ARIXTRA 5 mg/0.4 ml, solution for injection in pre-filled syringe
B/2 (CIP: 34009 365 647 4 9)
B/7 (CIP: 34009 365 648 0 0)
B/10 (CIP: 34009 365 649 7 8)

ARIXTRA 7.5 mg/0.6 ml, solution for injection in pre-filled syringe
B/2 (CIP: 34009 365 650 5 0)
B/7 (CIP: 34009 365 651 1 1)
B/10 (CIP: 34009 365 652 8 9)

ARIXTRA 10 mg/0.8 ml, solution for injection in pre-filled syringe
B/2 (CIP: 34009 365 653 4 0)
B/7 (CIP: 34009 365 654 0 1)
B/10 (CIP: 34009 365 655 7 9)

Applicant: GlaxoSmithKline

<table>
<thead>
<tr>
<th>INN</th>
<th>fondaparinux sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (2012)</td>
<td>B01AX05 (Antithrombotic agent). Selective indirect factor Xa inhibitor</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Re-assessment of the Actual Benefit at the request of the Committee (pursuant to Article R 163-21 of the French Social Security Code) following questions raised by the Afssaps (French Health Products Safety Agency) on 28 December 2011</td>
</tr>
<tr>
<td>Lists concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)</td>
</tr>
<tr>
<td>Indications concerned</td>
<td>“Treatment of acute deep vein thrombosis (DVT) and acute pulmonary embolism (PE), except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy”</td>
</tr>
<tr>
<td>Actual Benefit (AB)</td>
<td>Substantial</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Improvement in Actual Benefit (IAB)</td>
<td>The Committee considers that ARIXTRA (5 mg/0.4 ml; 7.5 mg/0.6 ml and 10 mg/0.8 ml) no longer provides an improvement in actual benefit (IAB V, non-existent) in the treatment of acute deep vein thrombosis (DVT) and acute pulmonary embolism (PE).</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>First-line therapy in the initial treatment of acute DVT and acute PE.</td>
</tr>
<tr>
<td>Recommendations</td>
<td></td>
</tr>
</tbody>
</table>

HAS - Medical, Economic and Public Health Assessment Division
**01 ADMINISTRATIVE AND REGULATORY INFORMATION**

<table>
<thead>
<tr>
<th>Marketing Authorisation (procedure)</th>
<th>Initial date (European centralised procedure): 12 November 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing and dispensing conditions / special status</td>
<td>List I</td>
</tr>
<tr>
<td></td>
<td>ARIXTRA has a European Risk Management Plan (RMP) and, since January 2007, has had national pharmacovigilance monitoring.</td>
</tr>
</tbody>
</table>

**02 BACKGROUND**

In its 28 December 2011 letter to the HAS alerting them to the serious haemorrhagic accidents observed with ARIXTRA 2.5 mg in at-risk patients (the elderly, patients with low body weight or with renal impairment), the Afssaps questioned HAS about the possibility of re-assessing the 1.5 mg dose, suggesting that it may be of benefit to these patients. The Committee decided to re-assess the actual benefit of ARIXTRA (all dosages with a Marketing Authorisation) in all of its indications.

In this Opinion, only the indications for curative treatment of acute venous thromboembolic events will be re-assessed.

**03 INDICATIONS**

“Treatment of acute deep vein thrombosis (DVT) and acute pulmonary embolism (PE), except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy”

**04 DOSAGE**

“The recommended dose of fondaparinux is 7.5 mg (patients with body weight ≥ 50 kg, ≤ 100 kg) once daily administered by subcutaneous injection. For patients with body weight < 50 kg, the recommended dose is 5 mg. For patients with body weight > 100 kg, the recommended dose is 10 mg.

Treatment should be continued for at least 5 days and until adequate oral anticoagulation is established (International Normalised Ratio 2 to 3). Concomitant oral anticoagulation treatment should be initiated as soon as possible and usually within 72 hours. The average duration of administration in clinical trials was 7 days and the clinical experience with treatment beyond 10 days is limited.

**Special populations:**

**Elderly patients:** No dosing adjustment is necessary.
In patients ≥ 75 years, fondaparinux should be used with care, as renal function decreases with age.

**Renal impairment:** Fondaparinux should be used with caution in patients with moderate renal impairment (see section 4.4). There is no experience in the subgroup of patients with both high...
body weight (>100 kg) and moderate renal impairment (creatinine clearance 30-50 ml/min). In this subgroup, after an initial 10 mg daily dose, a reduction of the daily dose to 7.5 mg may be considered, based on pharmacokinetic modelling. Fondaparinux should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min).

**Hepatic impairment:** No dosing adjustment is necessary in patients with either mild or moderate hepatic impairment. In patients with severe hepatic impairment, fondaparinux should be used with care as this patient group has not been studied.”
**CLINICALLY RELEVANT COMPARATORS**

**05.1 Medicinal products**

**Treatment for acute deep vein thrombosis (DVT):**

Medicinal products from the category of indirect thrombin and factor Xa inhibitors, supplied as oral anticoagulants:

- Low Molecular Weight Heparins (LMWHs) administered via subcutaneous injection:

<table>
<thead>
<tr>
<th>Proprietary medicinal products</th>
<th>INN</th>
<th>AB (opinion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRAGMIN</td>
<td>Dalteparin sodium</td>
<td>Substantial [TC 5227 - 19/12/07]</td>
</tr>
<tr>
<td>FRAXIPARIN</td>
<td>Nadroparin calcium</td>
<td>Substantial [TC 2812 - 18/10/06]</td>
</tr>
<tr>
<td>FRAXODI</td>
<td>Nadroparin calcium</td>
<td>Substantial [TC 2812 - 18/10/06]</td>
</tr>
<tr>
<td>INNOHEP</td>
<td>Tinzaparin sodium</td>
<td>Substantial [TC 6965 - 16/12/09]</td>
</tr>
<tr>
<td>LOVENOX</td>
<td>Enoxaparin sodium</td>
<td>Substantial [TC 7047 - 02/12/09]</td>
</tr>
</tbody>
</table>

- Unfractionated Heparins (UFHs)

<table>
<thead>
<tr>
<th>Proprietary medicinal products</th>
<th>INN</th>
<th>AB (opinion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALCIPARIN</td>
<td>Heparin calcium</td>
<td>Substantial [TC 4857 - 23/01/08]</td>
</tr>
<tr>
<td>HEPARIN CHOAY</td>
<td>Heparin sodium</td>
<td>Substantial [TC 4860 - 03/09/08]</td>
</tr>
</tbody>
</table>

Direct factor Xa inhibitor medicinal products:

- Rivaroxaban: XARELTO 15 and 20 mg, film-coated tablets (Substantial AB, IAB V in the treatment of DVT, see Committee Opinion of 14 March 2012)

**Vitamin K antagonists (as follow-up therapy only):**

- Acenocoumarol: SINTROM 4 mg and MINISINTROM 1 mg
- Fluindione: PREVISCAN 20 mg
- Warfarin: COUMADIN 2 mg and 5 mg.

Their Actual Benefit is substantial.

**Treatment of acute pulmonary embolism:**

As with DVT, medicinal products from the category of indirect thrombin and factor Xa inhibitors, supplied as oral anticoagulants:

- Two Low Molecular Weight Heparins (LMWHs) administered via subcutaneous injection:

<table>
<thead>
<tr>
<th>Proprietary medicinal products</th>
<th>INN</th>
<th>Indication</th>
<th>Actual Benefit (AB) (date of opinion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INNOHEP</td>
<td>Tinzaparin sodium</td>
<td>Curative treatment of PE with no clinical signs of severity in the absence of pre-existing cardiac or pulmonary disease, excluding emboli that are likely to have resulted from thrombolytic treatment or surgery: INNOHEP is not indicated in patients who have undergone recent surgery.</td>
<td>Substantial (16/12/09)</td>
</tr>
<tr>
<td>LOVENOX</td>
<td>Enoxaparin sodium</td>
<td>Curative treatment of diagnosed DVT, with or without PE, without signs of clinical severity, except for PEs likely to have resulted from thrombolytic treatment or surgery.</td>
<td>Substantial (02/12/09)</td>
</tr>
</tbody>
</table>

- Unfractionated Heparins

**Vitamin K antagonists (as follow-up therapy only)**
### SUMMARY OF PREVIOUS ASSESSMENTS

<table>
<thead>
<tr>
<th>Date of Opinion (Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use)</th>
<th>21 September 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Treatment of acute deep vein thrombosis (DVT) and acute pulmonary embolism (PE), except in patients who are haemodynamically unstable and in patients who require thrombolysis or pulmonary embolectomy.</td>
</tr>
<tr>
<td><strong>Actual Benefit (AB)</strong> (wording)</td>
<td>Substantial in these two indications, with a high efficacy/adverse events ratio and a low expected public health benefit.</td>
</tr>
<tr>
<td><strong>Improvement in Actual Benefit (IAB)</strong> (wording)</td>
<td>“Given the currently available data and its mechanism of action (biological plausibility), ARIXTRA does not appear to expose patients to the risk of immuno-allergic thrombocytopenia. Fonaparinux (ARIXTRA at doses of 5 mg/0.4 ml, 7.5 mg/0.6 ml and 10 mg/0.8 ml) solution for injection in pre-filled syringe provides a minor improvement in actual benefit (IAB level IV) in terms of safety compared with routine management in the 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).”</td>
</tr>
<tr>
<td><strong>Studies requested</strong></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

(see results in the Appendix)

In the absence of new clinical data, the Committee did not amend its conclusions during the review of the medicinal product within the scope of the request for continued inclusion; the Committee recommends continued inclusion on the list of medicines reimbursed by National Insurance in the indications and at the doses in the Marketing Authorisation (Continued inclusion Opinion of 18 November 2009).
07 ANALYSIS OF NEW CLINICAL DATA

07.1 Efficacy

The applicant has not presented any new clinical efficacy data.

07.2 Adverse events

- Nearly half of all reported haemorrhagic adverse events occurred in patients receiving the “curative” doses (5 mg, 7.5 mg or 10 mg) recommended in the treatment of DVT/PE (PSUR).
- There is no information on any potential misuse with these doses.

(See safety section from the re-assessment opinion for ARIXTRA 2.5 mg in its thromboprophylaxis indications)

08 USAGE DATA

Current data from the DOREMA and Thalès panels do not enable the prescriptions of ARIXTRA to be analysed by indication.

The applicant extracted the breakdown of prescriptions by dose and by mean treatment duration for the various dosages from the Thalès database. In order to estimate the breakdown of prescriptions by whether they were curative or preventive, a prescription for the 2.5 mg dosage was assumed to be preventive while the other dosages were assumed to be curative (see Table 1). This overestimates the number of preventive prescriptions.

<table>
<thead>
<tr>
<th>Table 1. Distribution of ARIXTRA prescriptions by dosage (source: Thales)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period: January to March 2012</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>PREVENTIVE ARIXTRA 2.5 mg</td>
</tr>
<tr>
<td>CURATIVE</td>
</tr>
<tr>
<td>ARIXTRA 5 mg</td>
</tr>
<tr>
<td>ARIXTRA 7.5 mg</td>
</tr>
<tr>
<td>ARIXTRA 10 mg</td>
</tr>
<tr>
<td>TOTAL Prescriptions ARIXTRA</td>
</tr>
</tbody>
</table>

For the 5 mg, 7.5 mg and 10 mg doses, the mean treatment duration was 13.8 days and the median treatment duration was 8 days.
The risk management plan (CHMP validation: August 2010) stipulates that the collection of spontaneous reports continue with an ongoing periodic review of data. Heightened monitoring of spontaneous cases of haemorrhage and off-label use is in progress.

The therapeutic objective in patients with deep venous thrombosis is to avoid the expansion of the thrombosis, to prevent the occurrence of a pulmonary embolism and to reduce the risk of long-term complications. Anticoagulant treatment includes either a UFH or an LMWH, followed by early initiation of a Vitamin K antagonist. Compared with UFHs, the benefit of LMWHs lies in their more practical methods of administration: 1 or 2 daily SC injections versus continuous IV infusion for UFHs, which requires venous access. Laboratory monitoring is also simpler for some LWMH patients. However, as with UFHs, LMWHs carry a risk of thrombocytopenia (although immuno-allergic heparin-induced thrombocytopenia [HIT] occurs less frequently with LMWHs) and patients taking LMWHs require monitoring of their platelet count. Orally administered rivaroxaban (XARELTO) is an alternative in this indication.

Patients with pulmonary embolism require initial inpatient intensive care. The aim of treatment is to prevent death, relapse and complications. The reference anticoagulant treatment is UFH (administered intravenously with an electronic syringe), regardless of the level of severity. Oral anticoagulant therapy should be implemented quickly. In patients with uncomplicated pulmonary embolism and no haemodynamic failure, an LMWH (tinzaparin) may be an alternative to UFHs. In the clinical studies available, LMWH was prescribed for an average of 7 days; follow-up was limited to a period of only 3 months. The impact on the occurrence of complications was not evaluated.

In these two indications, fondaparinux (ARIXTRA) has the same advantages as LMWHs. In addition:
- given the currently available data and its mechanism of action (biological plausibility), ARIXTRA does not appear to expose patients to a risk of immuno-allergic thrombocytopenia occurrence, unlike UFH and, to a lesser extent, LMWHs.
- given the fondaparinux dosage, which does not require any adjustment in patients weighing 50 to 100 kg.

There are no studies comparing fondaparinux (SC) with rivaroxaban (XARELTO, PO).
There are several good practice guidelines available:

- In the treatment of venous thromboembolic disease (acute DVT and PE), the AFSSAPS\(^1\) recommends ARIXTRA 5 mg, 7.5 mg and 10 mg as first-line treatment in addition to LMWHs and UFH (Grade A). LMWHs and ARIXTRA 5 mg, 7.5 mg and 10 mg are recommended over UFHs (Grade A) given their greater ease of use, the absence of the need for dose adjustment according to coagulation test results and the lower risk of HIT (with LMWHs, and in particular with fondaparinux).

- In 2012, the ACCP\(^2\) updated their 2008 guidelines\(^3\) for patients with acute lower limb DVT or acute PE, recommending initial parenteral anticoagulation with an LMWH, fondaparinux or IV or SC UFH (Grade 1B). In cases of acute DVT, the ACCP suggests the use of LMWHs or fondaparinux rather than IV (Grade 2C) or SC UFH (Grade 2B for LMWHs; grade 2C for fondaparinux). In cases of acute PE, ACCP suggests the use of LMWHs or fondaparinux rather than IV (grade 2C for LMWHs, grade 2B for fondaparinux) or SC UHF (Grade 2B for LMWHs, grade 2C for fondaparinux).

In summary, fondaparinux (ARIXTRA) remains a first-line therapy in the initial treatment of acute DVT and PE.

**Consideration of the risk of haemorrhage:**

According to the Marketing Authorisation:

- **Weight:** “for patients weighing less than 50 kg, the recommended dosage is 5 mg. For patients weighing over 100 kg, the recommended dosage is 10 mg."
- **Mean treatment duration:** “in clinical studies, the average duration is 7 days; clinical experience beyond 10 days is limited.”
- **The elderly:** “no dosing adjustment is necessary. In patients 75 years and older, fondaparinux should be used with caution as renal function decreases with age.”
- **Renal impairment:** “Fondaparinux should be used with caution in patients with moderate renal impairment. There is no experience in the sub-group of patients with both high body weight (>100 kg) and moderate renal impairment (creatinine clearance 30-50 ml/min). In this sub-group, after an initial 10 mg daily dosage, a reduction of the daily dosage to 7.5 mg may be considered, based on pharmacokinetic modelling”. Fondaparinux should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min).

In conclusion, for patients with renal impairment and a creatinine clearance < 30 ml/min, ARIXTRA should not be used.

In patients with a body weight < 50 kg and/or aged 75 years and over, the use of fondaparinux should only be considered with great caution given the risk of haemorrhage.

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\(^1\) PREVENTION ET TRAITEMENT DE LA MALADIE THROMBOEMBOLIQUE VEINEUSE EN MEDICINE. RECOMMANDATIONS DE BONNE PRATIQUE (PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLIC DISEASE IN MEDICINE. GOOD PRACTICE GUIDELINES) French Health Products Safety Agency (Afssaps), December 2009.


In view of all of the above information and following the debate and vote, the Committee’s opinion is as follows:

011.1 Re-assessment of the Actual Benefit (AB)

Venous thromboembolic disease (deep vein thrombosis [DVT] or pulmonary embolism [PE]) is a potentially life-threatening condition. PE may cause patient death, even after initiating anticoagulation treatment. The patient may relapse and serious, sometimes debilitating complications may occur (e.g., chronic venous impairment, venous ulcers). The efficacy/adverse events ratio for fondaparinux remains high in the treatment of the acute phase of DVT or PE. ARIXTRA is a first-line treatment.

Public health benefit:
The public health burden of venous thromboembolic disease (VTED) is substantial. Having access to safe, effective treatments for venous thromboembolic events that are haemorrhagically well tolerated, especially in at-risk patients, is a public health need.

Given the pharmacovigilance monitoring data for ARIXTRA (showing that half of all reported haemorrhagic events pertained to curative treatments and that there is misuse), as well as the currently existing treatments, ARIXTRA 5 mg, 7.5 mg and 10 mg do not have a additional impact on morbidity and mortality, even in patients under the age of 75 who do not have renal impairment. Therefore, these proprietary medicinal products only provide a very partial response to an identified public health need.

Consequently, ARIXTRA 5 mg, 7.5 mg and 10 mg are of no public health benefit in this indication (curative treatment of acute DVT and acute PE).

Alternative medicinal products exist:
- For acute deep vein thrombosis, the injection of an LMWH or an UFH and oral rivaroxaban (XARELTO) is indicated. If pulmonary embolism is associated with DVT, only enoxaparin (LOVENOX) and tinzaparin (INNOHEP) are indicated.
- For pulmonary embolism, a UFH (reference treatment) or tinzaparin is indicated.

As soon as possible, follow-up oral anticoagulation should be prescribed.

Consequently, the Committee considers that the actual benefit of ARIXTRA (at the 5 mg/0.4 ml, 7.5 mg/0.6 ml and 10 mg/0.8 ml dosages) is substantial as a curative treatment for acute (5 to 7 days) deep vein thrombosis and pulmonary embolism under Marketing Authorisation conditions.

Suggested reimbursement rate: 65%.

011.2 Re-assessment of the Improvement in Actual Benefit (IAB)

The Committee considers that ARIXTRA (5 mg/0.4 ml, 7.5 mg/0.6 ml and 10 mg/0.8 ml) no longer provides any improvement in actual benefit (IAB V, non-existent) in the treatment of acute deep vein thrombosis (DVT) and acute pulmonary embolism (PE).
011.3 Transparency Committee Recommendations

The Committee recommends the continued inclusion of ARIXTRA 5 mg, 7.5 mg and 10 mg on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use in the “treatment of acute deep vein thrombosis (DVT) and acute pulmonary embolism (PE), with the exception of haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy.”

Packaging

The packaging is appropriate for the prescription conditions.
APPENDIX

Summary of results available during the previous assessment:

The efficacy and safety of ARIXTRA were evaluated in 3 clinical studies, including two phase III trials:

- The MATISSE–TVP (n = 2,205 patients) study was a randomised, double-blind, non-inferiority study that compared the efficacy and safety of ARIXTRA via subcutaneous injection once daily with enoxaparin via subcutaneous injection twice daily in the treatment of symptomatic acute deep vein thrombosis. Included patients needed to be at least 18 years old and present with acute deep vein thrombosis. The clinical diagnosis was confirmed by specialised ultrasonography. The primary endpoint was defined as the incidence of symptomatic venous thromboembolic event recurrence during the three-month study period. Symptomatic thromboembolic event recurrence was defined as a pulmonary embolism or deep vein thrombosis that did not lead to death or a fatal thromboembolic event, where death may have been caused by the event or of unknown origin (without ruling out pulmonary embolism).

- The MATISSE–EP (n = 2,213 patients) study was a randomised, open-label, non-inferiority study that compared the efficacy and safety of ARIXTRA administered once daily via subcutaneous injection to that of UFH administered via IV infusion in the treatment of symptomatic acute pulmonary embolism. Included patients needed to be at least 18 years old, present with diagnosed symptomatic acute pulmonary embolism and require anti-thrombotic treatment. Randomised patients could have been previously treated with an unfractionated heparin (UFH) during the selection phase. The primary endpoint was defined as the incidence of symptomatic venous thromboembolic event recurrence during the three-month study period. Thromboembolic event recurrence was defined as a symptomatic pulmonary embolism or deep vein thrombosis that did not lead to death, or a fatal thromboembolic event, where death may have been related to the event or of unknown origin.

In both of these studies, the comparison between the two treatments involved a non-inferiority analysis. The non-inferiority limit selected between the percentage of ARIXTRA thromboembolic events and the percentage of enoxaparin thromboembolic events (MATISSE-TVP study) or UFH thromboembolic events (MATISSE-EP study) was set at 3.5%.

Results:
In both studies:
- the mean age was 60 years
- the diagnostic criteria complied with current strategies and diagnoses
- the evaluation endpoints and comparator medicines were relevant.

In acute DVT treatment, the incidence of recurrent thromboembolic events was 3.9% (43 patients) in the ARIXTRA group and 4.1% (45 patients) in the enoxaparin sodium group (MATISSE-TVP). Non-inferiority was thus observed (confidence interval for the difference ranged from – 1.8% to + 1.5%).

In the treatment of acute (non serious) pulmonary embolism, the incidence of thromboembolic event recurrence was 3.8% (42 patients) in the ARIXTRA group and 5.0% (56 patients) in the UFH group (MATISSE-EP). Non-inferiority was thus observed (confidence interval for the difference ranged from – 3% to + 0.5%).

A sub-group analysis based on the demographic characteristics of patients enabled the comparable efficacy to be revealed, regardless of the weight of the patients treated, especially in those weighing over 100 kg.
There was no difference in safety (in particular, the occurrence of major haemorrhage) between the two treatments. No immuno-allergic thrombocytopenia was observed in the clinical studies that evaluated fondaparinux (12,000 patients) or since its commercial launch (pharmacovigilance data available for nearly 350,000 patients). There is no cross-reaction with serum from patients with HIT. Platelet count monitoring is no longer required for the majority of patients. However, the efficacy/adverse event ratio for fondaparinux was not specifically evaluated in subjects with a history of HIT, in whom its prescription is not currently recommended (see Marketing Authorisation). However, the risk of HIT is lower with LMWHs (0.1% to 1%) than it is with UFHs (1 to 5%).