1. NAME OF THE MEDICINAL PRODUCT

DABIFIB 75 (Dabigatran Etexilate Hard Capsules 75 mg)

DABIFIB 110 (Dabigatran Etexilate Hard Capsules 110 mg)

DABIFIB 150 (Dabigatran Etexilate Hard Capsules 150 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DABIFIB 75 (Dabigatran Etexilate Hard Capsules 75 mg)

Each capsule contains 75 mg of Dabigatran.

Each capsule contains 86.475 mg Dabigatran Etexilate Mesylate equivalent to 75 mg Dabigatran Etexilate.

DABIFIB 110 (Dabigatran Etexilate Hard Capsules 110 mg)

Each capsule contains 110 mg of Dabigatran.

Each capsule contains 126.830 mg Dabigatran Etexilate Mesylate equivalent to 110 mg Dabigatran Etexilate.

DABIFIB 150 (Dabigatran Etexilate Hard Capsules 150 mg)

Each capsule contains 150 mg of Dabigatran.

Each capsule contains 172.950 mg Dabigatran Etexilate Mesylate equivalent to 150 mg Dabigatran Etexilate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

DABIFIB 75 (Dabigatran Etexilate Hard Capsules 75 mg)

White to light yellow coloured blend compressing granular powder, pellets in size ‘2’ capsule having white opaque cap imprinted ‘MD’ and white opaque body imprinted ‘75’ with black ink.

DABIFIB 110 (Dabigatran Etexilate Hard Capsules 110 mg)

White to light yellow coloured blend compressing granular powder, pellets in size ‘1’ capsule having white opaque cap imprinted ‘MD’ and white opaque body imprinted ‘110’ with black ink.

DABIFIB 150 (Dabigatran Etexilate Hard Capsules 150 mg)

White to light yellow coloured blend compressing granular powder, pellets in size ‘0’ capsule having white opaque cap imprinted ‘MD’ and white opaque body imprinted ‘150’ with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<u>75 mg capsule:</u>

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

<u>110 mg capsule:</u>

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

150 mg capsule:

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

4.2 Posology and Method of Administration

Adults:

Primary prevention of Venous Thromboembolism (pVTEp) events in adult patients who have undergone elective knee replacement surgery:

The recommended dose of DABIFIB is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 10 days.

Primary prevention of Venous Thromboembolism (pVTEp) events in adult patients who have undergone elective hip replacement surgery:

The recommended dose of DABIFIB is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1- 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):

The recommended daily dose of DABIFIB is 300 mg taken orally as 150 mg hard capsules twice daily. Therapy should be continued life-long.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):

The recommended daily dose of DABIFIB is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section “Special warnings and precautions”). Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

SPAF, DVT/PE:

For the following groups the recommended daily dose of DABIFIB is 220 mg taken as one 110 mg capsule twice daily:

- Patients aged 80 years or above
- Patients who receive concomitant verapamil

For the following groups the daily dose of DABIFIB of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:

- Patients between 75-80 years
- Patients with moderate renal impairment
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk of bleeding

For DVT/PE the recommendation for the use of DABIFIB 220 mg taken as one 110 mg capsule twice daily is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting.

In case of intolerability to dabigatran, patients should be instructed to immediately consult their treating physician in order to be switched to alternate acceptable treatment options for prevention of stroke and SEE associated with atrial fibrillation or for DVT/PE.

Special patient populations

Renal impairment:

Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with DABIFIB to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30ml/min). There are no data to support use in patients with severe renal impairment (< 30 mL/min creatinine clearance); treatment in this population with DABIFIB is not recommended (see "Contraindications").

While on treatment renal function should be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).
Dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies.

Primary prevention of venous thromboembolism events in adult patients who have undergone elective hip replacement surgery or total knee replacement surgery (pVTEp):

In patients with moderate renal impairment (creatinine clearance 30-50 ml/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see sections on Special Warning & Precaution and Properties).

Treatment with DABIFIB should be initiated orally within 1 - 4 hours of completed surgery with a single capsule of 75 mg and continuing with 2 capsules of 75 mg once daily thereafter for a total of 10 days (following knee replacement surgery) or 28-35 days (following hip replacement surgery).
For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):

In patients with moderate renal impairment (CrCl 30-50ml/min) the renal function should be assessed at least once a year.

No dose adjustment necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg hard capsules twice daily.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):

Treatment with DABIFIB in patients with severe renal impairment (CrCL < 30 mL/min) is contraindicated.

No dose adjustment is necessary in patients with mild renal impairment (CrCL 50 - ≤ 80 mL/min). For patients with moderate renal impairment (CrCL 30-50 mL/min) the recommended dose of DABIFIB is also 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of DABIFIB to 220 mg taken as one 110 mg capsule twice daily should be considered. Close clinical surveillance is recommended in patients with renal impairment.

Elderly:

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function.

See also dose and administration in renal impairment.

Primary prevention of venous thromboembolism events in adult patients who have undergone elective hip replacement surgery or total knee replacement surgery (pVTEp):

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with DABIFIB to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30ml/min). The renal function should also be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).

In elderly patients (> 75 years) there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see sections on Special Warning & Precaution and Properties).

After knee replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

After hip replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with DABIFIB to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30ml/min). The renal function should also be assessed at least once a year in patients treated with DABIFIB or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).

Patients aged 80 years and above should be treated with a dose of 220 mg of DABIFIB daily, taken orally as one 110 mg capsule twice a day.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):

Patients between 75-80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. A dose of 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.

Patients aged 80 years or above should be treated with a daily dose of 220 mg taken as one 110 mg capsule twice daily due to the increased risk of bleeding in this population.

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the CrCL prior to initiation of treatment with DABIFIB to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min). The renal function should also be assessed at least once a year in patients treated with DABIFIB or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).

Weight:

Given the available clinical and kinetic data no adjustment is necessary (see section Pharmacokinetics), but close clinical surveillance is recommended in patients with a body weight < 50 kg (see section Special Warning & Precaution).

Gender:

Given the available clinical and kinetic data, no dose adjustment is necessary.

Concomitant use of DABIFIB with strong P-glycoprotein inhibitors, e.g. amiodarone, quinidine or verapamil:

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):

Dosing should be reduced to DABIFIB 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive DABIFIB and amiodarone, quinidine or verapamil. (see section on Drug Interactions).

Treatment initiation with verapamil should be avoided in patients who have undergone elective total hip replacement surgery or total knee replacement surgery who are already treated with DABIFIB. Simultaneous initiation of treatment with DABIFIB and verapamil should also be avoided.

Treatment with DABIFIB should be initiated orally within 1 - 4 hours of completed surgery with a single capsule of 75 mg and continuing with 2 capsules of 75 mg once daily thereafter for a total of 10 days (following knee replacement surgery) or 28-35 days (following hip replacement surgery). For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):

No dose adjustment is necessary for concomitant use of amiodarone or quinidine.

Dosing should be reduced to 220 mg taken as one 110 mg capsule twice daily in patients who receive concomitantly dabigatran etexilate and verapamil. In this situation DABIFIB and verapamil should be taken at the same time.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):

No dose adjustment is necessary for concomitant use of amiodarone or quinidine.

Dosing should be reduced to 220 mg taken as one 110 mg capsule twice daily in patients who receive concomitantly dabigatran etexilate and verapamil. In this situation DABIFIB and verapamil should be taken at the same time.

Patients at risk of bleeding:

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF): The presence of the following factors may increase the risk of bleeding: e.g. age ≥ 75 years, moderate renal impairment (30-50 ml CrCL/min), concomitant treatment with strong P-gp inhibitors (see “PK in specific populations”), antiplatelets or previous gastro-intestinal bleed (see “Special warnings and precautions”). For patients with one or more than one of these risk factors, a reduced daily dose of 220 mg given as 110 mg twice daily may be considered at the discretion of the physician.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):

Patients with an increased bleeding risk should be closely monitored clinically (looking for signs of bleeding or anaemia). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk

to an individual patient. A coagulation test (see "Special warnings and precautions") may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a reduced dose of 220 mg taken as one 110 mg capsule twice daily is recommended. When clinically relevant bleeding occurs, treatment should be interrupted.
For subjects with gastritis, esophagitis, or gastroesophageal reflux, the dose of 220 mg taken as one 110 mg capsule twice daily may be considered due to the elevated risk of major gastro-intestinal bleeding.

Hepatic impairment:
Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in the main trials. No treatment experience is available for this subpopulation of patients, and therefore the use of DABIFIB is not recommended in this population. Hepatic impairment or liver disease expected to have any impact on survival is contraindicated.

Post-surgical patients with an increased risk for bleeding:
DABIFIB should be resumed/ started after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.
Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (creatinine clearance 30 – 50 ml/min), should be treated with caution (see sections on Special Warning & Precaution and Pharmacodynamic Properties).

Paediatric population:
pVTEp and SPAF:
DABIFIB has not been investigated in patients <18 years of age in the indication of:

- Primary prevention of venous thromboembolic events in patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
- Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Treatment of paediatric patients with DABIFIB is therefore not recommended.

DVT/PE:
The safety and efficacy of DABIFIB have not been established in paediatric patients <18 years of age. Therefore, DABIFIB is not indicated in this patient population.

Switching from DABIFIB treatment to parenteral anticoagulant:
pVTEp:
It is recommended to wait 24 hours after the last dose before switching from DABIFIB to a parenteral anticoagulant (see section on Drug Interactions).

SPAF and DVT/PE:
It is recommended to wait 12 hours after the last dose before switching from DABIFIB to a parenteral anticoagulant.

Switching from parenteral anticoagulants treatment to DABIFIB:
DABIFIB should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous UFH).

Switching from Vit. K antagonists to DABIFIB:

SPAF and DVT/PE:

The Vit. K antagonist should be stopped. DABIFIB can be given as soon as the INR is < 2.0.

Switching from DABIFIB to Vit. K antagonists (VKA)*:*

SPAF and DVT/PE:

The starting time of the VKA should be adjusted according to the patient´s CrCL as follows:

- CrCL ≥ 50 ml/min, start VKA 3 days before discontinuing dabigatran etexilate.
- CrCL ≥ 30-< 50 ml/min, start VKA 2 days before discontinuing dabigatran etexilate.

Because DABIFIB can impact the International Normalized Ratio (INR), the INR will better reflect VKA's effect only after DABIFIB has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

Cardioversion:

SPAF and DVT/PE:

Patients can stay on DABIFIB while being cardioverted.

Catheter ablation for atrial fibrillation:

SPAF:

Catheter ablation can be conducted in patients on 150 mg twice daily DABIFIB treatment. DABIFIB treatment does not need to be interrupted (see "Pharmacological Properties").

Percutaneous coronary intervention (PCI) with stenting:

SPAF:

Patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with DABIFIB in combination with antiplatelets after haemostasis is achieved (see "Pharmacological Properties").

Missed dose

pVTEp:

Continue with your remaining daily doses of DABIFIB at the same time of the next day. Do not take a double dose to make up for missed individual doses.

SPAF and DVT/PE:

A forgotten DABIFIB dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted.

Do not take a double dose to make up for missed individual doses.

Method of administration

DABIFIB can be taken with or without food. DABIFIB should be swallowed as a whole with a glass of water, to facilitate delivery to the stomach.

Patients should be instructed not to open the capsule as this may increase the risk of bleeding.

Instruction For Use/ Handling

When removing a hard capsule from the blister, please note the following instructions:

- Tear off one individual blister from the blister card along the perforated line

- Peel off the backing foil and remove the capsule
- The capsule should not be pushed through the blister foil

4.3 Contraindication

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (CrCl < 30 ml/min)
- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances. These are switching anticoagulant therapy (see section 4.2), when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation (see section 4.5)
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with the following strong P-gp inhibitors: systemic ketoconazole, cyclosporine, itraconazole and dronedarone (see section 4.5)
- Prosthetic heart valves requiring anticoagulant treatment (see section on “Pharmacological Properties”).

4.4 Special Warnings and Precaution for Use

Haemorrhagic risk:

As with all anticoagulants, DABIFIB should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with DABIFIB. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site.

For situation of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effects of dabigatran is required, the specific reversal agent (PRAXBIND, idarucizumab) is available (see “Surgery and Interventions”, “Preoperative Phase” and “Overdose”.)

DABIFIB treatment does not require anticoagulant monitoring. The INR test is unreliable in patients on dabigatran etexilate mesylate and false positive INR elevations have been reported. Therefore, INR tests should not be performed.

Tests of anticoagulant activity such as thrombin time (TT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) are available to detect excessive dabigatran activity. Dabigatran related anticoagulation can be assessed by ECT or TT. If ECT or TT is not available, the aPTT test provides an approximation of DABIFIB’s anticoagulant activity.

<u>*For SPAF:*</u> In atrial fibrillation patients in RE-LY treated with 150 mg bid an aPTT of greater than 2.0 – 3.0 fold of normal range at trough was associated with an increased risk of bleeding.

Pharmacokinetic studies demonstrated an increase in drug exposure in patients with reduced renal function including age-related decline of renal function. DABIFIB is contraindicated in cases of severe renal impairment (CrCL < 30 mL/min). Patients who develop acute renal failure should discontinue DABIFIB.

Factors, such as decreased renal function (30 - 50mL/min CrCL), age ≥ 75 years, or strong P-gp-inhibitor comedication are associated with increased dabigatran plasma levels. The presence of one or more than one of these factors may increase the risk of bleeding (see section 4.2).

The concomitant use of DABIFIB with the following treatments has not been studied and may increase the risk of bleeding: unfractionated heparins (except at doses necessary to maintain patency of central venous or arterial catheter or during catheter ablation for atrial fibrillation) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, vitamin K antagonists, and P-gp inhibitors such as but not limited to itraconazole, tacrolimus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir.
The concomitant use of dabigatran etexilate mesylate with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasevir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.
The concomitant use of dronedarone increases exposure of dabigatran and is not recommended (see "PK in specific populations").
The concomitant use of ticagrelor increases the exposure to dabigatran and may show pharmacodynamic interaction, which may result in an increased risk of bleeding.
Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRI) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs).

Use of fibrinolytic agents for the treatment of acute ischemic stroke:
The use of fibrinolytic agents for the treatment of acute ischemic stroke may be considered if the patient presents with a thrombin time (TT), or Ecarin clotting time (ECT), or activated partial thromboplastin time (aPTT) not exceeding the upper limit of normal (ULN) according to the local reference range.
In situations where there is an increased haemorrhagic risk (e.g. recent biopsy or major trauma, bacterial endocarditis) close observation (looking for signs of bleeding or anaemia) is generally required.

For pVTEP: NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate mesylate. There is limited evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate mesylate and this has not suggested additional bleeding risk.

For SPAF: Co-administration of antiplatelet (including ASA and clopidogrel) and NSAID therapies increase the risk of bleeding. Specifically, with concomitant intake of antiplatelet or strong P-gp inhibitors in patients aged ≥75 years, the risk of major bleeding, including gastrointestinal bleeding, increases. If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool or testing for a drop in hemoglobin is suggested.

Interaction with P-gp inducers:
The concomitant use of dabigatran etexilate mesylate with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John`s Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations and should be co-administered with caution (see section 4.5 and "PK in specific populations").

Patients with antiphospholipid syndrome:
Patients with antiphospholipid syndrome (especially if triple-positive for antiphospholipid antibodies) are at an increased risk for thromboembolic events. While the efficacy of dabigatran etexilate mesylate is established for the treatment and prevention of venous thromboembolism it has not been studied specifically in the subpopulation of patients with antiphospholipid syndrome. Therefore, careful consideration of all treatment options (including standard treatment such as vitamin K antagonists) is recommended before use of DABIFIB in patients with antiphospholipid syndrome.

Surgery and Interventions:

Patients on DABIFIB who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of DABIFIB (see "Pharmacokinetics").

In case of emergency surgery or urgent procedures when rapid reversal of the anticoagulation effect is required the specific reversal agent (PRAXBIND, idarucizumab) to DABIFIB is available.

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. DABIFIB treatment can be re-initiated 24 hours after administration of PRAXBIND (idarucizumab), if the patient is clinically stable and adequate hemostasis has been achieved.

For SPAF: Patients can stay on DABIFIB while being cardioverted. DABIFIB treatment (150 mg twice daily) does not need to be interrupted in patients undergoing catheter ablation for atrial fibrillation (see section 4.2).

Preoperative Phase:

Due to an increased risk of bleeding DABIFIB may be stopped temporarily in advance of invasive or surgical procedures.

Emergency Surgery or Urgent Procedure:

The specific reversal agent (PRAXBIND, idarucizumab) of DABIFIB is available for the rapid reversal of the anticoagulation effect (see "Surgery and Interventions").

Acute Surgery/Intervention:

DABIFIB should be temporarily discontinued. An acute surgery/ intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed there may be an increase in the risk of bleeding.

Elective Surgery/Intervention:

If possible, DABIFIB should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete hemostasis may be required consider stopping DABIFIB 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures (see Table 1 and also section on Pharmacokinetics).

Table 1 summarizes discontinuation rules before invasive or surgical procedures.

Renal function (CrCL in ml/min)	Estimated half-life (hours)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥ 80	~ 13	2 days before	24 hours before
≥ 50 - <80	~ 15	2-3 days before	1-2 days before
≥ 30 - <50	~ 18	4 days before	2-3 days before (> 48 hours)

DABIFIB is contraindicated in patients with severe renal dysfunction (CrCl <30 mL/min) but should this occur then DABIFIB should be stopped at least 5 days before major surgery.

Spinal Anaesthesia/Epidural Anaesthesia/Lumbar Puncture:

Procedures such as spinal anesthesia may require complete hemostatic function.

The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 1 hour should elapse before the administration of the first dose of DABIFIB. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma.

Post Procedural Period:

DABIFIB treatment can be resumed / started after complete haemostasis is achieved.

4.5 Interaction with other Medicinal Products and Other Forms of Interaction

The concomitant use of DABIFIB with treatments that act on haemostasis or coagulation including Vitamin K antagonists can markedly increase the risk of bleeding (see section 4.4).

Dabigatran etexilate and dabigatran are not metabolized by the cytochrome P450 system and had no effects in vitro on human cytochrome P450 enzymes. Therefore, related drug-drug interactions are not expected with dabigatran etexilate or dabigatran (see "PK in specific populations").

P-glycoprotein interactions

P-glycoprotein inhibitors:

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, systemic ketoconazole, dronedarone, ticagrelor, clarithromycin and the fixed-dose combination glecaprevir/pibrentasvir) is expected to result in increased dabigatran plasma concentrations.

Concomitant administration of systemic ketoconazole is contraindicated.

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):

For the concomitant use of P-gp inhibitors and dosing of DABIFIB in this indication, please see section 4.2 and "PK in specific populations".

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):

For the P-gp inhibitors listed above no dose adjustments are required for DABIFIB in this indication.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):

For the P-gp inhibitors listed above no dose adjustments are required for DABIFIB in this indication.

Amiodarone: Dabigatran exposure in healthy subjects was increased by 1.6 fold (+ 60 %) in the presence of amiodarone (see "PK in specific populations").

For SPAF: In patients in the RE-LY trial concentrations were increased by no more than 14 % and no increased risk of bleeding was observed.

Verapamil: When dabigatran etexilate mesylate (150 mg) was co-administered with oral verapamil, the C_{max} and AUC of dabigatran were increased but the magnitude of this change differs, depending on timing of administration and formulation of verapamil (see "PK in specific populations").

For SPAF: In patients in the RE-LY trial concentrations were increased by no more than 21 % and no increased risk of bleeding was observed.

Quinidine: Dabigatran exposure in healthy subjects was increased by 1.5 fold (+53 %) in the presence of quinidine (see "PK in specific populations").

Clarithromycin: Dabigatran exposure in healthy subjects was increased by about 19 % in the presence of clarithromycin without any clinical safety concern (see "PK in specific populations").

Ketoconazole: Dabigatran exposure was increased by 2.5 fold (+ 150 %) after single and multiple doses of systemic ketoconazole (see "Contraindications" and "PK in specific populations").

Dronedarone: Dabigatran exposure was increased by 2.1 fold (+114 %) after single or 2.4 fold (+136 %) after multiple doses of dronedarone, respectively (see "PK in specific populations").

Ticagrelor: Dabigatran exposure in healthy subjects was increased by 1.46 fold (+ 46 %) in the presence of ticagrelor at steady state or by 1.73 fold (+73 %) when a loading dose of ticagrelor was administered simultaneously with a single dose of 75 mg dabigatran etexilate. Dabigatran steady state exposure in healthy subjects was increased by 1.26 fold (+ 26 %) in the presence of ticagrelor at steady state or by 1.49 fold (+49 %) when a loading dose of ticagrelor was administered simultaneously with 110 mg dabigatran etexilate. The increase in exposure was less pronounced when the 180 mg ticagrelor loading dose was given two hours after dabigatran intake (+27 %).

P- glycoprotein substrate:

Digoxin: In a study performed with 24 healthy subjects, when dabigatran etexilate mesylate was co-administered with digoxin, no changes on digoxin and no clinical relevant changes on dabigatran exposure have been observed (see "PK in specific populations").

P-glycoprotein inducers:

After 7 days of treatment with 600 mg rifampicin qd total dabigatran $AUC_{0-\infty}$ and C_{max} were reduced by 67 % and 66 % compared to the reference treatment, respectively.

The concomitant use with P-gp inducers (e.g., rifampicin) reduces exposure to dabigatran and should be avoided (see section 4.4 and "PK in specific populations").

4.6 Fertility, Pregnancy and Lactation

Pregnancy

No clinical data on exposed pregnancies are available. The potential risk for humans is unknown.

Women of child-bearing potential should avoid pregnancy during treatment with DABIFIB and when pregnant, women should not be treated with DABIFIB unless the expected benefit is greater than the risk.

Lactation

No clinical data are available. As a precaution, breast-feeding should be stopped.

Fertility

No clinical data available. Non-clinical reproductive studies did not show any adverse effects on fertility or postnatal development of the neonate.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

Adverse reactions identified from studies and post-marketing data in:

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp)
- Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF)
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

Blood and lymphatic system disorders

Anemia, thrombocytopenia, neutropenia*, agranulocytosis*

Immune system disorders

Drug hypersensitivity including pruritus, rash and urticaria, bronchospasm*, angioedema*, anaphylactic reaction*.

Nervous system disorders
Intracranial haemorrhage

Vascular disorders
Haematoma, haemorrhage

Respiratory, thoracic and mediastinal disorders
Epistaxis, haemoptysis

Gastrointestinal disorders
Gastrointestinal haemorrhage, abdominal pain, diarrhoea, dyspepsia, nausea, gastrointestinal ulcer, including oesophageal ulcer, gastrooesophagitis, gastrooesophageal reflux disease, vomiting, dysphagia

Hepatobiliary disorders
Hepatic function abnormal

Skin and subcutaneous tissue disorders
Skin haemorrhage, alopecia*

Musculoskeletal, connective tissue and bone disorders
Haemarthrosis

Renal and urinary disorders
Urogenital haemorrhage

General disorders and administration site conditions
Injection site haemorrhage, catheter site haemorrhage

Injury, poisoning and procedural complications
Traumatic haemorrhage, incision site haemorrhage
* including post-marketing data

Additional specific adverse reactions identified per indication
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):
Vascular disorders
Wound haemorrhage

General disorders and administration site conditions
Bloody discharge

Injury, poisoning and procedural complications
Post-procedural haematoma, post-procedural haemorrhage, anaemia post-operative, post-procedural discharge, wound secretion

Surgical and medical procedures

Wound drainage, post-procedural drainage

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF): None
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE): None

4.9 Overdose

Symptoms

Overdose following administration of DABIFIB may lead to haemorrhagic complications due to its pharmacodynamic properties. Doses of DABIFIB beyond those recommended expose the patient to increased risk of bleeding.

Therapy

In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained.
Depending on the clinical situation appropriate standard treatment, e.g. surgical haemostasis as indicated and blood volume replacement, should be undertaken.
For situations when rapid reversal is required the specific reversal agent (PRAXBIND, idarucizumab) antagonising the pharmacodynamics effect of DABIFIB is available (see section 4.4; “Surgery and Interventions”, “Pre-operative Phase”).
In addition, consideration may be given to the use of fresh whole blood or fresh frozen plasma. Coagulation factor concentrations (activated or non-activated) or recombinant Factor VIIa may be taken into account. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgement.
As protein binding is low, dabigatran is dialysable, however there is limited clinical experience in using dialysis in this setting (see “PK in specific populations”).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: oral direct thrombin inhibitor
ATC code: B01AE07 – dabigatran etexilate

Mode of Action

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase- catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma.

Pharmacodynamics

Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.
In-vivo and ex-vivo animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran etexilate after oral administration in various animal models of thrombosis.

There is a close correlation between plasma dabigatran concentrations and degree of anticoagulant effect. Dabigatran prolongs the aPTT, ECT and TT.

5.2 Pharmacokinetic properties

Absorption

After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations with peak concentration (C_{max}) attained within 0.5 and 2.0 hours post administration. C_{max} and the area under the plasma concentration-time curve (AUC) were dose proportional.
The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate as HPMC capsule was approximately 6.5 %.
Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours. The oral bioavailability may be increased by about 1.4-fold (+37 %) compared to the reference capsule formulation when the pellets are taken without the HPMC capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages) (see section 4.2).

Distribution

Low (34-35 %) concentration independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigatran of 60 – 70 L exceeded the volume of total body water indicating moderate tissue distribution of dabigatran.

Biotransformation

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O acylglucuronide exist, each accounts for less than 10 % of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 ml/min corresponding to the glomerular filtration rate.

Elimination

After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half- life of approximately 11 hours in healthy elderly subjects. After multiple doses a terminal half-life of about 12- 14 hours was observed. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown below, in Table 2.

Metabolism and excretion of dabigatran were studied following a single intravenous dose of radiolabeled dabigatran in healthy male subjects. After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85%). Faecal excretion accounted for 6% of the administered dose. Recovery of the total radioactivity ranged from 88 - 94 % of the administered dose by 168 hours post dose.

Table 2: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function

glomerular filtration rate (CrCl)	**gMean (gCV%; range) half-life**
[mL/min]	**[h]**
> 80	13.4 (25.7%; 11.0-21.6)
> 50 - ≤ 80	15.3 (42.7%; 11.7-34.1)
> 30 - ≤ 50	18.4 (18.5%; 13.3-23.0)
≤ 30	27.2 (15.3%; 21.6-35.0)

PK in specific populations

Renal impairment:

The exposure (AUC) of dabigatran after the oral administration of dabigatran etexilate in a phase I study was approximately 3-fold higher in volunteers with moderate renal insufficiency (CrCL between 30 - 50ml/min) than in those without renal insufficiency.

In a small number of volunteers with severe renal insufficiency (CrCL 10 - 30 ml/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see "Dosage and Administration" and "Contraindications").

Clearance of dabigatran by hemodialysis was investigated in patients with end-stage renal disease (ESRD) without atrial fibrillation. Dialysis was conducted with 700ml/min dialysate flow rate, four hour duration, a blood flow rate of either 200 ml/min or 350 - 390 ml/min. This resulted in a removal of 50% or 60% of free- or total dabigatran concentrations, respectively. The amount of drug cleared by dialysis is proportional to the blood flow rate. The anticoagulant activity of dabigatran decreased with decreasing plasma concentrations and the PK/PD relationship was not affected by the procedure.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF): The median CrCL in RE-LY was 68.4 ml/min. Almost half (45.8 %) of the RE-LY patients had a CrCL > 50-< 80 ml/min. Patients with moderate renal impairment (CrCL between 30-50 ml/min) had on average 2.29-fold and 1.81-fold higher pre- and post-dose dabigatran plasma concentrations, respectively, when compared with patients without renal impairment (CrCL ≥80 ml/min).

Treatment of acute deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):

The median CrCl in the RE-COVER study was 100.3 mL/min. 21.7% of patients had mild renal impairment (CrCl > 50-< 80 mL/min) and 4.5% of patients had a moderate renal impairment (CrCl between 30-50 mL/min). Patients with mild and moderate renal impairment had on average 1.7-fold and 3.4-fold higher steady state dabigatran trough concentrations compared with patients with CrCl > 80 mL/min. Similar values for CrCl were found in RE-COVER II.

Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE): The median CrCl in the RE-MEDY and RE-SONATE studies were 99.0 mL/min and 99.7 mL/min respectively. 22.9 % and 22.5% of the patients had a CrCl > 50-< 80 mL/min, and 4.1% and 4.8% had a CrCl between 30-50 mL/min in in the RE-MEDY and RE-SONATE studies.

Elderly:

The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance. The effect by age on exposure to dabigatran was confirmed with an about 1.3 fold (+31 %) higher trough concentration for subjects ≥ 75 years and by about 22 % lower trough level for subjects < 65 years compared to subjects of age between 65 and 75 years.

Hepatic insufficiency:

No change in dabigatran exposure was seen.

Body weight:

The dabigatran trough concentrations were about 20 % lower in patients with a BW > 100 kg compared with 50 - 100kg.

Gender:

No clinical relevance.

Ethnic origin:

Ethnic origin does not affect the pharmacokinetics of dabigatran in a clinically relevant manner.

Drug-drug interactions:

Atorvastatin: When dabigatran etexilate was co-administered with atorvastatin, a CYP3A4 substrate, exposure of atorvastatin, atorvastatin metabolites and of dabigatran were unchanged indicating a lack of interaction.

Diclofenac: When dabigatran etexilate was co-administered with diclofenac, a CYP2C9 substrate, pharmacokinetics of both drugs remained unchanged indicating a lack of interaction between dabigatran etexilate and diclofenac.

P-gp inhibitor / inducer interactions:

The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-glycoprotein (Pgp). Therefore, co-medications with P-gp transporter inhibitors and inducers have been investigated.

Co-medication with P-gp inhibitors:

Amiodarone: When dabigatran etexilate was coadministered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and Cmax were increased by about 1.6-fold and 1.5-fold (+60 % and 50 %), respectively.

For SPAF: No important changes in dabigatran trough levels were observed in patients who received amiodarone (see section 4.5).

Dronedarone: When dabigatran etexilate and dronedarone were given at the same time total dabigatran $AUC_{0-\infty}$ and Cmax values increased by about 2.4-fold and 2.3-fold (+136 % and 125%), respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold (+114% and 87%), respectively, after a single dose of 400 mg. The terminal half-life and renal clearance of dabigatran were not affected by dronedarone. When single and multiple doses of dronedarone were given 2 h after dabigatran etexilate, the increases in dabigatran $AUC_{0-\infty}$ were 1.3-fold and 1.6 fold, respectively.

Verapamil: When dabigatran etexilate was coadministered with oral verapamil, the Cmax and AUC of dabigatran were increased depending on timing of administration and formulation of verapamil.

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of C_{max} by about 2.8-fold (+180%) and AUC by about 2.5-fold (+150%)). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 1.9-fold (+90%) and AUC by about 1.7-fold (+70%)) or administration of multiple doses of verapamil (increase of C_{max} by about 1.6-fold (+60%) and AUC by about 1.5-fold (+50%)). This can be explained by the induction of P-gp in the gut by chronic verapamil treatment.

There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 10% and AUC by about 20%). This is explained by completed dabigatran absorption after 2 hours (see "Dosage and Administration").

No data are available for the parenteral application of verapamil; based on the mechanism of the interaction, no meaningful interaction is expected.

For SPAF: In the population pharmacokinetics study, no important changes in dabigatran trough levels were observed in patients who received verapamil (see section 4.5).

Ketoconazole: Systemic ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by about 2.4-fold (+138 % and 135 %), respectively, after a single dose of 400 mg, and about 2.5-fold (+153 % and 149 %), respectively, after multiple dosing of 400 mg ketoconazole qd. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole.

Clarithromycin: When clarithromycin 500 mg twice daily was administered together with dabigatran etexilate no clinically relevant PK-interaction was observed (increased of C_{max} by about 15 % and AUC by about 19 %).

Quinidine: Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1000 mg. Dabigatran etexilate was given bid over 3 consecutive days, on the 3rd day either with or without quinidine. Dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased on average by about 1.5-fold (+53 % and 56 %), respectively with concomitant quinidine.

Ticagrelor: When a single dose of 75 mg dabigatran etexilate was co-administered simultaneously with a loading dose of 180 mg ticagrelor, the dabigatran AUC and C_{max} were increased by 1.73-fold and 1.95-fold (+73 % and 95 %), respectively. After multiple doses of ticagrelor 90 mg b.i.d. the increase of dabigatran exposure is reduced to 1.56-fold and 1.46-fold (+56 % and 46 %) for C_{max} and AUC, respectively. Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran $AUC_{\tau,ss}$ and by $C_{max,ss}$ by 1.49fold and 1.65-fold (+49 % and 65 %), respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ was reduced to 1.27-fold and 1.23-fold (+27 % and 23 %), respectively, compared with dabigatran etexilate given alone. Concomitant administration of 90 mg ticagrelor BID (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.

Co-medication with P-gp substrates:

Digoxin: When dabigatran etexilate was co-administered with digoxin, a P-gp substrate, no PK-interaction was observed. Neither dabigatran nor the pro-drug dabigatran etexilate is a clinically relevant P-gp inhibitor.

Co-medication with P-gp inducers:

Rifampicin: Pre-dosing of the probe inducer rifampicin at a dose of 600 mg qd for 7 days decreased total dabigatran peak and total exposure by 65.5 and 67 %, respectively. The inducing effect was diminished resulting in dabigatran exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days.

Co-medications with platelet-inhibitors:

Acetylsalicylic acid (ASA): Co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12 % to 18 % and 24 % with 81 mg and 325 mg ASA, respectively. It was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110 or 150 mg bid may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was however, also observed for warfarin.

NSAIDs: NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate.
For SPAF: NSAIDs increased the risk of bleeding in all treatment groups.
Clopidogrel: In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ and the coagulation measures for dabigatran effect, aPTT, ECT or TT (anti FIIa), or the inhibition of platelet aggregation (IPA) as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300 or 600 mg clopidogrel, dabigatran $AUC_{t,ss}$ and $C_{max,ss}$ were increased by about 1.3- to 1.4-fold (+30 to 40%) (see above subsection on ASA).

Antiplatelets or other anticoagulants: The concomitant use of dabigatran etexilate and antiplatelets or other anticoagulants may increase the risk of bleeding (see section 4.4).

Co-medication with selective serotonin re-uptake inhibitors:
SSRIs increased the risk of bleeding in all treatment groups.

Co-medication with gastric pH-elevating agents:
The changes in dabigatran exposure determined by population pharmacokinetic analysis caused by PPIs and antacids were not considered clinically relevant.

Pantoprazole: When dabigatran etexilate was coadministered with pantoprazole, a decrease in dabigatran area under the plasma concentration-time curve of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors were co-administered with dabigatran etexilate and no effects on bleeding or efficacy were observed.
For SPAF: PPI co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (- 11 %). Accordingly, PPI comedication seemed to be not associated with a higher incidence of stroke or SEE, especially in comparison with warfarin, and hence, the reduced bioavailability by pantoprazole co-administration seemed to be of no clinical relevance.

Ranitidine: Ranitidine administration together with dabigatran etexilate had no meaningful effect on the extent of absorption of dabigatran.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Pellet Blend
Tartaric acid
Hydroxypropyl methyl cellulose
Talc

Dabigatran Blend
Dabigatran etexilate mesylate
Hydroxy propyl cellulose
Croscarmellose sodium
Magnesium stearate

Hypromellose Hard Capsule Shell Cap & Body
Titanium dioxide
Hypromellose

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

24 months

6.4 Special Precautions for Storage

Store below 30°C.

Store in original package in order to protect from moisture.

Do not put the capsules in pill boxes or pill organizers unless capsules can be maintained in the original package.

7. DOSAGE FORM AND PACKAGING AVAILABLE

DABIFIB is available in 3 x 10's pack size

10's capsules of DABIFIB are packed in a blister of 1.6 gsm Polyester/ 0.02 Alu Foil/ 15 gsm LDPE Lid Foil and 45-micron Aluminium Foil. 3 blisters are packed into an outer box with one package insert.

8. MANUFACTURER

MSN Laboratories Private Limited,
Formulations Division, Unit-II,
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Nandigama (Village & Mandal),
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9. PRODUCT REGISTRATION HOLDER IN MALAYSIA

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10. DATE OF REVISION OF THE TEXT

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