HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

30 June 2010

FRAGMINE 7,500 anti-Xa IU/0.3ml, solution for injection in pre-filled syringe
B/10 (CIP code: 397 430-0)

FRAGMINE 12,500 anti-Xa IU/0.5ml, solution for injection in pre-filled syringe
B/5 (CIP code: 397 432-3)

FRAGMINE 15,000 anti-Xa IU/0.6ml, solution for injection in pre-filled syringe
B/5 (CIP code: 397 434-6)

FRAGMINE 18,000 anti-Xa IU/0.72ml, solution for injection in pre-filled syringe
B/5 (CIP code: 397 435-2)

Applicant: PFIZER

dalteparin sodium
ATC code: B01AB04

List I

Date of the initial marketing authorisation (national procedure): 20 January 2010

Reason for request: Inclusion on list of products refundable by National Health Insurance and for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

Dalteparin sodium

1.2. Indication

"Patients with solid tumours: Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence."

NB: The 7,500 anti-Xa IU/0.75 mL dose of FRAGMINE is also indicated in "curative treatment of established deep-vein thrombosis (with early switch to oral anticoagulant) and in the treatment of unstable angina and the acute phase of non-Q wave myocardial infarction, administered concurrently with aspirin."

1.3. Dosage

"This presentation of FRAGMIN is suitable for adults. Regular monitoring of platelet count throughout treatment is imperative, because of the risk of heparin-induced thrombocytopenia (HIT).

Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence during the 1st month following the event

Frequency of administration: 1 injection per day

Dose to administer: the dose per injection is 200 anti-Xa IU/kg. The total daily dose should not exceed 18,000 IU.
The bottle should be used with syringes of a maximum volume of 1 mL, and graduated in 0.01 mL increments. The table below gives examples of volumes to be administered per day, depending on the patient's body weight. Pre-filled syringes can also be used, if the patient's weight corresponds to the dose contained in the syringe.

Body weight (kg)	Volume (mL) of dalteparin recommended per injection Multidose bottle of 25,000 IU /mL	Pre-filled syringe corresponding to 25 000 IU /mL
40-42	0.32	
43-47	0.36	
48-52	0.40	Pre-filled syringe 10,000
53-56	0.44	
57-59	0.47	
60-64	0.50	Pre-filled syringe 12,500
65-68	0.53	
69-72	0.56	
73-77	0.60	Pre-filled syringe 15,000
78-82	0.64	
83-87	0.68	
≥88	0.72*	Pre-filled syringe 18,000*

*This maximum dose of 0.72mL (18,000 IU) has been used in patients weighing up to 132 kg, in the CLOT study.

Prevention of recurrence of venous thromboembolism in the 2-6 months following the event

Frequency of administration: 1 injection per day

Dose to administer: the dose per injection is 150 anti-Xa IU/kg. The total daily dose should not exceed 18,000 IU.

Pre-filled syringes should be used with the aid of the table below.

Body weight (kg)	**Recommended dalteparin dose (IU /day) Pre-filled syringe 25,000 IU /mL**
40-56	7,500 IU in 0.3 mL
57-68	10,000 IU in 0.4 mL
69-82	12,500 IU in 0.5 mL
83-98	15,000 IU in 0.6 mL
>99	18,000 IU in 0.72 mL

Recommended duration of treatment: 6 months. Relevance of continuing treatment beyond this period will be evaluated according to individual risk/benefit ratio, taking into account particularly the progression of cancer. If anticoagulant treatment needs to be continued, as no data are available for dalteparin beyond 6 months of treatment, a switch to oral anticoagulant treatment should be planned, under the usual prescription conditions.

Renal impairment

- Creatinine clearance ≤ 30 ml/min using the Cockcroft formula: as there are no data, this medicinal product is contraindicated except during dialysis.
- Creatinine clearance between 30 and 60 ml/min: the dose of Fragmin should be adjusted based on anti-Factor Xa activity.

Method of Administration: FRAGMINE should be injected subcutaneously (not IM) once daily: 1 mL of FRAGMINE 12,500 anti-Xa IU/0.5 mL corresponds to approximately 25,000 anti-Xa IU of dalteparin sodium.

Regular monitoring of the weight of cancer patients is necessary, so that treatment can be adjusted to the most recent weight.

Subcutaneous injection technique

- Do not purge the air bubble from the pre-filled syringes.
- Subcutaneous injection of dalteparin should preferably be injected, when the patient is supine, into the abdominal subcutaneous tissue anterolaterally or posterolaterally, or into the right side and left side or anterior surface of the thigh if there is local intolerance.
- The total length of the needle should be introduced vertically, not at an angle, into the thick part of a skin fold, produced by squeezing the skin between thumb and forefinger. The skin fold should be held throughout the injection."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

B : Blood and blood forming organs
B01 : Antithrombotic agents
B01A : Antithrombotic agents
B01AEB : Heparin group
B01AB04 : Dalteparin

2.2. Medicines in the same therapeutic category

None.

2.3. Medicines with a similar therapeutic aim

Oral anticoagulants (vitamin K antagonists).

According to good clinical practice guidelines (AFSSAPS, November 2009), three types of LMWH are recommended for use in adult patients with progressive cancers: dalteparin (FRAGMINE), and, with lower quality of evidence (and without marketing authorisation in this indication), tinzaparin (INNOHEP) and enoxaparin (LOVENOX).

Products based on unfractionated heparin (UFH: CALCIPARIN and heparin sodium CHOAY) or low molecular weight heparin (LMWH) are indicated for curative short-term treatment of deep vein thrombosis and pulmonary embolism. They are not indicated for extended treatment (secondary prevention), and early switch to an oral anticoagulant is recommended (see the SPCs for these products). The same is true for fondaparinux (ARIXTRA).

See Appendix 1 for indications for comparator medicinal products.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy data from the CLOT study

The objective of the CLOT study was to compare the efficacy and tolerance (at 6 months) of anticoagulant treatment with dalteparin (FRAGMINE) with those of an oral anticoagulant (VKA) after an initial symptomatic venous thromboembolic event in patients with cancer.

This was an open-label, prospective, randomised comparative two-arm study versus oral anticoagulant involving subjects in 8 countries (none were enrolled in France).

Endpoints
- The primary endpoint was time to the first recurrence of symptomatic thromboembolism within 6 months, measured using ultrasound or venous Doppler scan for DVT, and pulmonary angiography, scintigraphy or helical CT scan for pulmonary embolism.
- The incidence of major and minor bleeding, and mortality at 6 and 12 months, were secondary endpoints.

The initial calculation of the sample size was based on an estimated risk of recurrent thrombosis of 20 percent at six months among patients treated with oral anticoagulant therapy. In order to detect a 50 percent reduction in risk with a power of 0.85 and a significance level of 0.05, it was determined that 70 primary efficacy outcome events were required. In order to adjust for the loss to follow-up from early death, the sample size was increased by 20 percent. On reassessment of the sample size specified in the protocol the targeted enrolment was raised by an additional 90 patients. Accordingly, it was determined that 676 patients would be required.

An analysis of efficacy end points was performed according to the intention-to-treat principle and included all randomized patients who had a confirmed, qualifying thrombotic event and active cancer. The primary analysis of efficacy was based on the time from randomization to the first recurrent thromboembolic event. The risk of recurrence over time was estimated according to the Kaplan–Meier method, and the treatment groups were compared using the two-sided log-rank test. A Cox proportional-hazards regression model was used to examine the influence of potentially prognostic base-line factors (e.g., age, ECOG status, type of qualifying thrombotic event, and presence or absence of metastases) on the risk of recurrent thromboembolism. Interactions between treatment group and covariates were assessed in the model. Death from all causes was also calculated according to the Kaplan–Meier method and compared using the two-sided log-rank test. Patients who received at least one dose of the study drug were included in the tolerance analyses. The proportions of patients in each group who had a major bleeding event after the first dose and up to 48 hours after the permanent discontinuation of the study drug were compared using a two-sided Fisher's exact test.

Treatments given
All patients initially received 200 IU/kg once daily of subcutaneous dalteparin. Subsequently, those who were randomised into the oral anticoagulant group continued with dalteparin treatment for at least 5 days, during which time warfarin treatment (or acenocoumarol in centres in Spain and the Netherlands) was begun, providing an overlap period during which both treatments were given. Dalteparin was discontinued after a minimum of five days and once the INR had remained above 2.0 for two consecutive days. Oral treatment was continued for 6 months. Patients randomised to the dalteparin arm initially continued treatment at the same dosage level for 1 month, and then the dosage was reduced to 150 IU/kg once daily until the 6th month.

Among the exclusion criteria were: weight of 40 kg or less, Eastern Cooperative Oncology Group (ECOG) performance status score of 3 or 4, active or serious bleeding within the

previous two weeks, and creatinine level at least three times the upper limit of the normal range.

Population characteristics

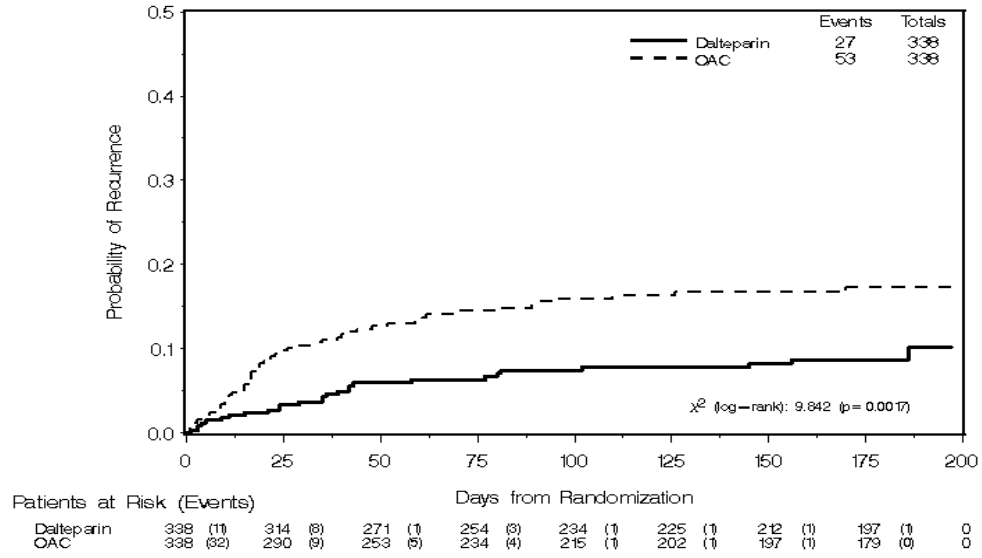
Between May 1999 and October 2002, 676 patients were randomised. At inclusion, 90% of the patients had solid tumours and 67% had metastatic disease. The most commonly diagnosed cancers were gastro-intestinal and pancreatic (23.7%), genitourinary (prostate, testicular, ovarian, cervical, endometrial and bladder) (21.5%), breast (16.0%), lung (13.3%). 10.4% had a blood cancer. 75.1% had metastases.

The mean duration of study treatment was 125 days in the dalteparin group and 115 days in the oral-anticoagulant group. For patients who did not have an outcome event throughout the study period, the mean duration of study treatment was 170 days in both groups. In the oral-anticoagulant group, the mean (±SD) INR was 2.5±0.75.

	Dalteparin N = 338		Oral anticoagulant N = 338	
	n	%	n	%
Type of VTE				
DVT	235	69.5	230	68.0
PE	64	18.9	65	19.2
PE and DVT	39	11.5	43	12.7
History of VTE				
None	299	88.5	302	89.3
DVT	21	6.2	21	6.2
PE	10	3.0	7	2.1
PE and DVT	4	1.2	4	1.2
No data	4	1.2	4	1.2

Efficacy results

Time to occurrence of the first symptomatic thromboembolism recurrence within 6 months - Kaplan-Meier curve (ITT population)



Recurrence of thromboembolism (ITT population)

	Dalteparin N = 338 n	Oral anticoagulant N = 338 n	p-value
DVT/PE	27 (8.8%)	53 (17.4%)	0.0017
DVT	14 (4.1%)	37 (10.9%)	
Non-fatal PE	8 (2.4%)	9 (2.7%)	
Fatal PE	5 (1.5%)	7 (2.1%)	

Recurrence of venous thromboembolic event (VTEE) was observed in 27 of the 338 patients (8.0%) in the dalteparin group and in 53 of the 338 patients (15.7%) in the oral anticoagulant group, meaning that dalteparin use gave a 52% reduction in the risk of initial recurrence of symptomatic thromboembolism (DVT and/or PE) (RR 0.48; 95% CI [0.30; 0.77]; p=0.0016).
According to these results, on average 13 patients need to be treated with FRAGMINE (dalteparin) in order to prevent one VTEE (NNT = 13).

3.2 Adverse effects

Data from the CLOT study: 19 patients in the dalteparin group (5.6%) experienced 22 instances of major bleeding; 12 in the oral anticoagulant group (3.6%) experienced 13 instances of major bleeding (p=0.27).

The numbers of deaths in the two groups were similar at 6 months (38.8% for dalteparin and 40.9% for oral anticoagulant) and at 12 months (56.2% vs 57.9%).
Nearly 90% of the deaths were due to progressive cancer.

3.3. Other clinical data:

Excerpt from the AFSSAPS Good Practice Guidelines (November 2009):

Table 74. Meta-analysis of four trials comparing LMWH and VKA in extended treatment of VTE in cancer patients

Randomised trial	LMWH versus VKA	Thromboembolic recurrence at 3 months		Major haemorrhage at 3 months		Hazard ratio for mortality
		LMWH	VKA	LMWH	VKA	
Meyer, CANTHANOX [347]	N = 146	*2/67* 3.0%	*3/71* 4.2%	*5/71* 7.0%	*12/75* 16%	0.72 [0.41;1.26]
Lee, CLOT [348]	N = 672	*27/336* 8.0%	*53/336* 15.8%	*19/338* 5.6%	*12/338* 3.5%	0.93 [0.73;1.18]
Deitcher, ONCENOX [349]	N = 102	*4/61* 6.5%	*3/30* 10%	*6/67* 8/9%	*1/34* 2.9%	1.19 [0.56;2.51]
Hull, LITE [350]	N = 200	*6/100* 6%	*10/100* 10%	*7/100* 7%	*7/100* 7%	0.97 [0.65;1.46]
Total	*N = 1120*	*RR = 0.54 [0.37 ; 0.79] RRR=46%, P < 0.001 P_{Het} = 0.96*		*RR = 1.08 [0.67 ; 1.76] ARR=8%, P = 0.74 P_{Het} = 0.15*		*HR = 0.92 [0.77; 1.11] RRR = 8%, P = 0.4 P_{Het} = 0.78*

* Results at 6 months

It should be noted that target INR levels were only reached 46% of the time in this study, according to a linear interpolation analysis over time using the published data.

3.5 Conclusion

The randomised, open-label CLOT study compared dalteparin and oral anticoagulant (the current gold standard treatments) as extended anticoagulant treatments in 676 patients with active cancer who had experienced one acute symptomatic thromboembolic event (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]). Patients were randomised to receive either dalteparin 200 IU/kg once daily subcutaneously (maximum 18,000 IU/day) for 1 month, and then 150 IU/kg/day from the 2nd to 6th months inclusive, or oral anticoagulant for 6 months (with target INR of between 2 and 3) following on from dalteparin treatment at a dose of 200 IU/kg once daily (subcutaneously), (maximum 18,000 IU /day) for 5 to 7 days. The most commonly diagnosed cancers were gastro-intestinal and pancreatic, genitourinary, breast and lung. 75.1% of patients had metastases. The thromboembolic event that led to inclusion was isolated DVT in almost 70% of cases, and PE with or without DVT in 30% of cases.

A total of 27 of 338 patients (8.0%) in the dalteparin group and 53 of 338 patients (15.7%) in the oral anticoagulant group experienced a further thromboembolic event (DVT or PE). The dalteparin group was observed to have a significant 52% reduction in risk at 6 months of recurrence of thromboembolic event (RR=0.48, 95% CI [0.30-0.77], p=0.0016). In the dalteparin group, 19 patients (5.6%) had at least one episode of major bleeding, compared with 12 patients in the oral anticoagulant group (3.6%). 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 oral anticoagulant group. No significant difference in terms of death rates was observed between the two groups at 6 or 12 months.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

In cancer patients, the risk of recurrence of venous thromboembolism is around three times higher during and after discontinuation of oral anticoagulant treatment. In patients with cancer, the frequency of recurrence is 10-20% in the year following cessation of anticoagulant treatment, and is particularly high in patients with metastatic disease or who are receiving chemotherapy. Patients with some forms of cancer, such as adenocarcinoma, could be at higher risk of recurrence. In such conditions, the presence of progressive cancer or cancer that is currently being treated must be considered to be a significant continuing risk factor.

FRAGMINE is a first-line medicinal product for curative and preventive use.

Public health benefit

The public health burden of venous thromboembolic disease (VTED) is considerable. Cancer also represents a significant burden. However, the public health burden of patients affected by the indication given in the marketing authorisation (patients with cancer who have had a VTE) is low, because of the more restricted numbers involved.

Improved management of cancer is a public health need that falls within the scope of identified priorities [Public health law 2004[1], Cancer Plan, GTNDO[2]]. Having access to effective and safe prophylactic treatments for bleeding, particularly for subjects who are at significant risk, is also a public health need.

Given the available data (particularly the results of the CLOT study and AFSSAPS-INCA guidelines), FRAGMINE is expected to have an impact on morbidity and mortality [reduction in VTE, facilitation of laboratory monitoring with a reduced risk of hospital-acquired conditions and drug interactions] for this patient population and in comparison with existing treatments. This benefit would be moderate at best.

However, it is difficult to be certain that these data will be representative of the actual treatment situation in France, as the data come from just one clinical study, which is old, international and was not carried out in France.

It is reasonable, however, to assume that FRAGMINE will be able to provide a partial response to the identified public health need.

A benefit public health is therefore expected for FRAGMINE in this indication. This benefit is low.

The efficacy/adverse effects ratio for FRAGMINE is high.
Alternative anticoagulant treatments are available: oral anticoagulant therapies.

The actual benefit provided by FRAGMINE in the indication: "Patients with solid tumours: Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence" is substantial.

4.2. Improvement in actual benefit (IAB)

FRAGMINE provides a minor improvement in actual benefit (IAB IV) in comparison with oral anticoagulants in the extended treatment of symptomatic venous thromboembolic disease and in the prevention of recurrence of such events in patients with progressive cancer.

4.3. Therapeutic use of FRAGMINE

The objective of therapeutic management of symptomatic VTE is to prevent the death of the patient (particularly in cases of PE), embolism migration, thrombus extension, early and late

[1] French public health law 2004 - no. 2004-806 dated 9 August 2004 [DREES indicators report - July 2005]
[2] GTNDO: National Technical Group for Defining Objectives (DGS-2003)

recurrence of DVT and PE, and development of post-thrombotic syndrome and chronic pulmonary arterial hypertension.

According to recent French good practice guidelines[3,4], treatment of venous thromboembolic disease using oral anticoagulants in patients with progressive cancers is less effective and less safe than in patients without cancer.

Extended treatment with a low molecular weight heparin provides a significant and major reduction in the risk of recurrence, without increasing the risk of haemorrhage. These results were obtained using LMWH doses that were slightly lower than the usual curative doses, except for tinzaparin.

For confirmed VTED arising in a patient with cancer, switching to a LMWH after initial treatment is recommended (Grade A).
AFSSAPS recommends the use of dosage levels that were established in the studies cited in the INCa SOR (Standards, Options, Guidelines) document:

- dalteparin 200 IU/kg once daily for one month, and then 150 IU/kg once daily;
- tinzaparin 175 IU/kg once daily;
- enoxaparin 150 IU/kg once daily.

In cases of thrombocytopenia that arise during chemotherapy (platelets < 50 x 10^9/L), it is recommended that LMWH treatment be discontinued, and that it be restarted once the platelet level is restored to above this level (professional consensus).

Duration of antithrombotic treatment in patients with cancer

The duration of LMWH treatment should be 3-6 months, depending on toleration of the therapy, cancer progression and changes to treatment. If the patient is still receiving cancer treatment and is able to tolerate the heparin treatment after 6 months, it is recommended that LMWH treatment be continued after this point. If the cancer is no longer being treated, or if the patient can no longer tolerate LMWH, a switch to oral anticoagulant therapy is recommended (professional consensus).

The choice between LMWH and oral anticoagulant is contingent on the risk-benefit ratio (drug interactions, chemotherapy, invasive procedures, patient's general condition) and the acceptability of the treatment (professional consensus).

Initial outpatient management of proximal DVT and PE
The recommendation is to admit (professional consensus) patients with proximal DVT and symptoms of severe obstruction or signs that DVT is in the iliocaval region and patients with severe renal insufficiency (creatinine clearance < 30 mL/min), those who require anticoagulant treatment and who have a condition that entails a risk of bleeding, with pulmonary embolism, those who are in shock and are haemodynamically unstable, or those for whom geographic and medical constraints mean that optimal management cannot be provided at home.

In other cases, patients with proximal DVT can be treated with LMWH on an outpatient basis or following a short admission, having first assessed the risks of recurrence of thromboembolism and bleeding (Grade A). Patients with stable pulmonary embolism can be treated on an outpatient basis, if these precautions are observed (Grade C).

If outpatient treatment of VTED is being considered, the following guidelines should be borne in mind (Grade A):
- a definite diagnosis of thromboembolic disease should be obtained;
- remember that it is essential to plan for a period of education for patients about their drug and non-drug treatment, as was the case for all studies in which outpatient treatment of proximal DVT was assessed;

3 Good practice guidelines. Prevention and treatment of venous thromboembolic disease in medicine. French Healthcare Product Safety Agency (AFSSAPS), November 2009.

4 Curative treatment of venous thromboembolic disease in patients with cancer. Prevention and treatment of catheter-induced venous thrombosis in patients with cancer. Institut national du cancer [French National Cancer Institute] guidelines, April 2008.

- monitoring of anticoagulant treatment should be initiated and organised in co-operation with the treating physician and nurse;
- risk factors for recurrence of thromboembolism and bleeding should be assessed, and psychosocial factors that might limit management should be considered.

4.4. Target Population

Qualitative definition: target population is defined as adult patients with cancer who have experienced one symptomatic venous thromboembolic event (deep vein thrombosis or pulmonary embolism).

Method for estimating target population size
The annual incidence of VTED in the general population is estimated at between 1 and 2 per 1000[5,6]. According to an article by Heit JA et al., the risk of deep-vein thrombosis in patients with cancer is 4 times higher than in the general population, and 6 times higher in patients on chemotherapy[7]. The annual incidence of VTED in patients with cancer can therefore be estimated at between 0.4 and 1.2%.
According to PMSI-MCO (French electronic patient records) data, 951,366 patients were admitted to hospital with a diagnosis of cancer in 2007[8].
We can thus calculate that between 4,000 and 12,000 patients with cancer will be affected by VTED each year.

4.5. Conclusion

The Transparency Committee recommends for inclusion of FRAGMINE on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication "Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence in patients with solid tumours."

NB: The products involved are:

FRAGMINE 7,500 anti-Xa IU/0.3ml, solution for injection in pre-filled syringe
- Box of 10 syringes (CIP 397 430-0)

FRAGMINE 12,500 anti-Xa IU/0.5ml, solution for injection in pre-filled syringe
- Box of 5 syringes (CIP 397 432-3)

FRAGMINE 15,000 anti-Xa IU/0.6ml, solution for injection in pre-filled syringe
- Box of 5 syringes (CIP 397 434-6)

FRAGMINE 18,000 anti-Xa IU/0.72ml, solution for injection in pre-filled syringe
- Box of 5 syringes (CIP 397 435-2)

Packaging: suitable for the conditions of prescription.

Reimbursement rate: 65%.

[5] Oger E. Incidence of venous thromboembolism: a community-based study in Western France. Thromb Haemost 2000; 83: 657-60
[6] Silverstein MA et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998;158(6): 585-93
[7] Heit JA and al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case control study. Arch Intern Med 2000;160:809-815
[8] INCA 2009. Cancer in France, 2009

APPENDIX 1: COMPARATOR MEDICINAL PRODUCTS, from SPCs

	INN	**INDICATIONS**	**DOSAGE**
Oral anti-coagulant	Acenocoumarol Warfarin Fluindione	Treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrence of these conditions, as a follow-on treatment from heparin.	Because of significant variability between individuals, the dosage of oral anticoagulants is specific to the individual. It should be adjusted depending on INR levels.
UFH	Heparin calcium	Curative treatment of established DVT and PE, in the acute phase.	At the same time as the first subcutaneous injection a bolus of 50-100 IU/kg of IV heparin may be administered intravenously, in order to achieve effective blood heparin levels from the start of treatment. The initial dose is 500 IU/kg per 24 hours subcutaneously, divided into two (one every 12 hours) or three injections (every 8 hours) per day, depending on the volume to be injected. Subcutaneous injection of more than 0.6 mL of heparin can reduce the heparin absorption rate. The heparin dose will subsequently be adapted in line with the laboratory test results. Switch from heparin to oral anticoagulants (VKA): - When this is possible, oral anticoagulants should be introduced between the 1st and 3rd days of treatment, ensuring that the total duration of heparin therapy does not exceed 7-10 days. Because of the latency period that elapses before an oral anticoagulant reaches its full effect, heparin treatment should not be discontinued until INR has been within the target range for 2 consecutive days. The target range will vary, depending on the condition being treated. During this period, APTT should be particularly closely monitored, in order to reduce the risk of bleeding.
	Heparin sodium	Curative treatment of established DVT and PE, in the acute phase.	The initial dose is 20 IU/kg/hour intravenously, to be adjusted subsequently depending on APTT.
LMWH	Enoxaparin	Solution for injection containing 6,000 IU anti-Xa/0.6 mL, 8,000 anti-Xa IU/0.8 mL, 10,000 IU anti-Xa/1 mL, 30,000 IU anti-Xa/3 mL: Curative treatment of established deep vein thrombosis with or without pulmonary embolism with no signs of clinical seriousness, except for pulmonary embolisms that are likely to have resulted from thrombolytic or surgical treatment.	2 injections/day of 100 anti-Xa IU/kg, given 12 hours apart (subcutaneously). The dose of LMWH adjusted for body weight has not been assessed for patients weighing > 100 kg or < 40 kg. LMWH 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. Duration of treatment for DVT: LMWH treatment should be switched rapidly to oral anticoagulant treatment, unless the latter is contraindicated. The duration of LMWH treatment should not be greater than 10 days, including any time required to stabilise oral anticoagulant treatment, unless there are difficulties in stabilising oral treatment. Oral anticoagulant treatment must therefore be initiated as early as possible.
	Dalteparin	Patients with solid tumours: Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence.	- Month 1 following event Frequency of administration: 1 injection per day Dose to administer: the dose per injection is 200 anti-Xa IU/kg. The total daily dose should not exceed 18,000 IU. - Prevention of recurrence of venous thromboembolism in the 2-6 months following the event Frequency of administration: 1 injection per day Dose to administer: the dose per injection is 150 anti-Xa IU/kg. The total daily dose should not exceed 18,000 IU.
	Tinzaparin	- Curative treatment of established deep vein thrombosis. - Curative treatment of pulmonary embolism with no clinical signs of seriousness, in the absence of pre-existing cardiac or	1 injection of 175 IU/kg (subcutaneously). The dose of LMWH adjusted for body weight has not been assessed for patients weighing > 100 kg or < 40 kg. LMWH 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.

		pulmonary disease and excluding emboli that are likely to have resulted from thrombolytic or surgical treatment. If there are signs of haemodynamic instability, unfractionated heparin and, in some cases, thrombolysis or surgical embolectomy should be used in preference. This treatment is not indicated for patients who have undergone recent surgery.	- Duration of treatment for DVT: LMWH treatment should be switched rapidly to oral anticoagulant treatment, unless the latter is contraindicated. The duration of treatment should not exceed 10 days, including any period required to achieve stability on oral anticoagulant treatment, unless there are difficulties in achieving stability. Oral anticoagulant treatment must therefore be initiated as early as possible. - Duration of treatment for non-serious pulmonary embolism: mean duration of treatment is 7 days.
	Nadroparin	Curative treatment of established DVT.	FRAXIPARIN: 2 injections/day of 85 anti-Xa IU/kg (subcutaneously), given 12 hours apart. FRAXODI: 1 injection of 171 anti-Xa IU/kg. The dose of LMWH adjusted for body weight has not been assessed for patients weighing > 100 kg or < 40 kg. LMWH 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. - Duration of treatment for DVT: LMWH treatment should be switched rapidly to oral anticoagulant treatment, unless the latter is contraindicated. The duration of LMWH treatment should not be greater than 10 days, including any time required to stabilise oral anticoagulant treatment, unless there are difficulties in stabilising oral treatment. Oral anticoagulant treatment must therefore be initiated as early as possible.
Anti-thrombotic	Fondaparinux	Treatment of acute deep vein thrombosis (DVT) and acute pulmonary embolism (PE), except in patients who are haemodynamically unstable and those who require thrombolysis or pulmonary embolectomy.	The recommended dose of fondaparinux is 1 injection/day of 7.5 mg (subcutaneously) for patients weighing between 50 and 100 kg. For patients weighing less than 50 kg, the recommended dose is 5 mg. For patients weighing over 100 kg, the recommended dose is 10 mg.