INNOHEP 10,000 anti-Factor Xa IU/0.5 ml, solution for injection (SC) in pre-filled syringe  
B/2 (CIP: 34009 339 723 9 4)  
B/10 (CIP: 34009 339 725 1 6)  

INNOHEP 14,000 anti-Factor Xa IU/0.7 ml, solution for injection (SC) in pre-filled syringe  
B/2 (CIP: 34009 339 726 8 4)  
B/10 (CIP: 34009 339 728 0 6)  

INNOHEP 18,000 anti-Factor Xa IU/0.9 ml, solution for injection (SC) in pre-filled syringe  
B/2 (CIP: 34009 339 729 7 4)  
B/10 (CIP: 34009 339 731 1 7)  

Applicant: LEO Pharma

<table>
<thead>
<tr>
<th>INN</th>
<th>Tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code</td>
<td>B01AB10 (anticoagulant, low-molecular-weight heparin)</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Extension of indication</td>
</tr>
</tbody>
</table>
| Lists concerned | National Health Insurance (French Social Security Code L.162-17)  
Inclusion for hospital use (French Public Health Code L.5123-2) |
<p>| Indication concerned | “Extended treatment of symptomatic venous thromboembolism and prevention of its recurrence in patients who have active cancer and/or are undergoing chemotherapy”. |</p>
<table>
<thead>
<tr>
<th>Actual Benefit</th>
<th>Substantial in this extension of indication.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in Actual Benefit</td>
<td>INNOHEP does not provide any improvement in actual benefit (level V, non-existent) in the therapeutic strategy for extended treatment of symptomatic venous thromboembolism and prevention of its recurrence in patients who have progressive cancer and/or are undergoing chemotherapy. There are no direct comparisons between LMWHs in this indication, in particular not between tinzaparin (INNOHEP) and dalteparin (FRAGMINE), and the therapeutic benefit of INNOHEP versus oral vitamin K antagonist anticoagulants has not been solidly established.</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>1st-line therapy</td>
</tr>
</tbody>
</table>
01 ADMINISTRATIVE AND REGULATORY INFORMATION

| Marketing Authorisation (national procedure) | Date of initial Marketing Authorisation: 13 October 1995  
| Date of variation of Marketing Authorisation for the extension of indication: 19 June 2013  
| Prescribing and dispensing conditions | List I  

| ATC Classification | 2013  
| B | Blood and bloodforming organs  
| B01A | Antithrombotic agents  
| B01AB | Heparin group  
| B01AB10 | tinzaparin  

02 BACKGROUND

Application for inclusion of the dosages 10,000 anti-Factor Xa IU/0.5 ml, 14,000 anti-Factor Xa IU/0.7 ml and 18,000 anti-Factor Xa/0.9 ml of the proprietary medicinal product INNOHEP (tinzaparin, a LMWH) on the lists of medicines refundable by National Health Insurance and approved for hospital use in the extension of indication: extended treatment of symptomatic VTE and prevention of its recurrence in patients who have cancer.

INNOHEP at these curative doses is reimbursed in its other Marketing Authorisation indications (reimbursement rate: 65%; B/10 approved for hospital use).

It is the second LMWH to be granted Marketing Authorisation in this indication, following FRAGMINE (dalteparin), which was allocated a substantial AB and minor IAB (level IV) compared with VKAs in the opinion of 30 June 2010.

03 THERAPEUTIC INDICATIONS

“This heparin is a low-molecular-weight heparin (LMWH). Its indications are as follows:

- Extended treatment of symptomatic venous thromboembolism and prevention of its recurrence in patients who have progressive cancer and/or are undergoing chemotherapy
- Curative treatment of established deep vein thrombosis
- Curative treatment of pulmonary embolism with no signs of seriousness, in the absence of pre-existing cardiac or pulmonary disease and excluding emboli that are likely to respond to thrombolytic or surgical treatment. If there are signs of haemodynamic instability, unfractionated heparin (UFH) and, in some cases, thrombolysis or surgical embolectomy should be used as a preference. This treatment is not indicated for patients who have recently undergone surgery.”

04 DOSAGE

“Extended treatment of symptomatic venous thromboembolism and prevention of its recurrence in patients who have progressive cancer and/or are undergoing chemotherapy:

- Treatment should be administered at the standard curative dosage of 175 anti-Factor Xa IU/kg once daily by subcutaneous injection.
- The recommended duration of treatment is 3 to 6 months. If the anticoagulant treatment must be continued beyond 6 months, the patient should be switched to VKAs because of the lack of data on using tinzaparin beyond this period.”
The dose of LMWHs adjusted for body weight has not been assessed for patients weighing > 100 kg or < 40 kg. LMWHs could be less effective for patients weighing over 100 kg, and there could be an increased risk of bleeding for patients weighing less than 40 kg. Such situations require particularly close monitoring.

By way of example, the doses to administer based on the patient’s weight are:

<table>
<thead>
<tr>
<th>Body weight</th>
<th>INNOHEP volume per injection (once daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 ml solution = 20,000 anti-Factor Xa IU</td>
</tr>
<tr>
<td>45 kg</td>
<td>0.4 ml = 8,000 anti-Factor Xa IU</td>
</tr>
<tr>
<td>55 kg</td>
<td>0.5 ml = 10,000 anti-Factor Xa IU</td>
</tr>
<tr>
<td>70 kg</td>
<td>0.6 ml = 12,000 anti-Factor Xa IU</td>
</tr>
<tr>
<td>80 kg</td>
<td>0.7 ml = 14,000 anti-Factor Xa IU</td>
</tr>
<tr>
<td>90 kg</td>
<td>0.8 ml = 16,000 anti-Factor Xa IU</td>
</tr>
<tr>
<td>≥ 100 kg</td>
<td>0.9 ml = 18,000 anti-Factor Xa IU</td>
</tr>
</tbody>
</table>

Monitoring anti-Factor Xa activity:
As most clinical studies demonstrating the efficacy of LMWHs have been conducted using a weight-adjusted dose and without any specific laboratory monitoring, the usefulness of laboratory monitoring for assessing the efficacy of a LMWH treatment has not been established. However, laboratory monitoring with anti-factor Xa activity assays may be useful for managing the bleeding risk in some clinical situations that are commonly associated with a risk of overdose. These situations primarily involve the curative indications for LMWHs, due to the doses administered, when there is:
- mild to moderate renal impairment (estimated clearance using the Cockcroft formula: around 30 to 60 ml/min): unlike standard unfractionated heparin, LMWHs are primarily excreted renally and any renal impairment may lead to a relative overdose. In severe renal impairment, curative doses of LMWH are contraindicated;
- extremes weight (emaciation even cachexia, obesity);
- unexplained bleeding."

05 THERAPEUTIC NEED

The therapeutic management of a symptomatic venous thromboembolic event (VTEE) aims to prevent the death of the patient (particularly in cases of pulmonary embolism (PE)), embolism migration, thrombus extension, early and late recurrence of deep vein thrombosis (DVT) and PE, and development of post-thrombotic syndrome and chronic pulmonary arterial hypertension.

According to French good practice guidelines,¹,² using oral anticoagulants (VKAs) to treat venous thromboembolism (VTE) in patients with progressive cancer is less effective and less safe than in patients without cancer. Extended treatment with a LMWH reduces the risk of recurrence significantly and substantially, without increasing the risk of haemorrhage. These results were obtained using LMWH doses that were slightly lower than the standard curative doses, except in the case of tinzaparin. When confirmed VTE occurs in a patient with cancer, switching to a LMWH after the initial treatment is recommended (Grade A).

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The medicinal products that are indicated for extended curative treatment of venous thromboembolism and for preventing its recurrence in patients with cancer are:

<table>
<thead>
<tr>
<th>NAME (INN)</th>
<th>Same TC* Yes / No</th>
<th>Indication</th>
<th>Date of opinion</th>
<th>AB</th>
<th>IAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRAGMINE (dalteparin) Pfizer</td>
<td>Yes</td>
<td>Extended treatment of symptomatic venous thromboembolism and prevention of its recurrence in patients with cancer</td>
<td>30/06/2010</td>
<td></td>
<td>Minor (level IV) in comparison with VKAs</td>
</tr>
<tr>
<td>PREVISCAN (fluindione) Merck Santé</td>
<td></td>
<td>Treatment of DVT and PE, and prevention of their recurrence, as a follow-on treatment from heparin.</td>
<td>27/07/2011</td>
<td>substantial</td>
<td></td>
</tr>
<tr>
<td>SINTROM MINI-SINTROM (acenocoumarol) Novartis Pharma</td>
<td>No</td>
<td></td>
<td>03/11/2010</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>COUMADINE (warfarin) Bristol-Myers Squibb</td>
<td></td>
<td></td>
<td>01/02/2012</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* therapeutic category; N/A: not applicable.

NB:
- The non-VKA anticoagulants (DOAC: ELIQUIIS, PRADAXA and XARELTO) do not have Marketing Authorisation in this indication.
- The other low-molecular-weight heparins (LMWHs) and fondaparinux (ARIXTRA) are indicated for short-term curative treatment of deep vein thrombosis and pulmonary embolism. They are not indicated for extended treatment (secondary prevention) (see the SPCs for these products). According to good clinical practice guidelines (AFSSAPS, November 2009), in adult patients with progressive cancer, “three types of LMWH are recommended: dalteparin (FRAGMINE) and, with a lower level of evidence, tinzaparin (INNOHEP) and enoxaparin (LOVENOX).” To date, LOVENOX still has no Marketing Authorisation for this indication in France. VKAs are considered to be second-line medicines in this indication.

**Conclusion**

The clinically relevant comparators for INNOHEP in the extended treatment of symptomatic venous thromboembolism and prevention of its recurrence in patients who have progressive cancer and/or are undergoing chemotherapy are FRAGMINE (dalteparin) and, as a follow-on treatment from heparin, PREVISCAN, SINTROM and COUMADINE.
INNOHEP has Marketing Authorisation for this new indication in Germany, Denmark, Portugal, Spain and Sweden.

ANALYSIS OF AVAILABLE DATA

In the extended treatment of symptomatic venous thromboembolism (VTE) and prevention of recurrence in patients who have progressive cancer and/or are undergoing chemotherapy, the application is supported by two pivotal trials that included patients with deep vein thrombosis (DVT) and/or pulmonary embolism (PE): the LITE-Cancer study (a substudy of the Main-LITE study, Hull 2006;³ Hull 2007⁴) and the Romera 2009 trial.⁵ In these studies, the efficacy and adverse effects of tinzaparin were compared with those from treatment with VKAs.

The company submitted results from other studies which are not detailed in this opinion for the following reasons:

- The studies (Home LITE,⁶ Daskalopoulos 2005,⁷ Perez de Llano 2010⁸) included patients with and without cancer interchangeably, with no stratification on this criterion.
- The observational studies⁹,¹⁰,¹¹ are not comparative and did not exclusively concern patients with cancer.

Two meta-analyses were submitted by the pharmaceutical company:

- A meta-analysis conducted by ANSM [French National Agency for Medicines and Health Products Safety] examining the two pivotal trials.
- A meta-analysis examining the five studies that compared tinzaparin with a VKA in extended treatment of VTE in patients with or without cancer (Laporte, 2012¹²).

There are no direct comparisons between LMWHs in this indication, specifically not between tinzaparin (INNOHEP) and dalteparin (FRAGMINE) or enoxaparin (LOVENOX).

08.1 Efficacy

Methodology:
The two studies accepted are open-label, comparative, randomised, parallel-group, multicentre trials.

Main-LITE/LITE Cancer Study
The primary objective was to compare the efficacy of extended treatment with tinzaparin with treatment with UFH followed by warfarin (a VKA). The duration of treatment was 3 months. Out of the 737 patients randomised (369 in the tinzaparin group and 368 in the UFH/warfarin group in the Main-LITE overall population), 100 patients in each group had cancer on inclusion (LITE Cancer substudy). No calculation of the number of subjects necessary was done for this substudy. Tinzaparin was prescribed at a fixed dose of 175 anti-Factor Xa IU/kg as a daily injection for 3 months. Patients in the VKA group received UFH which was quickly switched to warfarin, continued for 3 months. The endpoints were recurrent thromboembolism (RTE, the primary endpoint), death, and occurrence of bleeding and thrombocytopenia at 3 and 12 months.

ROMERA Study
The primary objective was to compare the efficacy of extended treatment with tinzaparin with treatment with tinzaparin followed by acenocoumarol (a VKA). The duration of treatment was 6 months. Out of the 241 randomised patients with symptomatic thromboembolism, a subgroup of 69 patients had cancer on inclusion. In the tinzaparin group (n=36), treatment was started at a fixed dose of 175 anti-Factor Xa IU/kg as a daily injection and was continued for 6 months. In the VKA group (n=33), treatment was started with tinzaparin at the dose of 175 anti-Factor Xa IU/kg as a daily injection, then changed to acenocoumarol which was continued for 6 months. The endpoints were recurrent thromboembolism (RTE) at 6 months and 12 months. In this study, no calculation of the number of subjects necessary was performed.

Although these studies included patients with and without cancer, a subgroup analysis of patients with cancer is acceptable because the patients with cancer were stratified on randomisation (Main-LITE, Hull, 2006) or pre-specified in the protocol or analysis plan (Romera, 2009).

Results:
Main-LITE/LITE Cancer Study
In the overall study population (Main-LITE), there was no difference in the incidence of RTE at 3 months and 12 months between the two groups.

In the population of patients with cancer (LITE Cancer), the incidence of RTE at 3 months was 6% in the tinzaparin group and 10% in the VKA group, also a non-significant difference. After 12 months of treatment, this incidence was lower in the tinzaparin group ([7 (7%)] than in the UFH/warfarin group ([16 (16%)]), with an absolute difference of -9.0% [-21.7; -0.7], p=0.04 and a relative risk reduction for RTE of 56% (RR=0.44) in comparison with the control group.

<table>
<thead>
<tr>
<th></th>
<th>tinzaparin* N=100</th>
<th>VKA N=100</th>
<th>E** (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>M3</td>
<td>6 (6)</td>
<td>10 (10)</td>
<td>-4.0 (-12.0; 4.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>M12</td>
<td>7 (7)</td>
<td>16 (16)</td>
<td>-9.0 (-21.7; -0.7)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

*175 IU/kg/day; **absolute difference; N/A = not available.

The 12-month results in the stratified subgroup of patients with cancer are in favour of extended treatment with tinzaparin. However, these results should be interpreted with caution because there is no significant difference between the two groups in the overall population.
ROMERA Study:
In the population of patients with cancer, there was no difference in the incidence of RTE between the tinzaparin and tinzaparin/acenocoumarol groups after 6 and 12 months of treatment.

Table: Efficacy of tinzaparin versus acenocoumarol on RTE in the ROMERA study

<table>
<thead>
<tr>
<th></th>
<th>Recurrent thromboembolism n (%)</th>
<th>95% CI, p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tinzaparin</td>
<td>tinzaparin/acenocoumarol</td>
</tr>
<tr>
<td>Total population</td>
<td>N=119</td>
<td>N=122</td>
</tr>
<tr>
<td>Period from D0 to M12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M6</td>
<td>5 (4.2)</td>
<td>7 (5.7)</td>
</tr>
<tr>
<td>M12</td>
<td>6 (5)</td>
<td>13 (10.65)</td>
</tr>
<tr>
<td>Period following the initial treatment period (from D12 to M12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M12</td>
<td>1 (0.85)</td>
<td>7 (5.7)</td>
</tr>
<tr>
<td>Patients with cancer</td>
<td>n=36</td>
<td>n=33</td>
</tr>
<tr>
<td>Period from D0 to M12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M6</td>
<td>2 (5.5)</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>M12</td>
<td>2 (5.5)</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>Period following the initial treatment period (from D12 to M12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M12</td>
<td>0 (0)</td>
<td>5 (15.16)</td>
</tr>
</tbody>
</table>

*175 IU/kg/day.

Meta-analysis by AFSSAPS in 2009:
This meta-analysis (unpublished) included studies where patients with cancer were stratified on randomisation or pre-specified in the protocol or analysis plan (ref. 3).

- Recurrent thromboembolism:
  - At 3-6 months of treatment: RR=0.60 (95% CI [0.26; 1.41]), a non-significant difference.
  - At 12 months of follow-up: RR=0.39 (95% CI [0.19; 0.81]), a significant difference favouring tinzaparin.

- Major bleeding (overall pop. from five studies): RR=0.62 (95% CI [0.34; 1.13], a non-significant difference.

- All bleeding (overall pop. from four studies): RR=0.71 (95% CI [0.54; 0.94], a significant difference favouring tinzaparin.

Meta-analysis by Laporte (2012)
The objective of this meta-analysis was to assess the therapeutic benefit of curative-dose tinzaparin in comparison with a VKA in the extended treatment of patients with venous thromboembolism. Five studies comparing tinzaparin to a VKA as extended treatment in patients with or without cancer were selected. The endpoints evaluated were the incidence of recurrent thromboembolism (RTE) and the mortality rate after 3-6 months and after 12 months, as well as net clinical benefit after 6 months and incidence of major bleeding after 6 months. The results in the subgroups of patients with cancer identified in three studies are given in the figure below.
According to this meta-analysis, in the subgroup of patients with cancer, no difference between tinzaparin and the control group was demonstrated after 3 to 6 months of treatment:
- in terms of reducing RTEs (RR=0.62, 95% CI [0.30 to 1.31])
- in terms of major bleeding (RR=0.82, 95% CI [0.34 to 2.01])
- in terms of net clinical benefit.

After 12 months of treatment: a difference favouring tinzaparin was demonstrated, with a 59% reduction in the relative risk of RTE (RR=0.41, 95% CI [0.21 to 0.79]).

These results are consistent with the results of the ANSM meta-analysis.

### 08.2 Adverse effects

#### 08.2.1 Clinical trial data

Main-LITE and LITE Cancer studies
After 12 months of treatment, the number of deaths was similar in both groups (n=47), as was the incidence of bleeding (2/3 of cases were minor). Thrombocytopenia was more common on tinzaparin (6% <100,000/mm³, 11% <150,000/mm³) than on the VKA (4% <100,000/mm³, 7% <150,000/mm³) after 3 months of treatment.

ROMERA Study
One out of 119 patients (0.8%) in the tinzaparin group had a major bleed versus three out of 122 patients (2.5%) in the control group (the presence or absence of cancer in these patients was not reported), p=0.6. Minor bleeding and thrombocytopenia were not reported. There were two deaths in each group related to cancer progression.
08.2.2 PSUR data for the period 1 March 2008 to 28 February 2012

Two hundred and five (205) cases corresponding to 433 adverse effects were extracted from the company’s database. Most cases were collected in France through spontaneous reports or via the health authorities.

The mean patient age was 62.8 years and the number of men and women was balanced. Sixty-five percent (65%) of patients had genitourinary, lung, gastrointestinal or breast cancer and 41.1% of patients for whom this information was recorded (65/158) had metastatic cancer. Information on cancer treatments was collected in 116 out of 205 cases (56.6%). More than half the patients were undergoing chemotherapy.

The mean duration of treatment with tinzaparin was about 3 months, but this data may be biased due to treatment being stopped prematurely because of adverse effects. However, 16.7% of patients were treated for more than 6 months.

More than 18% of the adverse effects reported occurred during extended tinzaparin treatment in cancer patients, particularly as a result of the events “off-label use” and “incorrect drug administration duration”; 25% were due to “bleeding” (108/433), 9.9% to “recurrent thromboembolism” (43/433), 8.7% to “local reactions” (38/433) and 7.1% to “thrombocytopenia” (31/433) including suspected heparin-induced thrombocytopenia (HIT). Out of 13 cases of suspected HIT, 6 cases (1.4%) were confirmed with a positive anti-PF4 ELISA test. Forty-four deaths were reported, of which 30.6% were due to cancer progression, 26.5% had no identified cause, 14.3% were due to bleeding and 14.3% were due to cardiorespiratory conditions.

NB. During this 4-year period, the peak in adverse effects reports in 2009, of 4.2 cases per 1000 patient-years, could relate to over-reporting following the publication of the French guidelines on extended treatment of cancer patients with LMWHs. Subsequent increases in sales volumes in 2010 (+21%) and 2011 (+18%) did not translate into higher numbers of reports; the notification rate was 2.9 cases per 1000 patient-years and 2.6 cases per 1000 patient-years in 2010 and 2011 respectively.

08.2.3 Data from all studies assessed by ANSM during the MA application (Report from the cardiology work group dated 15 April 2013)

These data are from 1868 patients, distributed by study as follows: Main-LITE (n=737), ROMERA (n=241), Home LITE (n=480), Daskalopoulos (n=108), Perez de Llano (n=102), Pautas (n=200), and bearing in mind that the number of patients lost to follow-up in these studies was low (<1%). In the overall population, according to the analysis conducted by the company, the incidence of bleeding was lower on tinzaparin (80/1035, 7.7%) than on VKAs (112/833, 13.4%), p<0.001. No difference in mortality was demonstrated between the two groups.

According to data from the meta-analysis (Laporte, 2012), in the overall population, there is no significant difference between the 2 groups in terms of major bleeding at the end of the treatment period, but a significant reduction of about 29% in the endpoint “all bleeding” was observed in the tinzaparin group compared with the VKA group after 12 months of follow-up. For patients with cancer, only the results of the LITE Cancer study are available. In this study, the incidence of major bleeding was the same in both groups (7/100). For the endpoint “all bleeding”, the incidence was 27/100 and 24/100 in the tinzaparin and VKA groups respectively.

The incidence of thrombocytopenia, defined as a platelet count <150,000/mm³, was higher on tinzaparin (38/1035, 3.7%) than on VKAs (12/833, 1.4%).

More cases of thrombocytopenia (<100 x 10⁹/l) were observed in the tinzaparin group than in the VKA group in the LITE (10 vs. 4) and Home-LITE (3 vs. 1) studies. Another study in 200 very elderly patients (Pautas, 2002: proportion of cancer patients unknown) also found 2 cases of HIT. According to the ANSM cardiology work group, a HIT incidence of about 1/100, as found in the application data, corresponds to a quite high risk, which justifies systematic (as opposed to light) monitoring of the patients in this vulnerable population.
08.2.4 SmPC data
The proprietary medicinal products INNOHEP 10,000 anti-Factor Xa IU/0.5 ml, 14,000 anti-Factor Xa IU/0.7 ml and 18,000 anti-Factor Xa IU/0.9 ml are restricted to curative treatment of DVT and pulmonary embolism and are administered as a single daily injection.

Risk of bleeding:
Serious haemorrhagic events have particularly been observed in:
- elderly patients, especially as a result of age-related renal deterioration
- patients with renal impairment
- patients weighing less than 40 kg
- cases of treatment continued beyond the recommended average duration of 10 days
- cases where the recommended procedures for treatment were not followed (particularly duration of treatment and weight-based dose adjustment for curative treatment)
- cases of concomitant use with medicines that increase the risk of bleeding.

Risk of heparin-induced thrombocytopenia (HIT):
When a patient treated with LMWH (at curative or preventive doses) presents with a thrombotic event, such as worsening of the thrombosis for which he or she is treated, phlebitis, pulmonary embolism, acute leg ischaemia, or even myocardial infarction or ischaemic cerebrovascular accident, heparin-induced thrombocytopenia (HIT) should routinely be considered and a platelet count should be performed urgently.

Routine laboratory monitoring is necessary in patients with a history of exposure to UFH or LMWH in the previous 6 months, given that the incidence of HIT is >0.1% or even >1%, and in patients with significant comorbidities, particularly cancer, given the potential seriousness of HIT in these patients.

Renal impairment, renal function:
Before starting treatment with LMWH, it is essential to assess renal function, and particularly in patients aged over 75 years, by calculating creatinine clearance (CrCl) using the Cockcroft formula. If severe renal impairment (CrCl about 30 ml/min) is found, prescription in the curative indications is contraindicated.

Other:
- Rare cases of skin necrosis at the injection site have been reported with heparin. Purpura or erythematous, infiltrating and painful plaques may precede these reactions. Treatment should be stopped immediately.
- As the product contains sodium metabisulfite, there is a risk of allergic reactions, including anaphylactic reactions and bronchospasm.

08.3 Usage/prescription data
The company has reported usage data for curative treatment with INNOHEP in patients with cancer. In fact, French professional guidelines (INCa 2008) and good practice guidelines (ANSM 2009) recommend this medicine is used in patients with cancer.

Prescription and/or sales data in France
Sales of INNOHEP (units and turnover) at the dosages (10,000 IU/0.5 ml, 14,000 IU/0.7 ml and 18,000 IU/0.9 ml) from 2008 to 2012 in community pharmacies and hospitals are indicated in the table below.
Table of sales of curative-dose INNOHEP in France (GERS [Group for the Production and Implementation of Statistics] data)

<table>
<thead>
<tr>
<th>Units</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community pharmacies</td>
<td>3,556,676</td>
<td>3,966,904</td>
<td>4,818,010</td>
<td>5,704,432</td>
<td>6,253,606</td>
</tr>
<tr>
<td>Hospitals</td>
<td>417,172</td>
<td>437,502</td>
<td>565,190</td>
<td>695,034</td>
<td>777,072</td>
</tr>
<tr>
<td>Total</td>
<td>3,973,848</td>
<td>4,404,406</td>
<td>5,383,200</td>
<td>6,399,466</td>
<td>7,030,678</td>
</tr>
</tbody>
</table>

- **Usage data and demographics of patients treated**

  According to prescription reports, 46% of patients treated are female. The mean age was 67.4 years. All the patients were treated at the dose of 175 IU/kg as a daily injection, and the mean duration of treatment was 48.2 days. (Data supplied by the company.)

### 08.4 Summary & discussion

For the extended treatment of symptomatic venous thromboembolism and the prevention of recurrence in patients with progressive cancer and/or who are undergoing chemotherapy, unlike dalteparin (FRAGMINE), there are no available studies specifically performed with tinzaparin.

Five studies are available, including two open-label pivotal trials, with a planned analysis in the subgroup of patients with cancer.

In the Main-LITE study, tinzaparin was compared with a treatment with UFH/warfarin. In the ROMERA study, it was compared with a treatment with tinzaparin/acenocoumarol. In the subgroup of patients with cancer in the Main-LITE study, there were fewer recurrent thromboembolisms (the primary endpoint) in the tinzaparin group than in the control group after 12 months of treatment only, and not after 3-6 months of treatment. No difference in major bleeding or mortality was demonstrated.

A meta-analysis of these two studies was performed by ANSM: there was no difference between the groups (INNOHEP and VKA) after 3 to 6 months of treatment in terms of recurrent venous thromboembolism. However, after 12 months of treatment, INNOHEP reduces the incidence of recurrent venous thromboembolism more than a VKA (RR=0.39 (95% CI [0.19-0.81])). The lack of any difference between the two arms after 3 to 6 months of treatment could be explained by a low power, as the effect size was low (200 patients in the Main-LITE study and 69 in the ROMERA study, i.e. 269 patients in total).

Another meta-analysis which looked at the results of five studies had similar results.

**The main points for discussion regarding the data are:**

1) **Critic of the methodology:**
   - The studies of tinzaparin have a low level of evidence: they are open-label studies based on subgroup analyses. The efficacy of extended tinzaparin treatment at preventing recurrent thromboembolism has not been established after 3-6 months in comparison with treatment with short-term UFH or LMWH followed by a VKA, but only after 12 months of treatment (see the meta-analyses). No difference in major bleeding or mortality was demonstrated between the two treatments.
   - The risk of thrombocytopenia on LMWH in comparison to VKAs should also be taken into account, although no difference in risk between tinzaparin and dalteparin is expected.

2) **Uncertain real life applicability:**
   - The number of patients with cancer included in these studies was low. Data in patients aged over 80 years and/or with a low body weight and/or with renal impairment, who are the most at risk of recurrent VTE and major bleeding, are limited (see the SmPC).
- The therapeutic benefit of tinzaparin (INNOHEP) has not been evaluated in comparison with dalteparin (FRAGMINE).

**09 THERAPEUTIC USE**

In the extended treatment of symptomatic venous thromboembolism and prevention of recurrence in patients who have progressive cancer and/or are undergoing chemotherapy, two classes of antithrombotics can be considered: LMWHs or oral vitamin K antagonist (VKA) anticoagulants. In cases of severe renal impairment, the standard antithrombotic treatment is still a short-term UFH followed by a VKA.

According to the AFSSAPS guidelines (2009), three LMWHs may be prescribed at the doses evaluated in the studies cited in the National Cancer Institute (INCa) guidelines:
- dalteparin 200 IU/kg once daily for one month, and then 150 IU/kg once daily (grade 1)
- tinzaparin 175 IU/kg once daily (grade 2)
- enoxaparin 150 IU/kg once daily (grade 2).

More recent international expert guidelines have confirmed this strategy.\(^{13,14}\)

If thrombocytopenia occurs during chemotherapy (platelets <50 \times 10^9/l), LMWH treatment should be stopped and resumed when the platelet count is above that level again (Professional consensus).

**Dosage of antithrombotic treatment in patients with cancer**

This varies depending on the LMWH:
- INNOHEP: 1 injection per day at a dose of 175 anti-Factor Xa IU/kg.
- FRAGMINE: 1 injection per day at a dose of 200 anti-Factor Xa IU/kg for the 1st month, then 150 anti-Factor Xa IU/kg in subsequent months. It should be noted that the multidose vial, which is useful for adjusting the dosage to weight especially in the first month of treatment, is not yet marketed in France (see SmPC).

**Duration of antithrombotic treatment in patients with cancer**

The duration of extended LMWH treatment should be 3-6 months depending on tolerance, cancer progression and changes to treatment.

If anticoagulant treatment needs to be continued after 6 months:
- If the cancer is still being treated and the patient is tolerating the heparin, the LMWH should be continued.
- If the cancer is no longer being treated, or if the patient can no longer tolerate LMWH, a switch to a VKA is recommended (professional consensus).

The choice between LMWH and VKA is contingent on the risk-benefit ratio (drug interactions, chemotherapy, invasive procedures, general health) and the acceptability of the treatment (professional consensus).

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Role of INNOHEP in the extended treatment of symptomatic venous thromboembolism and prevention of recurrence:

Only two of the three LMWHs have Marketing Authorisation for this indication in France. These are dalteparin (FRAGMINE) and now tinzaparin (INNOHEP), but on the basis of clinical data with a lower level of evidence (see expert recommendations). Dalteparin was more effective at preventing symptomatic recurrence of DVT/PE than treatment with VKAs according to the results of an open-label study (CLOT) in 676 patients with active cancer (75% of patients had metastases). A significant reduction of 52% at 6 months in the risk of recurrent thromboembolic event was observed favouring the dalteparin group (RR=0.48, 95% CI [0.30-0.77], p=0.0016). At 6 months, the cumulative probability of occurrence of an episode of major bleeding was 6.5% in the dalteparin group versus 4.9% in the VKA group. No difference in terms of mortality was observed between the two groups at 6 or 12 months.

Although tinzaparin (INNOHEP) has not been specifically evaluated in patients with cancer and it has a lower level of evidence for its efficacy in comparison with VKAs than dalteparin (FRAGMINE), it is a 1st-line alternative to VKAs in these patients.

The Marketing Authorisation for INNOHEP states that this product should be prescribed only in patients who have progressive cancer and/or are undergoing chemotherapy.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual benefit

In patients who have progressive cancer and/or are undergoing chemotherapy, symptomatic venous thromboembolism (VTE) can be life-threatening.

This product is intended as curative and preventive therapy for VTE.

The efficacy/adverse effects ratio for tinzaparin is high.

INNOHEP (tinzaparin) is a 1st-line medicine.

Public health benefit:

The public health burden of venous thromboembolism (VTE) is considerable. Cancer also represents a significant burden. However, the public health burden of patients concerned by the MA indication (patients with cancer who have had a VTE) is low, because of the more restricted numbers involved. Improving the management of cancer is a public health need which is an established priority. In addition, having access, as prophylaxis for venous thromboembolic events, to effective treatments that are well tolerated in terms of bleeding, especially in these patients at high risk of recurrence, is also a public health need.

Given the available data, INNOHEP (like FRAGMINE) is expected to have an impact on morbidity and mortality (reduction in VTE, facilitation of laboratory monitoring with a reduced risk of iatrogenesis and drug interactions) for this patient population and in its MA indication in comparison with vitamin K antagonist treatments. Nonetheless, tinzaparin has a less established efficacy record than dalteparin (FRAGMINE) and the applicability of the available data to actual clinical practice in France is uncertain (the pivotal trials were open-label, old and international without any patients included in France). Consequently, and in the absence of any data versus FRAGMINE, it is difficult to ascertain whether INNOHEP will be able to respond to the identified public health need. Therefore, the impact expected from the proprietary medicinal product INNOHEP on public health cannot be assessed in this indication.

There is an alternative to prescribing tinzaparin for extended treatment of venous thromboembolism and preventing recurrence in patients with cancer: dalteparin (FRAGMINE), or a VKA as a second-line treatment (as a follow-on treatment from a heparin).

Taking account of these points, the Committee considers that the actual benefit of INNOHEP is substantial in the Marketing Authorisation extension of indication.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the extension of indication “Extended treatment of symptomatic venous thromboembolism and prevention of its recurrence in patients who have progressive cancer and/or are undergoing chemotherapy” and at the dosages in the Marketing Authorisation.

Proposed reimbursement rate: 65%

010.2 Improvement in actual benefit (IAB)

INNOHEP does not provide any improvement in actual benefit (level V, non-existent) in the therapeutic strategy for extended treatment of symptomatic venous thromboembolism and prevention of recurrence in patients who have progressive cancer and/or are undergoing chemotherapy. There are no direct comparisons between LMWHs in this indication, in particular not between tinzaparin (INNOHEP) and dalteparin (FRAGMINE), and the therapeutic benefit of INNOHEP versus oral vitamin K antagonist anticoagulants has not been solidly established.

010.3 Target population

The target population is defined as adult patients with cancer who have had a symptomatic venous thromboembolic event (deep vein thrombosis or pulmonary embolism).

Estimate

Epidemiological data for VTE in France are limited.

The target population can be approximated using the following hypotheses:

- Using the EPI-GETBO study (Oger E, 2000\textsuperscript{16}). This study of the incidence of VTEE (DVT and PE) was carried out between April 1998 and March 1999 in the general population of Nord-Finistère. It can be used to estimate the incidence of VTEE according to age group and sex (see table below).

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>20-39</td>
<td>0.58</td>
<td>0.40</td>
</tr>
<tr>
<td>40-59</td>
<td>1.05</td>
<td>1.52</td>
</tr>
<tr>
<td>60-74</td>
<td>4.53</td>
<td>5.33</td>
</tr>
<tr>
<td>≥75</td>
<td>12.04</td>
<td>10.81</td>
</tr>
<tr>
<td>Total</td>
<td>2.03</td>
<td>1.52</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.83-2.26</td>
<td>1.34-1.72</td>
</tr>
</tbody>
</table>

- Using INSEE [National Institute for Statistics and Economic Studies] data from 1 January 2013 to estimate the distribution of the French population by age group and sex, which allows the ageing of the population between 1999 and 2012 to be taken into account. On 1 January 2013, the French population was thus estimated as 65,585,857 residents.

Table - Total population of France by age and sex on 1 January 2013 (source: INSEE)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of men</th>
<th>Number of women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19 years</td>
<td>8,268,829</td>
<td>7,906,688</td>
<td>16,175,517</td>
</tr>
<tr>
<td>20-39 years</td>
<td>8,031,710</td>
<td>8,144,758</td>
<td>16,176,468</td>
</tr>
<tr>
<td>40-59 years</td>
<td>8,655,332</td>
<td>8,975,763</td>
<td>17,631,095</td>
</tr>
<tr>
<td>60-74 years</td>
<td>4,589,621</td>
<td>5,098,812</td>
<td>9,688,433</td>
</tr>
<tr>
<td>≥75 years</td>
<td>2,223,138</td>
<td>3,691,206</td>
<td>5,914,344</td>
</tr>
<tr>
<td>Total</td>
<td>31,768,630</td>
<td>33,817,227</td>
<td>65,585,857</td>
</tr>
</tbody>
</table>

- Extrapolating the incidence of VTEE from the 1999 EPI-GETBO study to national level, taking into account the changes in age groups and distribution by gender in 2012. This gives an estimated number of 146,875 VTEEs in 2012.

Table – Estimated number of VTEEs in France in 2012

<table>
<thead>
<tr>
<th>Estimated VTEEs (DVT+PE)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>Male</td>
<td>Female</td>
<td>Total</td>
</tr>
<tr>
<td>0-19 years</td>
<td>165</td>
<td>158</td>
<td>324</td>
</tr>
<tr>
<td>20-39 years</td>
<td>3213</td>
<td>4724</td>
<td>7937</td>
</tr>
<tr>
<td>40-59 years</td>
<td>13,156</td>
<td>9,425</td>
<td>22,581</td>
</tr>
<tr>
<td>60-74 years</td>
<td>24,463</td>
<td>23,098</td>
<td>47,560</td>
</tr>
<tr>
<td>≥75 years</td>
<td>24,032</td>
<td>44,442</td>
<td>68,474</td>
</tr>
<tr>
<td>Total</td>
<td>65,029</td>
<td>81,846</td>
<td>146,875</td>
</tr>
</tbody>
</table>

- Hypothesis: between 20% and 25% of VTEEs are associated with a cancer.
  - Data from the scientific literature indicate that 20% of patients with VTE have cancer (Heit\textsuperscript{17,18}).
  - The following information is available from community pharmacy prescription reports:
    - The Pharmorama study conducted between 11 February and 13 March 2010 collected 510 prescriptions for LMWH as curative treatment from 185 pharmacies. In 22% of cases, treatment was started in the context of cancer.
    - The Pharmaccess study, which used a similar methodology, shows that 26% of patients on curative LMWH treatment have cancer.

Based on these hypotheses, the target population can be estimated as between 29,000 and 37,000 in 2012, bearing in mind that there are no data allowing the proportion of progressive cancers and/or cancers treated with chemotherapy in the overall population of cancer patients to be estimated.

These data also seem consistent with the estimated number of patients with cancer who received curative treatment with INNOHEP in 2012.


Note on PMSI data [Programme for Clinical Information Systems]: An analysis of PMSI data was carried out and considered the number of cancer patients with an accompanying diagnosis of thrombosis. The PMSI estimate of the number of cancer patients is reliable, but the assessment of accompanying diagnoses is not, tending to underestimate the number of VTEs associated with cancer, as these data are limited to hospitalised patients. The 2011 PMSI indicated about 21,000 cases of VTEE associated with cancer.

The number of patients with cancer who develop VTE was estimated at between 4000 and 12,000 per year during the assessment for FRAGMINE.

011  TRANSPARENCY COMMITTEE RECOMMENDATIONS

- Packaging
  Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.

NB:
The FRAGMINE multidose vial, not marketed in France, would be more suitable than the non-graduated pre-filled syringe for administering a weight-adjusted dose for patient weight intervals (kg) [40-47], [53-59], [66-70] and [79-85] for the initial treatment (1st month) and intervals [40-47], [53-63], [71-79], [88-94] and [106-113] for follow-up treatment (5 months) (see SPC).
The maximum dose difference between the dose calculated and the dose actually injected with the FRAGMINE pre-filled syringe is 1400 IU (an overdose) and -1400 (an underdose). This dose difference is 500 IU for INNOHEP, as the pre-filled syringes on the market have a graduation of 0.05 ml (1000 IU).
Therefore, with the packaging currently available on the French market, the LMWH dose can be more easily adjusted to the patient’s weight with INNOHEP than with FRAGMINE.