Package Insert

1. NAME OF THE MEDICINAL PRODUCT

Dabitored (Dabigatran Etexilate Capsules 150 mg)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each hard capsule contains 150 mg of Dabigatran Etexilate (as mesilate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule for oral use.

White to Yellow coloured pellets filled in size '0' HPMC capsule shell with opaque blue colour cap and opaque yellow colored body imprinted ' ' (logo) on cap and '802' on body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

110mg capsule:
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.

150mg 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 Dosage and Administration

Adults:

Primary prevention of Venous Thromboembolism (pVTEp) events in adult patients who have undergone elective knee replacement surgery:
The recommended dose of DABITORED 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 DABITORED 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 DABITORED 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 DABITORED 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 DABITORED is 220 mg taken as one 110 mg capsule twice daily:
- Patients aged 80 years orabove
- Patients who receive concomitantverapamil

For the following groups the daily dose of DABITORED 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 75-80years
- Patients with moderate renalimpairment
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk ofbleeding

For DVT/PE the recommendation for the use of DABITORED 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 Dabitored, 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 DABITORED 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 DABITORED 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).

Dabitored 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 Dabitored 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 DABITORED 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 DABITORED is also 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of DABITORED 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 DABITORED 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 DABITORED 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 DABITORED 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 DABITORED 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 DABITORED 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 DABITORED 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 DABITORED 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 Dabitored 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive Dabitored 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 DABITORED. Simultaneous initiation of treatment with DABITORED and verapamil should also be avoided.

Treatment with Dabitored 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 Dabitored and verapamil. In this situation DABITORED 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

Dabitored and verapamil. In this situation DABITORED 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 Dabitored exposure. When excessive Dabitored 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 DABITORED 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:
DABITORED should be resumed/ started after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequeate 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).

Children and adolescents:
pVTEp and SPAF:
DABITORED has not been investigated in patients <18 years of age. Treatment of children with DABITORED is therefore not recommended.

DVT/PE:
DABITORED is under investigation in patients < 18 years.
The safety and efficacy in children has not yet been established. Treatment of children with DABITORED is therefore not recommended.

Switching from DABITORED treatment to parenteral anticoagulant:
pVTEp:
It is recommended to wait 24 hours after the last dose before switching from DABITORED 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 DABITORED to a parenteral anticoagulant.

Switching from parenteral anticoagulants treatment to DABITORED:
DABITORED 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 DABITORED:
SPAF and DVT/PE:
The Vit. K antagonist should be stopped. DABITORED can be given as soon as the INR is < 2.0.

Switching from DABITORED 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 Dabitored.
• CrCL ≥ 30-< 50 ml/min, start VKA 2 days before discontinuing Dabitored.

Because DABITORED can impact the International Normalized Ratio (INR), the INR will better reflect VKA's effect

only after DABITORED 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 DABITORED while being cardioverted.

Catheter ablation for atrial fibrillation:
SPAF:
Catheter ablation can be conducted in patients on 150 mg twice daily DABITORED treatment. DABITORED 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 DABITORED in combination with antiplatelets after haemostasis is achieved (see "Pharmacological Properties").

Missed dose
pVTEp:
Continue with your remaining daily doses of DABITORED 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 DABITORED 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
DABITORED can be taken with or without food. DABITORED 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.

4.3 CONTRAINDICATIONS

- 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 on Dosage and Administration), 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 on Drug Interactions)
- 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 on Drug Interactions)
- Prosthetic heart valves requiring anticoagulant treatment (see section on Pharmacological Properties).

4.4 SPECIAL WARNINGS AND PRECAUTIONS

Haemorrhagic risk:
As with all anticoagulants, DABITORED should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with DABITORED. 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 Dabitored is required, the specific reversal agent (PRAXBIND, idarucizumab) is available (see "Surgery and Interventions", "Pre-operative Phase" and "Overdose".)

DABITORED treatment does not require anticoagulant monitoring. The INR test is unreliable in patients on DABITORED 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 Dabitored activity.

Dabitored related anticoagulation can be assessed by ECT or TT. If ECT or TT is not available, the aPTT test provides an approximation of DABITORED's anticoagulant activity.

For SPAF: 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. DABITORED is contraindicated in cases of severe renal impairment (CrCL < 30 mL/min).

Patients who develop acute renal failure should discontinue DABITORED.

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

The concomitant use of DABITORED 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, tacrolismus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir.

The concomitant use of DABITORED with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasevir has been shown to increase exposure of Dabitored and may increase the risk of bleeding.

The concomitant use of dronedarone increases exposure of Dabitored and is not recommended (see "PK in specific populations").

The concomitant use of ticagrelor increases the exposure to Dabitored 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 DABITORED. There is limited evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with DABITORED 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 antiplatelets 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 DABITORED with the strong P-gp inducer rifampicin reduces Dabitored plasma concentrations. Other P-gp inducers such as St. John`s Wort or carbamazepine are also expected to reduce Dabitored plasma concentrations, and should be co-administered with caution (see "Drug Interactions" 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 Dabitored 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 Dabitored in patients with antiphospholipid syndrome.

Surgery and Interventions:

Patients on DABITORED who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require the temporary discontinuation of DABITORED (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 DABITORED is available.

Reversing Dabitored therapy exposes patients to the thrombotic risk of their underlying disease. DABITORED 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 DABITORED while being cardioverted. DABITORED treatment (150 mg twice daily) does not need to be interrupted in patients undergoing catheter ablation for atrial fibrillation (see "Dosage and administration").

Preoperative Phase:
Due to an increased risk of bleeding DABITORED may be stopped temporarily in advance of invasive or surgical procedures.

Emergency Surgery or Urgent Procedure:
The specific reversal agent (PRAXBIND, idarucizumab) of DABITORED is available for the rapid reversal of the anticoagulation effect (see "Surgery and Interventions").

Acute Surgery/Intervention:
DABITORED 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, DABITORED 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 DABITORED 2-4 days before surgery. Clearance of Dabitored 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 Dabitored 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)

*for more details see Table 13 "Pharmacokinetics"

DABITORED is contraindicated in patients with severe renal dysfunction (CrCl <30 mL/min) but should this occur then DABITORED 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 DABITORED. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma.

Post Procedural Period:
DABITORED treatment can be resumed / started after complete haemostasis is achieved.

4.5 DRUG INTERACTIONS

The concomitant use of DABITORED with treatments that act on haemostasis or coagulation including Vitamin K antagonists can markedly increase the risk of bleeding (See "Special precautions and warnings").

Dabitored and Dabitored 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 Dabitored or Dabitored (see "PK in specific populations").

P-glycoprotein interactions

P-glycoprotein inhibitors:

Dabitored 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 Dabitored 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 DABITORED in this indication, please see "Dosage and administration" 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 DABITORED 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 DABITORED in this indication.

***Amiodarone*:** Dabitored 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 DABITORED (150mg) was coadministered with oral verapamil, the C_{max} and AUC of Dabitored 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: Dabitored exposure in healthy subjects was increased by 1.5 fold (+53 %) in the presence of quinidine (see "PK in specific populations").

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

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

***Dronedarone*:** Dabitored 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").

Tricagrelor: Dabitored 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 Dabitored.
Dabitored 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 Dabitored. The increase in exposure was less pronounced when the 180 mg ticagrelor loading dose was given two hours after Dabitored intake (+27%).

P- glycoprotein substrate:
Digoxin: In a study performed with 24 healthy subjects, when DABITORED was coadministered with digoxin, no changes on digoxin and no clinical relevant changes on Dabitored exposure have been observed (see "PK in specific populations").

P-glycoprotein inducers:
After 7 days of treatment with 600 mg rifampicin qd total Dabitored $AUC_{0-\infty}$ 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 Dabitored and should be avoided (see "Special warnings and precautions" 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 DABITORED and when pregnant, women should not be treated with DABITORED 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

The safety of DABITORED has been evaluated overall in 38,141 patients in 11 clinical trials; thereof 23,393 DABITORED patients were investigated.

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):
In the primary VTE prevention trials after elective total hip replacement or total knee replacement surgery a total of 10,795 patients were treated in 6 controlled studies with at least one dose of Dabitored (150 mg qd, 220 mg qd, enoxaparin). 6,684 of the 10,795 patients were treated with 150 or 220 mg once daily of Dabitored. In total, about 9% of patients treated for elective hip or knee surgery (short-term treatment for up to 42 days) experienced adverse reactions.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
In the RE-LY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation a total of 12,042 patients were treated with Dabitored. Of these 6,059 were treated with 150 mg twice daily of Dabitored, while 5,983 received doses of 110 mg twice daily. 22% of patient with atrial fibrillation treated for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years) experienced adversereactions.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):
In the acute DVT/PE treatment trials (RE-COVER, RE-COVER II) a total of 2,553 patients were included in the safety analysis for Dabitored. All patients were treated with Dabitored 150 mg bid. 14% of patients treated for acute DVT/PE treatment (long-term treatment up to 6 months) experienced adverse reactions.

Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):
In the recurrent DVT/PE prevention trials (RE-MEDY, RE-SONATE) a total of 2,114 patients were treated with Dabitored; 552 of the 2,114 patients were rolled over from the RE-COVER trial (acute DVT/PE treatment) into the RE-MEDY trial and are counted in both the acute and recurrent patient totals. All patients were treated with Dabitored 150 mg bid and 15% of patients treated for recurrent DVT/PE prevention (long-term treatment up to 36 months) experienced adverse reactions.

Bleeding
Bleeding is the most relevant adverse reaction of DABITORED; dependent of the indication bleeding of any type or severity occurred in approximately 14 % of patients treated short-term for elective hip or knee replacement surgery, in long-term treatment in yearly 16.6 % of patient with atrial fibrillation treated for the prevention of stroke and systemic embolism and in 14.4% of patients with acute DVT and/or PE. In the recurrent DVT/PE trial RE-MEDY 19.4% and in the RE-SONATE trial 10.5% of patients experienced any bleeding.

Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):
Overall bleeding rates were similar between treatment groups and not significantly different.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
Major bleeding fulfilled one or more of the following criteria:
• Bleeding associated with a reduction in hemoglobin of at least 20 grams per liter or leading to a transfusion of at least 2 units of blood or packed cells;

• Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding.
Major bleeds were classified as life-threatening if they fulfilled one or more of the following criteria:
• Fatal bleed; symptomatic intracranial bleed; reduction in hemoglobin of at least 50 grams per liter; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic agents; a bleed that necessitated surgical intervention.

Subjects randomized to Dabitored 110 mg twice daily and 150mg twice daily had a significantly lower risk for life-threatening bleeds, haemorrhagic stroke and intracranial bleeding compared to warfarin [$p < 0.05$]. Both dose strengths of Dabitored had also a statistically significant lower total bleed rate. Subjects randomized to Dabitored 110mg twice daily had a signficantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81, p=0.0027).

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):
The definition of major bleeding events (MBEs) followed the recommendations of the International Society on Thrombosis and Haemostasis. A bleeding event was categorised as an MBE if it fulfilled at least one of the following criteria:
- Fatal bleeding
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome. In order for bleeding in a critical area or organ to be classified as an MBE it had to be associated with a symptomatic clinical presentation.
- Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells.

In a pooled analysis of the two pivotal trials (RE-COVER, RE-COVER II) in acute DVT/PE treatment, subjects randomized to Dabitored had lower rates of the following bleeding events, which were statistically significant:
- Major bleeding events (hazard ratio 0.60 (0.36, 0.99))
- Major or clinically relevant bleeding events (CRBEs) (hazard ratio 0.56 (0.45, 0.71))
- Any bleeding events (hazard ratio 0.67 (0.59, 0.77)) All of which were superior vs. warfarin.

Bleeding events for both treatments are counted from the first intake of Dabitored or warfarin after the parenteral therapy has been discontinued (oral only treatment period). This includes all bleeding events which occurred during Dabitored therapy. All bleeding events which occurred during warfarin therapy are included except for those during the overlap period between warfarin and parenteral therapy.

Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE): The definition of MBEs followed the recommendations of the International Society on Thrombosis and Haemostasis. A bleeding in RE-MEDY event was categorised as an MBE if it fulfilled at least one of the following criteria:
- Fatal bleeding
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome. In order for bleeding in a critical area or organ to be classified as an MBE it had to be associated with a symptomatic clinical presentation.
- Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells.

In RE-MEDY, patients randomized to Dabitored had significantly less bleeds compared to warfarin for the following categories: major bleeding events or clinically relevant bleeding events (hazard ratio 0.55 (0.41, 0.72), $p<0.0001$) and any bleeding events (hazard ratio 0.71 (0.61, 0.83), $p<0.0001$).

A bleeding event in RE-SONATE was categorised as an MBE if it fulfilled at least one of the following criteria:
- Fatal bleeding
- Associated with a fall in haemoglobin of 2 g/dL or more
- Led to the transfusion of $\geq$ 2 units packed cells or whole blood
- Occurred in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal

In RE-SONATE, the rates of MBE were low (2 patients with MBEs (0.3%) for Dabitored vs. 0 patients with MBE (0%) for placebo. The rate of major bleeding events or clinically relevant bleeding events were higher with Dabitored compared with placebo (5.3% vs. 2.0%).

Tabulated summary of adverse reactions:
Adverse reactions classified by SOC and MedDRA preferred terms reported from any treatment group per population of all controlled studies are shown in the listings below.
Table 2 lists identified adverse reactions applicable to all indications. Table 3 lists indication specific adverse reactions identified.

Adverse reactions are generally associated to the pharmacological mode of action of Dabitored and represent bleeding

associated events that may occur in different anatomical regions and organs.

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):
In patients treated for VTE prevention after hip or knee replacement surgery the observed incidences of adverse reactions of Dabitored were in the range of enoxaparin.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
The observed incidences of adverse reactions of Dabitored in patients treated for stroke prevention in patients with atrial fibrillation were in the range of warfarin except gastrointestinal disorders which appeared at a higher rate in the Dabitored arms.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):
The overall frequency of adverse reactions in patients receiving DABITORED for acute DVT/PE treatment was lower for DABITORED compared to warfarin (14.2% vs. 18.9%).

Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):
The overall frequency of adverse reactions in patients treated for recurrent DVT/PE prevention was lower for DABITORED compared to warfarin (14.6% vs. 19.6%); compared to placebo the frequency was higher (14.6% vs. 6.5%).

Table 2: 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

Table 3: 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 DABITORED may lead to haemorrhagic complications due to its pharmacodynamic properties. Doses of DABITORED 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 Dabitored 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 DABITORED is available (see section “Special warnings & precautions; “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 Dabitored 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, Dabitored 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

Pharmacotherapy group:	oral direct thrombin inhibitor
ATC Code:	B01AE07 - Dabitored

Mode of Action
Dabitored is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, Dabitored is rapidly absorbed and converted to Dabitored by esterase- catalysed hydrolysis in plasma and in the liver. Dabitored 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. Dabitored 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 Dabitored after intravenous administration and of Dabitored after oral administration in various animal models of thrombosis.

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

5.2 PHARMACOKINETICS PROPERTIES

Absorption

After oral administration of Dabitored in healthy volunteers, the pharmacokinetic profile of Dabitored in plasma is characterized by a rapid increase in plasma concentrations with peak concentration (Cmax) attained within 0.5 and 2.0 hours post administration. Cmax and the area under the plasma concentration-time curve (AUC) were dose proportional.

The absolute bioavailability of Dabitored following oral administration of Dabitored as HPMC capsule was approximately 6.5 %.

Food does not affect the bioavailability of Dabitored 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 Dabitored. Therefore, patients should be advised not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages) (see "Dosage and administration").

A study evaluating post-operative absorption of Dabitored, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration, or at 7 to 9 hours following surgery (BISTRO Ib). It is noted however that contributing factors such as anesthesia, gastrointestinal paresis, and surgical effects will mean that a proportion of patients will experience absorption delay independent of the oral drug formulation.
Although this study did not predict whether impaired absorption persists with subsequent doses, it was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of Dabitored is rapid with peak plasma concentrations attained 2 hours after drug administration.

Distribution

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

Biotransformation

After oral administration, Dabitored is rapidly and completely converted to Dabitored, which is the active form in plasma. The cleavage of the prodrug Dabitored by esterase-catalysed hydrolysis to the active principle Dabitored is the predominant metabolic reaction. Dabitored 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 Dabitored in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabitored 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 Cmax, plasma concentrations of Dabitored 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 13.

Metabolism and excretion of Dabitored were studied following a single intravenous dose of radiolabeled Dabitored in healthy male subjects. After an intravenous dose, the Dabitored-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 13: Half-life of total Dabitored 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 Dabitored after the oral administration of Dabitored 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 Dabitored 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 Dabitored 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 Dabitored concentrations, respectively. The amount of drug cleared by dialysis is proportional to the blood flow rate. The anticoagulant activity of Dabitored 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 Dabitored 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 Dabitored 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:
Specific pharmacokinetic studies with elderly subjects in phase 1 studies showed an increase of 1.4- to 1.6- fold (+40 to 60%) in the AUC and of more than 1.25-fold (+25 %) in C_{max} compared to young subjects.
The $AUC_{\tau,ss}$ and $C_{max,ss}$ in male and female elderly subjects (> 65 y) were approximately 1.9 fold and 1.6- fold higher for elderly females compared to young females and 2.2 and 2.0 fold higher for elderly males than in male subjects of 18 - 40 years of age.

The observed increase of Dabitored exposure correlated with the age-related reduction in creatinine clearance.
The effect by age on exposure to Dabitored was confirmed in the RE-LY study 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 Dabitored exposure was seen in 12 subjects in a phase 1 study with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls.

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):
Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥ 2 Upper Limit Normal (ULN) were excluded in clinical trials.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF): Patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥ 2 Upper Limit Normal (ULN), or hepatitis A, B or C were excluded in clinical trials.

Treatment of acute deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE): Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥ 2 Upper Limit Normal (ULN) were excluded in clinical trials.

Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE): Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥ 2 Upper Limit Normal (ULN) were excluded in clinical trials.

Body weight:
The Dabitored trough concentrations were about 20% lower in patients with a BW > 100 kg compared with 50 - 100 kg. The majority (80.8%) of the subjects were in the ≥ 50 kg and < 100 kg category with no clear difference detected. Limited data in patients ≤ 50 kg are available.

Gender:
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):
Drug exposure in the primary VTE prevention studies was about 1.4- to 1.5-fold (+ 40 % to 50 %) higher in female patients. This finding had no clinical relevance.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF): In atrial fibrillation patients females had on average 1.3-fold (+30 %) higher trough and post-dose concentrations. This finding had no clinical relevance.

Ethnic origin:
The pharmacokinetics of Dabitored was investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin does not affect the pharmacokinetics of Dabitored in a clinically relevant manner.
Limited pharmacokinetic data in black patients are available which suggest no relevant differences.

Drug-drug interactions (studies):

In vitro interaction studies did not show any inhibition or induction of cytochrome P450. This has been confirmed by in vivo studies in healthy volunteers, who did not show any interaction between Dabitored treatment and the following drugs: atorvastatin (CYP3A4), and diclofenac (CYP2C9).

***Atorvastatin*:** When Dabitored was coadministered with atorvastatin, a CYP3A4 substrate, exposure of atorvastatin, atorvastatin metabolites and of Dabitored were unchanged indicating a lack of interaction.

***Diclofenac*:** When Dabitored was coadministered with diclofenac, a CYP2C9 substrate, pharmacokinetics of both drugs remained unchanged indicating a lack of interaction between Dabitored and diclofenac.

P-gp inhibitor / inducer interactions:

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

Co-medication with P-gp inhibitors:

***Amiodarone*:** When Dabitored 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 Dabitored AUC and Cmax were increased by about 1.6-fold and 1.5-fold (+60 % and 50 %), respectively.

For SPAF: In the population pharmacokinetics study from RE-LY, no important changes in Dabitored trough levels were observed in patients who received amiodarone (see “Drug interactions”).

***Dronedarone*:** When Dabitored and dronedarone were given at the same time total Dabitored AUC0-∞ 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 Dabitored were not affected by dronedarone. When single and multiple doses of dronedarone were given 2 h after Dabitored, the increases in Dabitored AUC0-∞ were 1.3-fold and 1.6 fold, respectively.

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

The greatest elevation of Dabitored exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to Dabitored intake (increase of Cmax 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 Cmax by about 1.9-fold (+90%) and AUC by about 1.7-fold (+70%)) or administration of multiple doses of verapamil (increase of Cmax 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 Dabitored (increase of Cmax by about 10% and AUC by about 20%). This is explained by completed Dabitored 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 from RE-LY, no important changes in Dabitored trough levels were

observed in patients who received verapamil (see “Drug interactions”).

Ketoconazole: Systemic ketoconazole increased total Dabitored AUC0-∞ 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 Dabitored 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. Dabitored was given bid over 3 consecutive days, on the 3rd day either with or without quinidine. Dabitored $AUC_{\tau,ss}$ 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 75mg Dabitored was coadministered simultaneously with a loading dose of 180 mg ticagrelor, the Dabitored AUC and Cmax 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 Dabitored exposure is reduced to 1.56-fold and 1.46-fold (+56% and 46%) for Cmax and AUC, respectively.
Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg Dabitored (in steady state) increased the Dabitored $AUC_{\tau,ss}$ and by $C_{max,ss}$ by 1.49-fold and 1.65-fold (+49% and 65%), respectively, compared with Dabitored given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg Dabitored (in steady state), the increase of Dabitored $AUC_{\tau,ss}$ and $C_{max,ss}$ was reduced to 1.27-fold and 1.23-fold (+27% and 23%), respectively, compared with Dabitored given alone. Concomitant administration of 90 mg ticagrelor BID (maintenance dose) with 110 mg Dabitored increased the adjusted Dabitored $AUC_{\tau,ss}$ and $C_{max,ss}$ 1.26-fold and 1.29-fold, respectively, compared with Dabitored given alone.

Co-medication with P-gp substrates:

***Digoxin*:** When Dabitored was coadministered with digoxin, a P-gp substrate, no PK-interaction was observed. Neither Dabitored nor the pro-drug Dabitored is a clinically relevant P-gp inhibitor.

Co-medication with P-gp inducers:

***Rifampicine*:** Pre-dosing of the probe inducer rifampicin at a dose of 600 mg qd for 7 days decreased total Dabitored peak and total exposure by 65.5 and 67 %, respectively. The inducing effect was diminished resulting in Dabitored 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): The effect of concomitant administration of Dabitored and acetylsalicylic acid (ASA) on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomized ASA coadministration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg Dabitored twice daily may increase the risk for any bleeding from 12 % to 18 % and 24% with 81 mg and 325 mg ASA, respectively.
From the data gathered in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with Dabitored 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 Dabitored. There is limited evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with Dabitored and this has not suggested additional bleeding risk.

For SPAF: NSAIDs increased the risk of bleeding in RE-LY in all treatment groups.

***Clopidogrel*:** In a phase I study in young healthy male volunteers, the concomitant administration of Dabitored and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. In addition, Dabitored $AUC_{\tau,ss}$ and $C_{max,ss}$ and the coagulation measures for Dabitored 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, Dabitored $AUC_{t,ss}$ 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 Dabitored and antiplatelets or other anticoagulants may increase the risk of bleeding (see “Special warnings and precautions”).

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

Co-medication with gastric pH-elevating agents:

The changes in Dabitored exposure determined by population pharmacokinetic analysis caused by PPIs and antacids were not considered clinically relevant because the magnitude of the effect were minor (fractional decrease in bioavailability not significant for antacids and 14.6% for PPIs.

***Pantoprazole*:** When Dabitored was coadministered with pantoprazole, a decrease in Dabitored area under the plasma concentration-time curve of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors were co-administered with Dabitored in clinical trials and no effects on bleeding or efficacy were observed.

For SPAF: In the phase III study, RE-LY, 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 Dabitored had no meaningful effect on the extent of absorption of Dabitored.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content: Tartaric acid, acacia, hypromellose, dimethicone, talc, hydroxypropyl cellulose.

HPMC capsule shell: Carragenan, potassium chloride, titanium dioxide, FD&C Yellow no. 6, FD&C Blue No. 2, hypromellose and purified water.

Printing ink: Red Iron Oxide, Yellow Iron Oxide, FD&C Blue No. 2, Carnauba Wax, White Shellac, Glyceryl Monooleate 1-Butanol & Dehydrated Ethyl Alcohol.

6.2 NATURE AND CONTENTS OF CONTAINER

60 hard capsules in each HDPE Bottle

6.2 STORAGE CONDITIONS

Store below 30°C. Store in original package in order to protect from moisture. After opening - Store below 25°C and Use within 60 days

7. NAME AND ADDRESS OF MANUFACTURER

Dr. Reddy’s Laboratories Limited,
FTO-SEZ-Process Unit-01, Survey No. 57 to 59, 60, 62 &72,
Sector No: 9 to 14 & 17 to 20, Devunipalavalasa (V),
Ranasthalam (M), Srikakulam District, Andhra Pradesh—
532409, INDIA.

8. PRODUCT REGISTRATION HOLDER

Dr. Reddy's Laboratories Malaysia Sdn. Bhd. (1238154-X)
Unit NO. SO-29-07 AND SO-29-08, MENARA 1, STRATA OFFICE, NO.3 JALAN BANGSAR, KL ECO CITY, 59200 KUALA LUMPUR MALAYSIA

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