Ontario Ministry of Health and Long Term Care. Ontario Health Insurance (OHIP) Schedule of Benefits and Fees. Schedule of Benefits for Laboratory Services. http://www health gov on ca/english/providers/program/ohip/sob/lab/lab_mn html [2015 [cited 2015 Dec. 15]; Available from: URL:http://www.health.gov.on.ca/english/providers/program/ohip/sob/lab/lab_mn.html

(48) Medical Advisory Secreteriat. Point-of-Care International Normalized Ratio (INR) Monitoring Devices for Patients on Long-term Oral Anticoagulation Therapy: An Evidence-Based Analysis. 9(12). 2009. Ontario Health Technology Assessment Series.

(49) Gold M, Franks P, Erickson P. Assessing the Health of the Nation: The Predictive Validity of a Preference-Based Measure and Self-Rated Health. *Medical Care* 1996; 34(2):163-177.

(50) Locadia M, Bossuyt PM, Stalmeier PF, Sprangers MA, van Dongen CJ, Middeldorp S et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. *Thromb Haemost* 2004; 92(6):1336-1341.

(51) Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. *J Am Med Inform Assoc* 1997; 4(1):49-56.

Appendix A: Health Equity Considerations for Low Molecular Weight Heparins and Fondaparinux

Identify populations that may experience significant unintended health impacts (positive or negative) as a result of the planned policy, program or initiative.	Proposed LMWH recommendations
Aboriginal peoples (e.g., First Nations, Inuit, Métis, etc.)	No accessibility issues identified. Coverage of medications, including LMWHs, for Aboriginal peoples is available through Ontario Ministry of Health and Long-term Care.
Age-related groups (e.g., children, youth, seniors, etc.)	Elderly: No restrictions for LMWHs were identified.
Disability (e.g., physical, D/deaf, deafened or hard of hearing, visual, intellectual/developmental, learning, mental illness, addictions/substance use, etc.)	No accessibility issues identified. Patients with disability and receiving Ontario Disability Support Program Income Support, receive prescription drug coverage through ODB.
Ethno-racial communities (e.g., racial/racialized or cultural minorities, immigrants and refugees, etc.)	No accessibility issues identified.
Francophone (including new immigrant francophones, deaf communities using LSQ/LSF, etc.)	No accessibility issued identified.
Homeless (including marginally or under-housed, etc.)	Not eligible for ODB coverage.
Linguistic communities (e.g., uncomfortable using English or French, literacy affects communication, etc.).	No accessibility issues identified.
Low income (e.g., unemployed, underemployed, etc.)	No accessibility issues identified; low income individuals who receive public drug coverage will have access to LMWHs through ODB.
Religious/faith communities	No accessibility issues identified.
Rural/remote or inner-urban populations (e.g., geographic or social isolation, under-serviced areas, etc.)	No accessibility issues identified.
Sex/gender (e.g., male, female, women, men, trans, transsexual, transgendered, two-spirited, etc.)	No accessibility issues identified for sex/gender in the review.
Sexual orientation, (e.g., lesbian, gay, bisexual, etc.)	No accessibility issues identified.
Other: please describe the population here.	None identified.

(based on Health Equity Impact Assessment http://www.health.gov.on.ca/en/pro/programs/heia

Appendix B: Description of Options (including indications and drugs reimbursed/covered)

	Option 1a	Option 1b	Option 1c	Option 2a	Option 2b	Option 3	Option 4
Tx of DVT (non-cancer patients)	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡🟡	🟢🟢🟢🟢🟢	🔴🟢🔴🔴○
Use in pregnant/ lactating females	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡🔴	🟢🟢🟢🟢🟢	🔴🟢🔴🔴○
Tx of DVT in patients who failed tx with warfarin	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡🟡	🟢🟢🟢🟢🟢	🔴🟢🔴🔴○
Tx of pulmonary embolism	○🟡○🟡○	○🟡○🟡○	○🟡○🟡○	○🟡○🟡○	🟡🟡🟡🟡🟡	🟢🟢🟢🟢🟢	○🟢○🔴○
Tx of DVT in patients in whom treatment with warfarin is not tolerated or is contraindicated	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡○	🟡🟡🟡🟡🟡	🟢🟢🟢🟢🟢	🔴🟢🔴🔴○
Extended tx of VTE in patients with cancer	🔴○○○○	🔴○○○○	🔴○○○○	🟡○○○○	🟡🟡○🟡🔴	🟢🟢🟢🟢🟢	🔴🟢○○○
Post-operative prophylaxis of VTE for lower limb surgery (and cannot use warfarin*)	🔴🔴○🔴🟡	🔴🔴○🔴🟡	🔴🔴○🔴🟡	🟡🟡○🟡🟡	🟡🟡🟡🟡🟡	🟢🟢🟢🟢🟢	🔴🟢○🔴🔴
Prevention of VTE in non-orthopedic surgical patients	○○○○○	🔴🔴🔴🔴🔴	🟡🟡🟡🟡🟡	🟡🟡🟡🟡🟡	🟡🟡🟡🟡🟡	🟢🟢🟢🟢🟢	🔴🟢🔴🔴🔴
Peri-operative bridging in patients who require long-term warfarin	🔴🔴○🔴○	🔴🔴○🔴○	🔴🔴○🔴○	🟡🟡○🟡○	🟡🟡🟡🟡🟡	🟢🟢🟢🟢🟢	🔴🟢🔴🔴○
Prevention of VTE in cancer patients with additional risk factors for VTE	○○○○○	🔴🔴🔴🔴○	🔴🔴🔴🔴○	🟡🟡🟡🟡○	○○○○○	🟢🟢🟢🟢🟢	🔴🟢🔴🔴○

The 5 contiguous circles correspond, respectively, to the five drugs considered: dalteparin, enoxaparin, nadroparin, tinzaparin, fondaparinux

*The current EAP listing for dalteparin, enoxaparin, tinzaparin indicates that these drugs can be used if patient is not able to use warfarin

○=not listed, 🔴=available through EAP, 🟡=listed as LU, 🟢=listed as General Benefit

Appendix C: Proposed LU Criteria for Low-molecular-weight heparins (LMWHs) and Fondaparinux

LU criteria	Drugs covered	LU authorization period (maximum)	Additional notes
Acute treatment of venous thromboembolism (VTE) in non-cancer patients	Dalteparin Enoxaparin Nadroparin Tinzaparin Fondaparinux	21 days	Fondaparinux (but not the LMWHs) is an option for patients with a history of heparin-induced thrombocytopenia.
Acute treatment and secondary prophylaxis (extended treatment) for venous thromboembolism in patients with cancer	Dalteparin Enoxaparin Tinzaparin	6 months	Prophylactic anticoagulant therapy (“primary prophylaxis”) is not recommended for all outpatients with active malignancy.
Treatment and prophylaxis of VTE in pregnant or lactating females	Dalteparin Enoxaparin Nadroparin Tinzaparin	1 year	
Post-operative prophylaxis of VTE for patients undergoing surgery of lower limbs (i.e., total knee arthroplasty, total hip arthroplasty, hip fracture surgery)	Dalteparin Enoxaparin Nadroparin Tinzaparin Fondaparinux	30 days	Fondaparinux (but not the LMWHs) is an option for patients with a history of heparin-induced thrombocytopenia.
Post-operative prophylaxis of VTE for patients undergoing non-orthopaedic surgery and who are at high risk of thromboembolic complications (e.g., abdominal-pelvic surgery in cancer patients)	Dalteparin Enoxaparin Nadroparin Tinzaparin Fondaparinux	30 days	Fondaparinux (but not the LMWHs) is an option for patients with a history of heparin-induced thrombocytopenia.
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	Dalteparin Enoxaparin Nadroparin Tinzaparin Fondaparinux	Up to 5 days before surgery plus up to 7 days after surgery	Fondaparinux (but not the LMWHs) is an option for patients with a history of heparin-induced thrombocytopenia.

Appendix D: Comparison of Current and Proposed LU Criteria

Current coverage			Proposed coverage			Comments on changes
LU or EAP criteria	**Drugs covered**	**Duration**	**LU criteria**	**Drugs covered**	**Duration**	
For acute treatment of deep venous thrombosis (DVT) **LU code 186**	Dalteparin Enoxaparin Nadroparin Tinzaparin	3 weeks	Acute treatment of venous thromboembolism (VTE) in non-cancer patients	Dalteparin Enoxaparin Nadroparin Tinzaparin Fondaparinux	21 days	1. Included fondaparinux (option in patients with HIT) 2. Amalgamated DVT and PE together under VTE 3. All LMWH included although only official indications for enoxaparin, tinzaparin and fondaparinux for PE 4. No change in duration
For the acute treatment of pulmonary embolism, maximum of three weeks **LU code 323**	Enoxaparin Tinzaparin	3 weeks				
For extended treatment of symptomatic acute venous thromboembolism (VTE) in patients with cancer, who cannot use warfarin **EAP**	Dalteparin	6 months	Treatment and secondary prophylaxis (extended treatment) for venous thromboembolism in patients with cancer	Dalteparin Enoxaparin Tinzaparin	6 months	1. Studies have been conducted with tinzaparin and enoxaparin for this indication. No studies for nadroparin or fondaparinux; therefore, not listed as LU. 2. Prophylactic anticoagulant therapy (“primary prophylaxis”) is not recommended for all outpatients with active malignancy. Patients receiving chemotherapy at high risk of thrombosis can be considered for prophylactic anticoagulant therapy.

Current coverage			Proposed coverage			Comments on changes
LU or EAP criteria	**Drugs covered**	**Duration**	**LU criteria**	**Drugs covered**	**Duration**	
For DVT in pregnant or lactating females **LU Code 187**	Dalteparin Enoxaparin Nadroparin Tinzaparin	1 year	Treatment and prophylaxis in pregnant or lactating females	Dalteparin Enoxaparin Nadroparin Tinzaparin	1 year	1. Explicitly included treatment and prophylaxis in criteria
For post-operative prophylaxis of DVT for patients who had hip or knee surgery, and cannot use warfarin; **EAP**	Dalteparin Enoxaparin Tinzaparin	30 days	Post-operative prophylaxis of VTE for patients undergoing surgery of lower limbs (i.e., total knee arthroplasty, total hip arthroplasty, hip fracture surgery)	Dalteparin Enoxaparin Nadroparin Tinzaparin Fondaparinux	30 days	1. Included all LMWHs and fondaparinux (all Health Canada approved) 2. To simplify, have used maximum supply of 30 days for all drugs 3. Included hip fracture surgery as indication (previously only included for 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 **LU Code 378**	Fondaparinux	9 days				
			Post-operative prophylaxis of VTE for patients undergoing non-orthopaedic surgery who are at high risk of thromboembolic	Dalteparin Enoxaparin Nadroparin Tinzaparin Fondaparinux	30 days	1. Based on risk for development of VTE, prophylaxis is recommended for various non-orthopaedic surgical procedures such as abdominal-pelvic surgery. 2. All LMWH and fondaparinux

Current coverage			Proposed coverage			Comments on changes
LU or EAP criteria	**Drugs covered**	**Duration**	**LU criteria**	**Drugs covered**	**Duration**	
			complications (e.g., abdominal-pelvic surgery in patients with cancer)			included (official Health Canada indication for all)
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 **EAP**	Dalteparin Enoxaparin Tinzaparin	10 days prior to surgery + up to 7 days after surgery	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	Dalteparin Enoxaparin Nadroparin Tinzaparin Fondaparinux	Up to 5 days before surgery plus up to 7 days after surgery	1. Added nadroparin as guidelines do not recommend any specific LMWH 2. Decreased number of days (from 10 to 5) prior to surgery. It is recommended that patients discontinue warfarin 5 days prior to surgery, and start LMWH 3 days prior to surgery. However, 5 days coverage for LMWH is suggested to account for potential surgery delays.
For DVT in patients whom treatment with warfarin is not tolerated, or contraindicated **LU Code 188**	Dalteparin Enoxaparin Nadroparin Tinzaparin	1 year				1. With the proposed coverage of LMWHs for additional indications as well as coverage of indications currently available through EAP (e.g., treatment in cancer patients), these codes are no longer needed.