(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☑ No ☐

The Applicants comprehensively address the public health need for thromboprophylaxis in patients undergoing surgical interventions. The annual incidence rate of venous thromboembolic events (VTE) - either deep vein thrombosis (DVT) or pulmonary embolism (PE) - per 100,000 persons is about 130 in UK, 100 in USA and 50 in Australia. The incidence of first-time VTE rises exponentially with age up to a rate of 450 to 600/100,000 per year (=0.5%/year) among individuals >80 years old.

Symptomatic VTE at approximately one month after major orthopedic surgery occur in 4.3% of patients (1.5% PE). However, asymptomatic VTE (diagnosed by venography) is reported in 40-60% patients after hip (THA) or knee arthroplasty (TKA) and 15-40% patients after general surgery.

Two third of patients undergoing surgical interventions are at risk of VTE and would need antithrombotic prevention but according to a large cross sectional study conducted in 358 hospitals across 32 countries in six continents (ENDORSE, Lancet 2008) only 60% receive it. Prescription rates vary widely across countries being lowest in Asia (Bangladesh, India, Pakistan, and Thailand 0.2% and 16.3%) and are only a little higher in Northern African countries (Egypt, Tunisia, Algeria).

The low prescribing attitude may result from cultural reasons (e.g., the misleading belief that the risk is low in Asian ethnicities), the poor awareness of the thrombotic risk, concern about bleeding, difficulty of assessing risk level of patients, and/or the insufficient availability or the high cost of medicines.

The Applicants aim at improving access to drugs with the highest (cost-)effectiveness in the prevention of VTE in order to reduce the burden of disease also in low and middle income countries. The Applicants recognize that this improvement can only be achieved in conjunction with an improved awareness of this life-threatening disease. The question is whether the availability of more expensive drugs may hamper the adoption of appropriate preventive strategies and the availability of several products with uncertain comparative (cost-)effectiveness may hinder the implementation of those strategies (see section (11)).

(2) Have all important studies that you are aware of been included in the application?
The bibliography provided by the Applicants is sufficient to support their application. In line with the Applicants’ suggestions it could also be useful to consider the “Cost-effectiveness of Dalteparin vs Unfractionated Heparin (UFH) for the Prevention of Venous Thromboembolism in Critically Ill Patients” (Fowler RA et al JAMA. 2014;312:2135-45. doi:10.1001/jama.2014.15101), an economic evaluation based on the PROTECT trial (N Engl J Med. 2011;364:1305-14).

The Cochrane Review on the risk of thrombocytopenia associated with LMWHs and UFH have been referred to. Other systematic reviews from the Cochrane Library may be taken into consideration including:

ID: CD001100
AU: Erkens Petra MG and Prins Martin H
TI: Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism
YR: 2010, DOI: 10.1002/14651858.CD001100.pub3

ID: CD009447
AU: Akl Elie A et al.
TI: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer
YR: 2014, DOI: 10.1002/14651858.CD009447.pub2

ID: CD003747
AU: Alikhan Raza et al.
TI: Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction)
YR: 2014, DOI: 10.1002/14651858.CD003747.pub4

ID: CD004318
AU: Rasmussen Morten Schnack et al.
TI: Prolonged thromboprophylaxis with Low Molecular Weight heparin for abdominal or pelvic surgery
YR: 2009, DOI: 10.1002/14651858.CD004318.pub2

ID: CD008303
AU: Barrera Luis M et al.
TI: Thromboprophylaxis for trauma patients
YR: 2013, DOI: 10.1002/14651858.CD008303.pub2

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?  
Yes ☒ No ☐

On the basis of results of meta-analyses the Applicants report the available evidence of the efficacy (and safety) of low molecular weight heparins (LWMHs) as compared with no prophylaxis and with low-dose unfractionated heparin (UFH) in different clinical settings.
The latter comparison are summarized in the following tables from American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (Chest 2012).

**Non orthopedic surgery**
LMWHs avoid 2 to 8 more symptomatic VTE than UFH per 1,000 patients treated depending on the level of risk and no PE irrespective of risk. This means that the NNT to avoid one VTE ranges from 500 to 125.

<table>
<thead>
<tr>
<th>Table 2. Risk of VTE in non orthopedic surgery: LMWH versus LDUH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td><strong>Fatal PE</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>Symptomatic VTE</strong></td>
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</tbody>
</table>

LMWHs induce 2 to 4 less major bleeding than UFH per 1,000 patients treated in the low and intermediated risk population, respectively. This means that the NNT to avoid one hemorrhagic event ranges from 500 to 250.

<table>
<thead>
<tr>
<th>Table 14. Risk of major bleeding in non orthopedic surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk of major bleeding (95% CI)</strong></td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>No prophylaxis</td>
</tr>
<tr>
<td>Lev risk population</td>
</tr>
<tr>
<td>12 per 1400</td>
</tr>
<tr>
<td>Medium risk population</td>
</tr>
<tr>
<td>45 per 1000 (30-66)</td>
</tr>
<tr>
<td><strong>LDUH</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Lev risk population</td>
</tr>
<tr>
<td>19 per 1400</td>
</tr>
<tr>
<td>Intermediate risk</td>
</tr>
<tr>
<td>31 per 1000 (26-37)</td>
</tr>
</tbody>
</table>

The consequent recommendations are as follows:

<table>
<thead>
<tr>
<th>Table 4. Recommendations for thromboprophylaxis in various risk groups in non orthopedic surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk of symptomatic VTE</strong></td>
</tr>
<tr>
<td>Very low (~0.5%)</td>
</tr>
<tr>
<td>Low (~1.5%)</td>
</tr>
<tr>
<td>Moderate (~3%)</td>
</tr>
<tr>
<td>High (~6%)</td>
</tr>
</tbody>
</table>

It is noteworthy that the same recommendations apply to both UFH and LMWHs: weak recommendations based on low-quality evidence in moderate-risk patients (grade 2B) and strong recommendations based on moderate-quality evidence in high-risk patients (grade 1B).

**Orthopedic surgery**
LMWHs avoid 2 more symptomatic VTE and 1 more PE than UFH per 1,000 patients treated. This means that the NNT to avoid one VTE is 500 and to avoid one PE is 1000.

LMWHs induce 1 less major bleeding than UFH per 1,000 patients (15 instead of 16/1,000). This means that the NNT to avoid one hemorrhagic event is 1000.

The consequent recommendations are as follows:
It is noteworthy that the same recommendations apply to both UFH and LMWHs: strong recommendation based on moderate-quality evidence in high-risk patients (grade 1B) for the initial prophylaxis and weak recommendation based on low-quality evidence in moderate-risk patients (grade 2B) for the extended prophylaxis.

**Trauma**
The Applicants mention one study comparing LMWHs Vs. pneumatic compression. However, the relevant Cochrane systematic review among those listed in section (2) includes two studies of LMWHs Vs. UFH in 331 patients with trauma. The review reports that LMWHs appeared to reduce the risk of DVT compared to UFH (RR 0.68; 95% CI 0.50 to 0.94). There was no statistically significant difference in the risk of PE and in the risk of bleed. No deaths were reported in either trial.

**Acutely ill medical patients**
The relevant Cochrane systematic review among those listed in section (2) included six trials comparing different LMWHs and UFH: LMWHs reduced the risk of DVT (OR 0.77; 95% CI 0.62 to 0.96; P = 0.02) and major bleeding (OR 0.43; 95% CI 0.22 to 0.83; P = 0.01). There was no clear evidence that the effects of LMWHs and UFH differed for the PE outcomes, all-cause mortality and thrombocytopenia.

Not fully consistent findings are contributed by the PROTECT trial (N Engl J Med 2011;364:1305-14) that compared the LMWH dalteparin and UFH in critically ill patients. There was no difference in leg DVT (5.1 Vs. 5.8%; HR 0.92; 95% CI 0.68 to 1.23; P=0.57) but the LMWH reduced rates of PE (1.3 Vs. 2.3%; HR 0.51; 95% CI 0.30 to 0.88; P=0.01) and heparin-induced thrombocytopenia (HIT) (0.3 Vs. 0.6%; HR 0.47, 95% CI 0.16 to 1.35; P=0.16). There was no significant between group difference in the rates of major bleeding (HR 1.00; 95% CI 0.75 to 1.34; P = 0.98) or in-hospital death (HR 0.92; 95% CI 0.80 to 1.05; P = 0.21).

(4) **Is there evidence of efficacy in diverse settings and/or populations?**

Yes ☒ No ☐

The efficacy of LMWHs has been tested in different clinical, geographical and ethnical setting. There are studies addressing the incidence of VTE and response to oral anticoagulants in different ethnic groups (White RH, et al. Ann Intern Med 1998;128:737-740; Stein PD, et al. Am J Med 2004). This reviewer is not aware of studies documenting the possible different efficacy/safety of heparins in different geographical or ethnical settings.
(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes ☒ refers to the 1st Q  No ☐

Bleeding
Please see section (3) for the hemorrhagic risk.

Heparin-induced thrombocytopenia (HIT)
One Cochrane systematic review addressed the incidence of HIT occurring during exposure to UFH or LMWHs after any surgical intervention. Only two studies (923 participants) were included in the review which showed a statistically significant reduction in the risk of HIT with LMWHs compared with UFH (RR 0.24, 95% CI 0.07 to 0.82; P = 0.02). This result suggests that patients treated with LMWHs would have a RRR of 76% in the probability of developing HIT compared with patients treated with UFH.

VTE complicating HIT occurred in 12 of 17 patients who developed HIT. Pooled analysis showed a statistically significant reduction in HIT complicated by VTE with LMWHs compared with UFH (RR 0.20, 95% CI 0.04 to 0.90; P =0.04). This result indicates that patients using LMWHs would have a RRR of 80% for developing HIT complicated by VTE compared with patients using UFH. In essence, 5 out of 1,000 patients treated with LMWHs would suffer from VTE complicating HIT instead of the 23 treated with UFH.

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☒  No ☐

There is no particular issue in this respect but the need to promote the extension of the use of heparins in the prevention of VTE in patients at risk.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐  No ☒

In most countries LMWHs are approved for the prevention of VTE in surgical patients with moderate or high risk for VTE; for the prevention of VTE in medical patients with congestive heart failure (NYHA class III or IV), respiratory failure, acute infection or acute rheumatologic disease with at least one risk factor; for VTE for treatment of DVT with or without PE; for the treatment of unstable angina and non-Q-wave AMI (in conjunction with aspirin); for the treatment of AMI with ST-segment elevation; for the prevention of blood
clot in the extra-corporeal circulation during hemodialysis. Indications may vary across LMWHs.
There is no apparent regulatory issue regarding these products.

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

   Yes □ No ☒

No WHO GRC-approved Guideline apparently deals with LMWHs.

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

The Applicants report that in different counties including Algeria, Argentina, Brazil, India, Morocco, Thailand, Tunisia, and Uganda the costs of prophylactic doses of the LMWH enoxaparin ranged from 2.25 to 9.5 USD per 20 mg dose to 4.75 to 18.5 USD per 40 mg dose, enoxaparin being the most widely used LMWH across countries. Biosimilar LMWHs can be found at lower costs, where available. In Italy the ex-factory price of brand prefilled syringes containing UFH (5,000IU) is 1,128€ (<1USD).

As for the cost-effectiveness, the Applicants refer to studies from Australia, Europe and North America showing that the use of pharmacological prophylaxis was associated with substantial cost savings. An economic evaluation based on the PROTECT trial (see section (3)) shows that the use of the LMWH dalteparin for VTE prophylaxis among critically ill medical-surgical patients was more effective and had similar or lower costs than the use of UFH. These findings were driven by lower rates of PE and HIT and corresponding lower overall use of resources with the LMWH.
No cost-effectiveness studies of VTE prophylaxis are available from developing countries.

(10) Any additional comments?

An open question regards the efficacy/safety profile of the prolonged prophylaxis. The issue has been addressed by the Cochrane systematic review of Rasmussen at al, which is referred to in section (2). The review could not find any study reporting on the prolonged use of UFH in the looked for setting of major abdominal or pelvic surgery. Instead the search exclusively detected trials evaluating prolonged thromboprophylaxis with LMWHs as compared to control or placebo. The incidence of overall VTE after major abdominal or pelvic surgery was 14.3% (95% CI 11.2% - 17.8%) in the control group as compared to 6.1% (95% CI 4.0% - 8.7%) in patients receiving out-of-hospital LMWHs. This difference was statistically significant, OR 0.41 (95% CI 0.26 -0.63), P < 0.0005. Prolonged thromboprophylaxis with LMWHs was also associated with a statistically significant reduction of even the incidence of symptomatic VTE from 1.7% (95% CI 0.8% - 3.4%) in the control group to 0.2% (95% CI 0.0% - 1.2%) in patients receiving prolonged thromboprophylaxis, OR 0.22 (95% CI 0.06 -0.80), P =
In February, the respective incidence of bleeding in the control and LMWH group were 3.7% (95% CI 2.4% -5.5%) and 4.1% (95% CI 2.7% -6.0%), OR 1.11 (95% CI 0.62 - 1.97), P = 0.73. The review suggests that administration of LMWHs for 4 weeks compared to 5-7 days after major abdominal or pelvic surgery significantly reduces the incidence of VTE without jeopardizing safety.

11. Please summarise the action you propose the Expert Committee takes.

The better efficacy and safety of LMWHs as compared to UFH is statistically documented in different settings. However, the level of evidence is of moderate or low-quality and the incremental clinical benefit is small:

-8 events (-5 VTE, -0 PE, -3 hemorrhages)/1000 treated patients, NNT 125, in the non orthopedic surgery
-4 events (-2 VTE, -1 PE, -1 hemorrhage)/1000 treated patients, NNT 250, in the orthopedic surgery

In comparison extending the prophylaxis with UFH to all 1,000 patients instead of the 60% of them as it currently happens would avoid 6 more VTE in addition to the 9 avoided at present.

One could argue that the adoption of LMWHs may help extending the practice of prophylaxis. However, the introduction of so many options and different dosages might also hamper the implementation of an overall preventive strategy. And so might the LMWH cost. In spite of their small benefit as compared to UFH the cost of LMWHs is at least twice as much.

If the Committee believes that the additional benefit provided by LMWHs is worthwhile and they should be regarded as EM, this reviewer proposes that LMWHs are included in the Complementary List, while keeping UFH in the Master List because of its lower cost. The question then is which LMWH should be included. Clearly the most cost-effective one, whose clinical results in RCTs have mostly driven the conclusions of the meta-analyses and backed the suggestions of the current guidelines and whose cost does not hinder affordability.

In short, the proposal of this reviewer is

1. First, to commit systematic reviews or ad-hoc RCTs to select one-two LMWHs on the basis of their (cost-)effectiveness.
2. Then, to introduce this/ these LMWHs in the complementary list.
3. Finally, to re-consider the opportunity to adopt one LMWH in the EML in the place of UFH considering that LMWHs cannot cover all the clinical indications of UFH.
4. Last but not least, to keep promoting educational programs to extend the use of anti-thrombotic prophylaxis in patients at risk. Though being a long-lasting process, this would be the most effective intervention in the long run.

February, 2015
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Declaration of CoI:
None.

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The views presented here are those of the reviewer and do not necessarily reflect those of his advisors.