

Low-Molecular-Weight Heparin

Stakeholder Review

April 2016

***Note:** The comments from the stakeholders have been collated whenever possible. Each black bullet point represents one stakeholder

Consolidated Report

Comment (Option 4):

- For Option 4 (preferential listing for enoxaparin), this is clearly driven by cost considerations rather than appropriate patient care and may involve significant unrecognized risks.
 - a. LMWHs are not considered interchangeable by Health Canada.
 - b. There are pharmacokinetic/pharmacologic differences among the LMWHs. For example, enoxaparin is almost solely eliminated by the kidneys, compared to tinzaparin and dalteparin which are also eliminated by hepatic function.
 - c. Enoxaparin has not shown benefit for extended treatment of VTE in cancer patients.
 - d. Other limitations include supply shortages with use of a single supplier, potential price increase of enoxaparin (due to monopoly market).
- I was particularly concerned about one of the options listed in the summary (Option 4) where all of the other LMWHs could be eliminated with only enoxaparin as the primary treatment option. In my opinion, this would be a bad idea, particularly for cancer patients. Enoxaparin is the smallest and least negatively charged of the LMWHs and is the most renally dependent. This is especially important in the cancer population because many of our drugs cause renal dysfunction either directly (e.g. cisplatin) or indirectly (e.g. dehydration causing prerenal renal failure). In this situation, enoxaparin will be poorly excreted from the body and the patient will be at increased risk for bleeding. The physician must therefore be highly vigilant for bleeding complications in this setting. Drugs such as dalteparin and especially tinzaparin are larger and more negatively charged molecules rendering them safer in renal dysfunction as they can be cleared by the reticuloendothelial system and to a much lesser extent, the kidney. Therefore, I strongly advocate that all 3 LMWHs be made accessible for physicians, particularly as it pertains to VTE patients with cancer.
- I favour option #3 or less optimally #2b, and oppose option #4. I am certain the committee is aware that LMWHs are not medications that are at risk of being abused. Prescribers of LMWH are trying to provide the best possible option (e.g., treatment of VTE in patients with cancer) or convenience (e.g., bridging anticoagulation in high risk patients with valves) and having LU codes and requiring EAP adds complexity to care. Option #4 is not ideal as it is critical to have different LMWH options available, and not limited to enoxaparin only. This is important for certain patient populations, or certain patient weights where the enoxaparin prefilled syringe would not be the optimal choice.
- Option 4 seems to me like a terrible solution. It would be reasonable to simplify

the regulated prescription of LMWH by first of all eliminating the EAP process and streamlining the LU-codes (Option 2b) or even better to move to General Benefit for all LMWH (Option 3).

- **First, I would be very strongly AGAINST Option 4. This option would cause chaos among the hundreds of patients in our service who are receiving LMWH for treatment of cancer-associated VTE. The majority of our outpatients are receiving dalteparin as per the CLOT Trial and to switch them all to enoxaparin would not only cause confusion with the patients, but also greatly disrupt the transition from hospital to community and the reverse. Not all hospitals carry enoxaparin on their formulary. I fear that this would mean cancer patients would be treated with warfarin in those settings instead. Warfarin is HIGHLY problematic in cancer patients due to thrombocytopenia secondary to chemotherapy, frequent need for invasive procedures, multiple drug interactions, poor venous access and poor oral intake - all of which have a tremendous impact on the quality of INR control and therefore the risk of bleeding complications.**
- **Because many patients are initiated on LMWH in a hospital setting, restricting choice to a single LMWH could lead to potential medication errors or unwanted safety concerns as switching upon admission and discharge may occur. Any consideration of limiting access to any LMWHs would set a precedent with far-reaching negative implications for hospitals and patients beyond Ontario. Therefore, available and choice of LMWH in the community is essential.**
- **With respect to the options option 2b is the preferable from my perspective. I would be supportive of increased oversight of the LU codes - as they are open to abuse – but to make access EAP will result in patients spending time in hospital awaiting approval who are now sent home without a hospital stay using LU codes. Option 3 is ideal, but would result in more abuse. Option 4 is unacceptable; of the three “true” LMWHs it is the least preferable for a general listing given its (a) bioaccumulation with renal insufficiency, and (b) limited data in cancer associated thrombosis, dialysis and in other renal insufficiency patients, and (c) lack of data to support prophylactic use in high risk patients.**
- **Option 4 is not a viable option for the following reasons:**
 - **LMWHs are biological products, sourced from pig intestines and then processed. Some of the sources are from China. This has led to intermittent shortages of one LMWH, but not another.**
 - **LMWHs are not considered bioequivalent by Health Canada, the FDA or the EMA. Guidelines consider them as a group, because there are no head-to-head trials, not because they are equivalent. Thus Health Canada has unique labelling for each LMWH, including recently adding that tinzaparin does not accumulate at creatinine clearances down to 20 mL/min. This affords renal safety not present with other LMWHs.**
 - **The prices of the LMWH in the report are at one static point in time. Overtime competition has steadily lowered the cost of LMWHs. Allowing the market forces of competition to be, is good for Ontario tax payers. Option 4 would scuttle this competition in a second.**
 - **The market effect of the DOACs is not appreciated in the report. Many indications for LMWH have been replaced by DOACs already (e.g., orthopedic prophylaxis). Ongoing studies are being performed with**

DOACs for prophylaxis in cancer-associated thrombosis.

- The LMWHs, though considered as a single drug class, have differences in pharmacokinetic properties, dosing regimens and clinical trial experience. These differences enable health care providers to select an agent that is best suited to an individual patient's needs, thereby allowing a personalized approach to the prevention and treatment of VTE.
- You must also consider unintended consequences of limiting LMWH drug choice. Many clinicians choose a LMWH brand that provides the closest ideal dose in a pre-filled syringe to avoid having patients draw up drug from multi-dose vials or "squirt out" drug from a graduated syringes. These maneuvers add complexity and burden to a very vulnerable patient population (and introduce risks of medication errors).
- It is our understanding that the medication with open access (as described in Option 4), enoxaparin, is not indicated for cancer patients. We are concerned that a recommendation is being recommended that places limitations on access to cancer patients. A recommendation that provides any hurdle to accessing the appropriate and medically indicated treatment is counterproductive to supporting patient access to badly needed medications. Therefore, we recommend deletion of Option 4 from further consideration and recommend a Limited Use code for all medications indicated in cancer.

Response: *Thank you for all of your comments. Based on many different factors including pharmacokinetic/pharmacologic differences among LMWHs, increased risk for medication errors with potential change in therapy from an acute to outpatient setting and lack of clinical indications for some agents, Option 4 (preferential listing) is not being considered as the final recommendation. 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.*

Comment (Option 3):

- I would be strongly IN FAVOUR of Option 3. LMWHs are not drugs that are at high risk for inappropriate use or abuse. Patients do not enjoy injecting themselves with needles. There isn't a clinic that goes by where I am not asked multiple times by my cancer-associated VTE patients if a switch to an oral agent is possible. When I do, occasionally, relent to this request, the end result is all most always a return to LMWH after erratic INRs make their already complicated lives significantly more difficult. By switching to "general benefit" as outlined in the report, access to LMWH, when deemed appropriate by physicians, will be facilitated and administrative paperwork/work load will be reduced.

Response: *Although Option 3 would allow for the greatest accessibility to LMWHs, there is some concern that the use would expand to other unapproved indications such as primary prophylaxis in cancer patients. As well, Option 3 does not allow for tracking of LMWH use in*

specific populations.

Comment (Option 2a):

- **Contrary to option 2a, options 2b and 3 are less driven by clinical evidence as they assume that all LMWHs produce similar efficacy and safety in various indications.**
 - **For the indication for “the extended treatment of VTE in cancer patients”, only dalteparin has an official indication from Health Canada.**
 - **For the “prevention of VTE in non-orthopedic surgical patients”, enoxaparin and dalteparin have the strongest clinical evidence and are approved for this indication.**

Response: *Our final recommendation is that LMWHs be listed as Limited Use for specific indications (Option 2b). Option 2a would result in at minimum ten Limited Use codes and would likely lead to confusion for clinicians. Note: Three LMWHs, namely tinzaparin, dalteparin and enoxaparin, have been studied for the extended treatment for patients with cancer. Although dalteparin is the only LMWH that has an official indication from Health Canada, the use of tinzaparin in cancer patients is included in the product monograph. For the prevention of VTE in non-orthopaedic surgical patients, all LMWHs are approved for use in “general surgery” patients.*

Comment (Option 2b):

- **I would strongly recommend Option 2b as the option that will provide the greatest benefit in terms of LMWH choices for patients and their healthcare providers. Having choices in anticoagulant management is important because the LMWHs have different dosing regimens, pharmacokinetic properties and clinical evidence, which allows for a patient-centred approach to anticoagulant management.**
- **Please consider ODB coverage of all three LMWHs. This will continue to foster competition in the marketplace including competitive pricing, innovation, service including patient support programs and educational initiatives for both healthcare professionals and patients. ODB coverage of LMWHs should ensure all patients have access to all available LMWHs.**
- **In reviewing the reimbursement options that are being considered for implementation, we favour Option 2B, which would allow a simplified use of limited use codes and would retain LMWH choices for health care providers and their patients. Based on the evidence in the field of anticoagulant management for venous thromboembolism (VTE), coupled with our collective clinical expertise in this area, we support Option 2B as we believe this will best serve patient care.**

Response: *Our final recommendation is that LMWHs be listed as Limited Use (Option 2b) with streamlined codes. This would not only provide choice in anticoagulant management but also simplify LU codes and eliminate EAP.*

Comment (Bridging):

- **Consider not including bridging: very few indications for bridging. If however, bridging is included, consider changing the maximum time for coverage to 5 days before surgery.**

Response: *Despite the publication of a recent trial that showed that forgoing bridging was noninferior to bridging in patients with atrial fibrillation, several guidelines still provide recommendations regarding peri-operative bridging in patients who require long-term warfarin therapy. Therefore, until guidelines are changed to reflect the new evidence, it is suggested that bridging be continued to be covered as an indication for LMWH. (Douketis et al. N Engl J Med 2015;373:823-33)*

Comment (Primary Prophylaxis in Cancer):

- **Due to lack of evidence, use of LMWH as primary prophylaxis in cancer patients should not be covered.**
- **Prophylaxis against thrombosis in cancer patients using LMWH is not rigorously proven. There is not one study with positive outcome. This is an ongoing area of research, largely with DOACs, which are far cheaper. In a cost-limiting environment covering LMWH for this indication seems premature.**

Response: *Based on the guidelines that were reviewed by the systematic review team, cancer patients with no additional risk factors for VTE should not receive routine thromboprophylaxis for VTE. We have not included this indication as part of the Limited Use criteria for LMWHs.*

Comment (EAP Process):

- **Personally, I find the EAP process cumbersome and inefficient. We see a high volume of cancer-associated VTE patients every day in our clinic and the time and effort involved in accessing EAP only serves to slow us down.**
- **EAPs are not convenient for busy thrombosis clinics where, for example, I personally see 40 patients in a day and may write 5-10 such scripts per day.**

Response: *Thank you for your comments. We understand from our qualitative review that the current EAP process (including the telephone request service) may be onerous for*

some clinicians to access. Our final recommendation suggests LU listing (but not EAP) for LMWHs.

Comment (Potential for Medication Errors):

- **Because many patients are initiated on LMWH in a hospital setting, restricting choice to a single LMWH could lead to potential medication errors or unwanted safety concerns as switching upon admission and discharge may occur. Any consideration of limiting access to any LMWHs would set a precedent with far-reaching negative implications for hospitals and patients beyond Ontario. Therefore, available and choice of LMWH in the community is essential.**

Response: *As noted in our report, there is a potential for an increase in medication errors occurring with Option 4 as not all hospitals in the province have enoxaparin as their formulary LMWH.*

Comment (Pediatric Use of LMWH):

- **From the pediatric perspective, LMWHs are often used for a longer time period than in the adult population. As well, there are numerous challenges using warfarin in this population including lack of appropriate formulations and fluctuation of INR.**

Response: *In our review of LMWHs, we focused our review on the adult population and did not review the use in pediatrics. However, we understand that the pediatric population is unique, and additional review of LMWHs in pediatrics is warranted.*

Comment (Fondaparinux):

- **Fondaparinux is not an issue, in my opinion, since its use is very limited and has actually decreased over the years (as seen in Exhibit 6). It is used for patients with heparin-induced thrombocytopenia increasingly and is vastly less expensive than danaparoid or argatroban. For patients with acute coronary syndromes it is only used in the hospital. For patients with hip replacement (for fractures or elective arthroplasty) it is sometimes used but gradually replaced by NOACs – mainly rivaroxaban.**
- **There should be a note associated with fondaparinux stating that it can be used in patients with heparin-induced thrombocytopenia.**

Response: *It is recommended that a note be added to the Limited Use criteria that list fondaparinux that indicates that fondaparinux can be used in patients with a history of heparin-induced thrombocytopenia. “Fondaparinux (but not the LMWHs) is an option for patients with a history of heparin-induced thrombocytopenia.”*

Comment (Disadvantages of Warfarin Use):

- I found the report areas that promulgated the use of warfarin over alternates (particularly in cancer with respect to LMWH) most difficult to understand. Warfarin is a terrible drug to use; its unpredictable PK and PD make its use very problematic outside expert centres (as demonstrated in numerous studies of community based, non-expert care), the need for monitoring is inconvenient and leads to worsened care, and its specific toxic effects, particularly intracerebral hemorrhage (a toxic effect of specific impact only with warfarin compared with other anticoagulants) makes it hard for me to believe that “experts’ could ever recommend the giant leap backwards of using in indications currently dominated by more modern, easier to use and less toxic interventions such as LMWH or DOACs (in the appropriate clinical situation). Although it may be seen to be costly (particularly in the context of cancer associated DVT) it is remarkable that it would even be considered to “cause” a toxic effect (increased risk of recurrent thrombosis) in the cancer VTE population. To force clinicians to regress to the era of warfarin for VTE in cancer patients is to knowingly force patients to suffer an otherwise frequent (15% of cases) and largely avoidable complication.
- The burden of warfarin treatment in cancer patients cannot be understated. The era when the pivotal trials comparing warfarin and LMWH were conducted, is long gone. Cancer patients are being treated more aggressively and as outpatients. The adoption of a more restrictive policy on LMWH for CAT would be a harmful step backwards.
- You must consider the burden of warfarin testing in cancer patients who often are too ill to go to labs for testing, have limited venous access for testing and require frequent testing (highly variable INRs due to variable diet with chemo, many interacting drugs etc).

Response: *In our rationale for our final recommendation for streamlined Limited Use codes, we note 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.”*

Comment (Enoxaparin in Patients with Cancer):

- There is evidence regarding the treatment and prevention of venous thromboembolism (VTE) in cancer patients using enoxaparin as an anticoagulant. This includes the use of enoxaparin for prophylaxis of VTE post abdominal or pelvic surgery for management of a malignant tumor for up to 28 days.

Response: *Enoxaparin has been included as an option for use in patients with acute treatment and secondary prophylaxis (extended treatment) of VTE in patients with cancer. As*

well, enoxaparin has been included in the post-operative prophylaxis of VTE for patients undergoing non-orthopaedic surgery (e.g., abdominal/pelvic surgery in cancer patients).

Comment (Availability of Tinzaparin):

- Based on the available clinical trial evidence, product monograph labeling and guideline recommendations, tinzaparin should be included in the options for the treatment of symptomatic acute VTE in patients with cancer.
- Tinzaparin allows for once daily dosing in cancer-associated thrombosis and there is no need for dose reduction or twice daily administration. As well, tinzaparin is available in 6 pre-filled treatment syringe formats, enabling tailored dosing and coverage for the broadest range of body weights.
- Tinzaparin has been used in patients with renal insufficiency and has demonstrated lack of accumulation and low bleeding rates in this patient population. Therefore, tinzaparin should be available as an option for patients with renal insufficiency.
- The safety of tinzaparin in renal impairment is supported by robust anti-Xa data. There is no evidence for bioaccumulation of tinzaparin when used at treatment doses in patients with severe renal impairment corresponding to CrCl as low as 20 mL/min.

Response: *Our final recommendation is for streamlined Limited Use codes. Tinzaparin has been included in all proposed Limited Use codes (i.e., acute treatment of VTE, use in patients with cancer-associated thrombosis, pregnant/lactating females, post-operative prophylaxis in orthopaedic and non-orthopaedic surgery (high-risk), peri-operative bridging).*

Comment (Education):

- I think there is a huge potential for education about indications for all of the anticoagulants, durations, LMWH self-injection (huge potential savings).

Response: *Education regarding use of all anticoagulants (i.e., DOACs, warfarin, LMWH, fondaparinux) would be beneficial, especially with recent changes in indication for many of these agents. However, the ODPRN is not equipped to provide such an educational program. Rather, this should be undertaken by other organizations.*

Comment (Miscellaneous):

- Consider using “VTE” or “DVT/PE” rather than “DVT” alone.

Response: *“VTE” is used throughout the consolidated report, when appropriate.*

Comment (Miscellaneous):

- **Limit VTE treatment in noncancer patients to 10 or 14 days, rather than 3 weeks.**

Response: *Oral anticoagulants are treatment of choice in patients with VTE. LMWHs are used in the treatment of VTE (including DVT and PE) for the initial period until therapeutic levels of the oral anticoagulant are reached. This period of overlap with the oral anticoagulant is generally 10 days or less. However, there may be certain situations where a longer time period is required (e.g., to reach a therapeutic INR for warfarin therapy). Therefore, no changes are recommended for this indication.*

Comment (Miscellaneous):

- **A patient advisory group including ad hoc members from the disease group under consideration should be created to assist the ODPRN. Patients provide a unique perspective of the issues both from a medical and societal perspective.**

Response: *The terms of reference and composition of the ODPRN Citizen's Panel will be reviewed; your suggestion for greater patient involvement (in particular with ad hoc members from the disease group) will be included in the review process.*

Comment (Miscellaneous):

- **Develop an active notification for active patient notification. For example, CADTH has an excellent proactive notification process for your consideration.**

Response: *Thank you for your suggestion. We are always looking for ways to improve our processes!*

Pharmacoepidemiology Report

Comment (Budget Impact Analysis):

- **The real work methodology used to calculate the estimated cost-savings of using only enoxaparin has serious limitations and must be interpreted with caution. The total cost savings by using enoxaparin alone, estimated at over \$10 million, must be interpreted with caution given the key limitation of the methodology, whereby average costs for dalteparin and enoxaparin were calculated for each LU code, not**

taking into account different variables of treatment (i.e., indication, length of treatment etc); the reliability of the use of the LU code, and the comparable cost per day of treatment.

- As of April 1st 2016, based on public reimbursement of prefilled syringes, the price per International Unit (IU) for dalteparin was 0.00214\$/IU, whereas the price for enoxaparin was 0.00216\$/IU, according to the ODB website list prices, which are equivalent to wholesale list prices in the province and the recognized conversion convention from mg of enoxaparin to IU. Furthermore, a recent report published by CADTH calculated a daily cost for enoxaparin that is 24% higher than that of dalteparin for the treatment of VTE. Using the prices from the April 1st 2016 ODB list, rather than the 2015 ODB list prices used in the CADTH report, brings this observation to a 27% price difference in favor of dalteparin. Hence, accounting only for the drug price cannot justify the potential cost savings estimated at over \$10 million by using enoxaparin, which is concluded in the report.
- In addition, the pharmacoepidemiology report notes: “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”, thus the pertinence of calculating an average cost per patient based on LU codes is questioned, particularly since not all LMWHs are approved for use in all the same indications.
- Further, given the defined use of LU codes 186 and 188 in the cancer population, the comparison of average calculated costs of dalteparin to enoxaparin by LU code alone, would imply a one-to-one use of enoxaparin in the cancer population. Even theoretical, such therapeutic interchange would not only require the assumption of therapeutic equivalence but also the assumptions of how to calculate the appropriate dose for enoxaparin in the cancer population. This leads to the important question of patient outcomes. As consistently noted, LMWHs are not interchangeable and cannot be used interchangeable unit for unit, as deemed by regulatory authorities, thus such practice may lead to off-label use and potential reduced safety and efficacy which may lead to further VTE or bleeding complications, and poor patient satisfaction may reduce patient compliance and therefore drug effectiveness. Given the assumptions needed and the current price per IU for both agents, the off-label use of enoxaparin in the context of cancer, with or without DVT, would most likely not result in cost-savings.

Response: *We agree with the stakeholder’s feedback that the results of this analysis should be interpreted with caution. We have added further language in our report to elucidate some of the limitations of our analysis. We also agree that future extensive analysis is needed that would control for length of therapy and indication.*

The purpose of this analysis was to explore the impact of variation on utilization and dosing (strength and regimen) would have on real-world cost. Simply using the cost on ODB formulary would not account for the real-world use of these agents as they do often vary in the dose used and the number of injections administered per day. It is also important to note that there was no evidence to support any selection bias of one indication based on LMWH and there is no evidence to suggest that length of therapy varied by agent. Because the ODPRN has decided not to make preferential listing one of the final recommendations, we have not conducted any further refinements on this analysis.

Comment (Budget Impact Analysis: Inclusion of Tinzaparin)

- **The budget impact conducted of LMWH utilization was only performed on two LMWHs. Tinzaparin should be included in this analysis. Similar cost savings may be realized through the use of tinzaparin based on real-world utilization patterns in the Ontario public payer market.**

Response: *This analysis was conducted as an exploration in variation of real-world costs. We selected the two most utilized LMWH (dalteparin and enoxaparin) since their use across indications appeared to be similar. We agree that future analysis could include all available LMWH for a true comparison if preferential listing were to be considered. Because this is not one of the options being considered by the ODPRN in our final report, we have not conducted further analysis.*

Comment (Miscellaneous):

- **The increase in use of LMWH seen is not due to abuse or inappropriate use because nobody enjoys injecting themselves with a drug that burns or hurts upon injection most of the times. It is rather related to better adherence to guidelines for treatment of cancer-related thrombosis. True – many physicians are wrongly using the LU-code 188 instead of EAP for this indication.**

Response: *We agree that the increase in utilization is not due to abuse or inappropriate use but is likely due to an aging population, expansion of indications, and better adherence to guidelines. We have added language in our report to make this point clearer.*

Pharmacoeconomic Report

Comment (Cost-Effectiveness Model):

- The de novo economic model developed to assess the cost-effectiveness of LMWHs compared with warfarin in the secondary prevention of cancer-related VTE presents a key limitation in the analysis, in that it was considered that all LMWHs are equal in terms of efficacy and safety.
 - Only one LMWH, dalteparin, has proven its efficacy in the secondary prevention of cancer-related VTE compared to VKA treatment. The CLOT study that describes this finding remains the only positive study showing superior efficacy of a LMWH vs VKA for the extended treatment of VTE in patients with cancer. As well, dalteparin is the only LMWH approved by Health Canada for this indication.
 - Enoxaparin failed to show benefit in this patient subset in two studies.
 - Two studies conducted with tinzaparin also failed to show statistical superiority over VKA.
 - Additionally, as per respective product monographs, LMWHs are not interchangeable and they should not be considered as a class.

Response: *Two analyses were conducted using different sources for the efficacy data for LMWHs within the model. In the first analysis the estimates of efficacy were sourced from the CLOT trial; however, in the second analysis, the efficacy estimates were sourced from the recent Cochrane meta-analysis. The Cochrane meta-analysis was published in 2015 and included all studies examining the secondary prevention of cancer-related VTE, not just dalteparin. The results of both analyses were similar.*

Comment (Cost-Effectiveness Model):

- Although the model was specifically structured to allow for recurrent VTE, the 52% relative risk reduction of recurrent VTE favoring dalteparin over warfarin does not seem to have been fully taken into account in the analysis. This ultimately impacts the findings. In addition, contrary to LMWHs, the use of warfarin does require frequent/routine INR monitoring which is ultimately associated with an indirect cost. Although this component was noted, given the higher frequency of INR monitoring required in patients with cancer vs. patients without cancer and the high established costs of such monitoring for warfarin, the high drug-related costs attributed to LMWHs is questioned.

Response: *The model does fully take into account the relative risk reduction of recurrent VTE within the analysis. The model accurately predicts the probability of the outcomes of deep vein thrombosis alone, non-fatal pulmonary embolism and fatal pulmonary embolism as reported within the Lee paper.*

Comment (Cost-Effectiveness Model):

- The pharmacoeconomic research questions also proposed to assess the comparative cost-effectiveness of LMWHs as compared to each other, yet this did not seem to be addressed. Although most guidelines do not differentiate between LMWHs, evidence exists regarding diverging outcomes related to the use of one product over another. Given the fact that a de novo economic evaluation was built by the ODPRN, the literature research could have been widened to include studies outside of economic evaluations, which would have provided well documented efficacy data. These studies can arguably provide sufficient quality data to build a network meta-analysis that could realistically differentiate between the various LMWHs. Expansion of the model to include each LMWH, as was done for comparison vs. warfarin, may provide a more complete economic evaluation.
- The pharmacoeconomic models only compared warfarin versus heparin. Should other comparator groups be included as well (e.g., tinzaparin and CATCH study)?

Response: *The routine monitoring of INR with warfarin was accounted for within the costing of warfarin within the model. In the base case patients were assumed to have their INR tested every two weeks. This is more frequent than the rate of every three weeks which is considered to be standard care (OHTAC 2009). We did however increase this frequency to every week within the sensitivity analysis in order to account for the potential for even greater frequency of testing within this population. This had little effect on the cost effectiveness results.*

We did not directly compare one LMWH versus another due to the lack of comparative evidence. We would encourage pharmaceutical companies to invest in comparative head to head clinical trials as this would enable this type of comparison. We conducted two analyses. The first used the data from the CLOT clinical trial and the second used the data from a very recent Cochrane meta-analysis which included all LMWHs within its research protocol. The limited number of studies within this area made the conduct of a meta-analysis challenging and would not be sufficient to allow the conduct of a network meta-analysis. The best way to differentiate between LMWHs would be through the conduct of head to head clinical trials.

Comment (Cost-Effectiveness Review):

- The pharmacoeconomics analysis modeled various options based on a daily cost of \$29-\$35 per patient. Where was this cost obtained from?

Response: *The dosing of dalteparin was consistent with that which was reported within the CLOT clinical trial. 200 IU/kg/day for the first month then 150 IU/kg/day for months 2-6. As the initial VTE was treated with LMWH in both the warfarin group and the dalteparin group, the costs for these days were not included. We assumed an average weight of 75 kg. The calculated daily dose for the first month is 14986 IU/day and 11240 IU/day for months 2 to 6.*

Assuming the dose is dispensed as prefilled syringes, syringes with 15000 IU would be dispensed for the first month and 12500 IU for months 2 to 6. Based on the Ontario Drug Benefit formulary the cost of the 15000 IU syringes is 32.0700 and the cost for the 12500 IU syringes is 26.7260. To this we added the mark up and one dispensing fee for the first month and two dispensing fees for the 2 to 6 month period. This arrived at the estimate of \$29 to \$35 per day per patient.

Comment (Cost-Effectiveness Literature Review):

- **Considering the absence of any good independent pharmacoeconomic analysis performed in this domain, it would have been an option to take into account the existing industry supported initiative in this area, particularly the CLOT study pharmacoeconomic analysis (Dranitasaris 2006). Additionally, a CADTH Rapid Response Report also noted that dalteparin may be cost-effective compared to warfarin in cancer patients. No economic evidence was identified for other LMWHs. Given the unusually large gap between this latter finding of cost-effectiveness within the accepted ICER threshold, and the finding from the ODPRN de novo economic model that the ICER for LMWHs versus warfarin was greater than \$1 million per QALY, further evaluation is needed.**

Response: *The Dranitasaris paper was reviewed as part of the pharmacoeconomic literature review. A number of concerns regarding the methodology of the paper were summarized. The main concern was with respect to the inadequacy of the approach taken to estimate QALYs. The approach taken was a time trade off method with nurses as patient surrogates. The major concern was with respect to the bias in the information presented to the nurses prior to conducting the time trade off evaluation. The nurses were provided with a selective subgroup analysis of the CLOT trial which was conducted post hoc and suggested a survival benefit with dalteparin. The CLOT trial clearly did not find any survival difference between the two treatments as was confirmed by the Cochrane meta-analysis. This nullifies the assessed QALYs within the analysis making the use of it in decision making inappropriate.*

Comment (Miscellaneous):

- **In the pharmacoeconomic section, display the unit cost for LMWH 2009-2015 e.g. for thromboprophylaxis (D5000, E40, T4500) and for treatment of a 75 kg patient (D15,000, E120, T14,000) to show if the cost per unit has increased, stayed the same or decreased over time. Also, eliminate the erroneous potential cost savings of switching to a single LMWH.**

Response: *Economic evaluation is based on the price facing the decision maker at the point of analysis. If the manufacturer was willing to commit to lower prices over time then*

scenario analysis can be conducted with the revised prices.

Systematic Review Team

Comment (Methodology):

- Caution should be taken when reviewing guidelines as some of the recommendations may be based on personal opinion rather than clinical evidence. The methodology chosen to conduct this review was mainly based on the assumption that all LMWHs are the same. Clinical guidelines rarely distinguish drugs from the same class; consequently it was obvious that LMWHs would not be differentiated in this review. However, LMWHs are not interchangeable (according to product monographs) and were proven to produce different clinical outcomes in certain indications (e.g., dalteparin in use for extended treatment in cancer patients). As well, the review did not focus on guidelines alone, but also on clinical expert consensus which may be produced with less rigorous methodology. Therefore, this review deviates from its initial mandate shared in August 2015 which was to solely focus on guidelines. As well, a methodology focusing more on the review of the “raw” clinical evidence (i.e., clinical trials outcomes) than a review of guidelines only, would likely have been more appropriate to detect these differences.**

Response: *We thank you for your comments and appreciate the feedback. We agree that a systematic review of randomized controlled trials would have been ideal. The project time lines for the ODPRN Drug Class Reviews are short and unfortunately a series of systematic reviews (or even rapid reviews) across the indications was not feasible.*

We do not believe that we have deviated from our original protocol which stipulated that we would include individual guidelines if an evidence-based development process was used and that evidence was presented along with recommendations. The guideline processes specifically related to the systematic review of available evidence for each report were carefully considered by two independent reviewers. The process for developing recommendations based on the evidence gathered in each guideline ranged from rigorous GRADE assessment to some sort of clinical consensus or opinion. We have detailed this in the tables which accompany our report and have updated the report to include a disclaimer. We highlight that the detailed tables should be reviewed for an accurate description of the level of evidence associated with each recommendation across all of the indications considered, and we have noted in these tables where opinion or consensus may have factored in to the recommendations presented.

“This document provides a summary of guidelines that followed an evidence-based development process following a detailed assessment by the review team. 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 summaries provided in the report appendices by indication.”

Comment (Miscellaneous):

- In the review, it is stated that: “Easaw et al (2015) advised of no available evidence to recommend one LMWH over another, but suggested tinzaparin might have a favourable biological profile in elderly patients with renal insufficiency”. This recommendation is not substantiated by any clinical data, but is an opinion provided by the author.

Response: *We thank you for your comments and appreciate the feedback. This statement has been removed from the final report.*

Environmental Scan

Comment (Miscellaneous):

- LMWHs are biologics and as such, any product entering subsequent to an originator LMWH will be a subsequent entry biologic (SEB). Therefore, standard generic market concepts are not applicable to LMWHs in Canada (nor reference to “generic” LMWH as per the US environment).

Response: *In the US, a generic version of enoxaparin is available (see FDA document describing the generic versions of LMWH. No change has been made regarding “generic” LMWH in the US environment. The statement regarding generic LMWH in Canada has been changed to read: “Note that enoxaparin is only available in Canada as the brand name product (Lovenox).”*
<http://www.fda.gov/Drugs/DrugSafety/Postmarketdrugsafetyinformationforpatientsandproviders/ucm220037.htm>.

Comment (Miscellaneous):

- Regarding Exhibit 4, fondaparinux is listed on the Nova Scotia and Newfoundland public drug plans. As well, nadroparin is listed as a restricted benefit in Newfoundland.

Response: *Fondaparinux is NOT listed on the Nova Scotia or Newfoundland formulary. As well, nadroparin is not listed on the Newfoundland formulary. No changes have been made to the report.*

Comment (Miscellaneous):

- **Regarding information from other jurisdictions, we recommend looking to the UK and western Europe where treatment practices are similar to those in Canada.**

Response: *Thank you for your suggestion. Listing information for public plans in the UK and western Europe are not always easily accessible. We have elected to use the Australian and New Zealand systems as comparators for our drug class reviews.*