SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HETSOLID 110mg(Dabigatran Etexilate Capsules 110mg).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsules

Cream opaque cap/Cream opaque body size '1' HPMC capsules imprinted with 'H' on cap and 'D16' on body with black ink, filled with mixture of off white to yellowish white pellets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Treatment of Venous Thromboembolism and prevention of recurrent Venous Thromboembolism in paediatric patients from birth to less than 18 years of age.

4.2 Posology and method of Administration

Posology

Primary prevention of Venous Thromboembolism in orthopaedic surgery

The recommended doses of dabigatran etexilate capsules and the duration of therapy for primary prevention of Venous Thromboembolism in orthopaedic surgery are shown in table 1.

Table 1: Dose recommendations and duration of therapy for primary prevention of Venous Thromboembolism in orthopaedic surgery

	Treatment initiation on the day of surgery 1-4 hours after completed surgery	**Maintenance dose starting on the first day after surgery**	**Duration of maintenance dose**
Patients following elective knee replacement surgery	single capsule of 110 mg dabigatran etexilate capsules	220 mg dabigatran etexilate once daily taken as 2 capsules of 110 mg	10 days
Patients following elective hip replacement surgery			28-35 days

Dose reduction recommended			
Patients with moderate renal impairment (creatinine clearance (CrCL 30-50 mL/min)	single capsule of 75 mg dabigatran etexilate capsules	150 mg dabigatran etexilate once daily taken as 2 capsules of 75 mg	10 days (knee replacement surgery) or 28-35 days (hip replacement surgery)
Patients who receive concomitant verapamil*, amiodarone, quinidine			
Patients aged 75 or above			

*For patients with moderate renal impairment concomitantly treated with verapamil see Special populations

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.

Assessment of renal function prior to and during dabigatran etexilate capsules treatment

In all patients and especially in the elderly (>75 years), as renal impairment may be frequent in this age group:

• Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with dabigatran etexilate capsules to exclude patients with severe renal impairment (i.e. CrCL <30 mL/min).

• Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products).

The method to be used to estimate renal function (CrCL in mL/min) is the Cockcroft-Gault method.

Missed dose

It is recommended to continue with the remaining daily doses of dabigatran etexilate at the same time of the next day.

No double dose should be taken to make up for missed individual doses.

Discontinuation of dabigatran etexilate

Dabigatran etexilate capsules treatment should not be discontinued without medical advice. Patients should be instructed to contact the treating physician if they develop gastrointestinal symptoms such as dyspepsia.

Switching

Dabigatran etexilate capsules treatment to parenteral anticoagulant:

It is recommended to wait 24 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant.

Parenteral anticoagulants to dabigatran etexilate capsules:

The parenteral anticoagulant should be discontinued and dabigatran etexilate should be started 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 Unfractionated Heparin (UFH)) (see section 4.5).

Special populations

Renal impairment

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

In patients with moderate renal impairment (CrCL 30-50 mL/min), a dose reduction is recommended.

Concomitant use of dabigatran etexilate with mild to moderate P-glycoprotein (P-gp) inhibitors, i.e. amiodarone, quinidine or verapamil

Dosing should be reduced as indicated in table 1. In this situation dabigatran etexilate capsules and these medicinal products should be taken at the same time.

In patients with moderate renal impairment and concomitantly treated with verapamil, a dose reduction of dabigatran etexilate capsules to 75 mg daily should be considered.

Elderly

For elderly patients >75 years, a dose reduction is recommended.

Weight

There is very limited clinical experience in patients with a body weight <50 kg or >110 kg at the recommended posology. Given the available clinical and kinetic data no adjustment is necessary, but close clinical surveillance is recommended.

Gender

No dose adjustment is necessary.

Paediatric population

There is no relevant use of dabigatran etexilate capsules in the paediatric population for the indication of primary prevention of venous thromboembolic events in patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

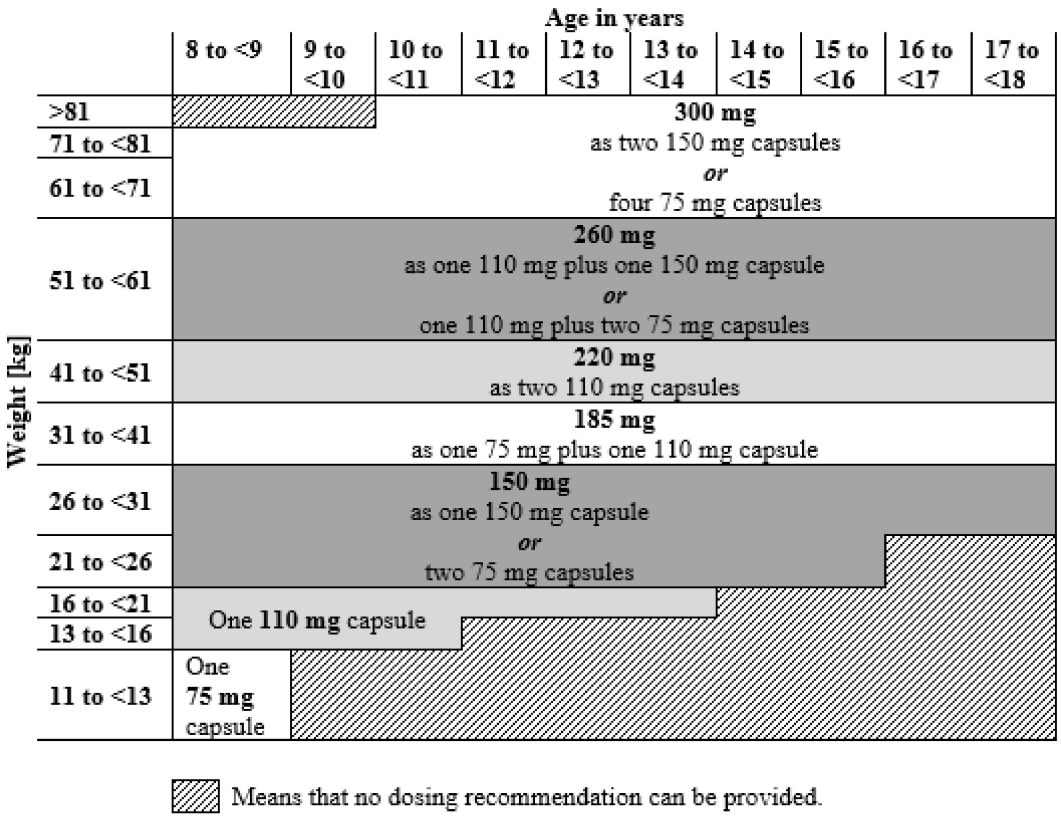
Treatment of* venous thromboembolic *and prevention of recurrent* venous thromboembolic *in paediatric patients

For the treatment of VTE in paediatric patients, treatment should be initiated following treatment with a parenteral anticoagulant for at least 5 days. For prevention of recurrent VTE, treatment should be initiated following previous treatment.

Dabigatran etexilate capsules should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose of dabigatran etexilate capsules is based on the patient's age and weight as shown in table 2. The table provides the single doses which are to be administered twice daily. The dose should be adjusted according to age and weight as treatment progresses.

Table 2: Single dabigatran etexilate dose in milligrams (mg) by weight in kilograms (kg) and age in years of the patient to be administered twice daily



Assessment of renal function prior to and during treatment

Prior to the initiation of treatment, the estimated glomerular filtration rate (eGFR) should be estimated using the Schwartz formula.

Treatment with dabigatran etexilate in paediatric patients with eGFR <50 mL/min/1.73m^2 is contraindicated (see section 4.3).

Patients with an eGFR ≥50 mL/min/1.73m^2 should be treated with the dose according to table 2.

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 co-medications, etc).

Duration of use

The duration of therapy should be individualised based on the benefit risk assessment.

Missed dose

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

A double dose to make up for missed individual doses must never be taken.

Discontinuation of dabigatran etexilate

Dabigatran etexilate treatment should not be discontinued without medical advice. Patients or their caregivers should be instructed to contact the treating physician if the patient develops gastrointestinal symptoms such as dyspepsia (see section 4.8).

Switching

Dabigatran etexilate treatment to parenteral anticoagulant:

It is recommended to wait 12 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant (see section 4.5).

Parenteral anticoagulants to dabigatran etexilate:

The parenteral anticoagulant should be discontinued and dabigatran etexilate should be started 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 Unfractionated Heparin (UFH)) (see section 4.5).

Dabigatran etexilate treatment to Vitamin K antagonists (VKA):

Patients should start VKA 3 days before discontinuing dabigatran etexilate.

Because dabigatran etexilate can impact the international normalised ratio (INR), the INR will better reflect VKA's effect only after dabigatran etexilate has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

VKA to dabigatran etexilate:

The VKA should be stopped. Dabigatran etexilate can be given as soon as the INR is <2.0.

Method of administration

Dabigatran etexilate capsules is for oral use.

The capsules can be taken with or without food. The capsules 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.

• Severe renal impairment (CrCL <30 mL/min) in adult patients

• eGFR <50 mL/min/1.73m2 in paediatric patients

• 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, 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

• 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, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir

• Prosthetic heart valves requiring anticoagulant treatment.

4.4 Special warnings and special precautions for use

Haemorrhagic risk

Dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding or with concomitant use of medicinal products affecting haemostasis by inhibition of platelet aggregation. Bleeding can occur at any site during therapy with Dabigatran etexilate capsules. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

For adult patients in situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, the specific reversal agent idarucizumab is available. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran. For adult patients, fresh whole blood or fresh frozen plasma, coagulation factor concentration (activated or non-activated), recombinant factor VIIa or platelet concentrates are other possible options.

Use of platelet aggregation inhibitors such as clopidogrel and acetylsalicylic acid (ASA) or non steroidal antiinflammatory drugs (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux increase the risk of GI bleeding.

Risk factors

Table 3 summarises factors which may increase the haemorrhagic risk.

	Risk factor
Pharmacodynamic and kinetic factors	Age ≥75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment in adult patients (30-50 mL/min CrCL) • Strong P-gp inhibitors • Mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, verapamil, quinidine and ticagrelor;) Minor: • Low body weight (<50 kg) in adult patients
Pharmacodynamic interactions	• ASA and other platelet aggregation inhibitors such as clopidogrel • NSAIDs • SSRIs or SNRIs • Other medicinal products which may impair haemostasis
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Recent biopsy, major trauma • Bacterial endocarditis • Esophagitis, gastritis or gastroesophageal reflux

Limited data is available in adult patients <50 kg.

The concomitant use of dabigatran etexilate with P-gp-inhibitors has not been studied in paediatric patients but may increase the risk of bleeding.

Precautions and management of the haemorrhagic risk

For the management of bleeding complications.

Benefit-risk assessment

The presence of lesions, conditions, procedures and/or pharmacological treatment (such as NSAIDs, antiplatelets, SSRIs and SNRIs), which significantly increase the risk of major bleeding requires a careful benefit-risk assessment. Dabigatran etexilate should only be given if the benefit outweighs bleeding risks.

Limited clinical data are available for paediatric patients with risk factors, including patients with active meningitis, encephalitis and intracranial abscess. In these patients, dabigatran etexilate should only be given if the expected benefit outweighs bleeding risks.

Close clinical surveillance

Close observation for signs of bleeding or anaemia is recommended throughout the treatment period, especially if risk factors are combined (see table 3 above). Particular caution should be exercised when dabigatran etexilate is co-administered with verapamil, amiodarone, quinidine or clarithromycin (P-gp inhibitors) and particularly in the occurrence of bleeding, notably in patients having a reduced renal function.

Close observation for signs of bleeding is recommended in patients concomitantly treated with NSAIDs.

Discontinuation of dabigatran etexilate

Patients who develop acute renal failure must discontinue dabigatran etexilate (see also section 4.3).

When severe bleedings occur, treatment must be discontinued, the source of bleeding investigated and use of the specific reversal agent (idarucizumab) may be considered in adult patients. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Use of proton-pump inhibitors

The administration of a proton-pump inhibitor (PPI) can be considered to prevent GI bleeding. In case of paediatric patients local labeling recommendations for proton pump inhibitors have to be followed.

Laboratory coagulation parameters

Although this medicinal product does not in general require routine anticoagulant monitoring, the measurement of dabigatran related anticoagulation may be helpful to detect excessive high exposure to dabigatran in the presence of additional risk factors.

Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but results should be interpreted with caution due to inter-test variability.

The international normalised ratio (INR) test is unreliable in patients on dabigatran etexilate and false positive INR elevations have been reported. Therefore INR tests should not be performed.

Table 4 shows coagulation test thresholds at trough for adult patients that may be associated with an increased risk of bleeding. Respective thresholds for paediatric patients are not known (see section 5.1).

Table 4: Coagulation test thresholds at trough for adult patients that may be associated with an increased risk of bleeding.

Test (trough value)	Threshold
dTT [ng/mL]	>67
ECT [x-fold upper limit of normal]	No data
aPTT [x-fold upper limit of normal]	>1.3
INR	Should not be performed

Use of fibrinolytic medicinal products for the treatment of acute ischemic stroke

The use of fibrinolytic medicinal products for the treatment of acute ischemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the upper limit of normal (ULN) according to the local reference range.

Surgery and interventions

Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of dabigatran etexilate.

Caution should be exercised when treatment is temporarily discontinued for interventions and anticoagulant monitoring is warranted. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures. In such cases a coagulation test may help to determine whether haemostasis is still impaired.

Emergency surgery or urgent procedures

Dabigatran etexilate should be temporarily discontinued. When rapid reversal of the anticoagulation effect is required the specific reversal agent (idarucizumab) to dabigatran is available for adult patients. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran.

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

Subacute surgery/interventions

Dabigatran etexilate should be temporarily discontinued. A surgery / intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed the risk of bleeding may be increased. This risk of bleeding should be weighed against the urgency of intervention.

Elective surgery

If possible, dabigatran etexilate 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 haemostasis may be required consider stopping dabigatran etexilate 2-4 days before surgery.

Table 5 summarises discontinuation rules before invasive or surgical procedures for adult patients.

Table 5: Discontinuation rules before invasive or surgical procedures for adult patients

Renal function (CrCL in mL/min)	Estimated half-life (hours)	Dabigatran etexilate should be stopped before elective surgery	
		High risk of bleeding or major	Standard risk

		surgery	
≥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)

Discontinuation rules before invasive or surgical procedures for paediatric patients are summarised in table 6.

Table 6: Discontinuation rules before invasive or surgical procedures for paediatric patients

Renal function (eGFR in mL/min/1.73m^2)	Stop dabigatran before elective surgery
>80	24 hours before
50 – 80	2 days before
<50	These patients have not been studied (see section 4.3).

Spinal anaesthesia/epidural anaesthesia/lumbar puncture

Procedures such as spinal anaesthesia may require complete haemostatic 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 2 hours should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

Postoperative phase

Dabigatran etexilate should be restarted 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 reduced renal function (see also table 3), should be treated with caution.

Patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events

There are limited efficacy and safety data for dabigatran etexilate available in these patients and therefore they should be treated with caution.

Hip fracture surgery

There is no data on the use of dabigatran etexilate in patients undergoing hip fracture surgery. Therefore treatment is not recommended.

Hepatic impairment

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

Interaction with P-gp inducers

Concomitant administration of P-gp inducers is expected to result in decreased dabigatran plasma concentrations, and should be avoided.

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Active cancer patients (paediatric VTE)

There is limited data on efficacy and safety for paediatric patients with active cancer.

Paediatric population

For some very specific paediatric patients, e.g. patients with small bowel disease where absorption may be affected, use of an anticoagulant with parenteral route of administration should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Transporter interactions

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (see table 7) is expected to result in increased dabigatran plasma concentrations.

If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with strong P-gp inhibitors. Dose reductions may be required in combination with some P-gp inhibitors.

Table 7: Transporter interactions

P-gp inhibitors	
Concomitant use contraindicated	
Ketoconazole	Ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by 2.38-fold and 2.35-fold, respectively, after a single oral dose of 400 mg, and by 2.53-fold and 2.49-fold, respectively, after multiple oral dosing of 400 mg ketoconazole once daily.
Dronedarone	When dabigatran etexilate and dronedarone were given at the same time total dabigatran $AUC_{0-\infty}$ and C_{max} values increased by about 2.4-fold and 2.3-fold, respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold, respectively, after a single dose of 400 mg.
Itraconazole, cyclosporine	Based on *in vitro* results a similar effect as with ketoconazole may be expected.
Glecaprevir / pibrentasvir	The concomitant use of dabigatran etexilate with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasvir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.
Concomitant use not recommended	
Tacrolimus	Tacrolimus has been found *in vitro* to have a similar level of inhibitory effect on P-gp as that seen with itraconazole and cyclosporine. Dabigatran etexilate has not been clinically studied together with tacrolimus. However, limited clinical data with another P-gp substrate (everolimus) suggest that the inhibition of P-gp with tacrolimus is weaker than that observed with strong P-gp inhibitors.
Cautions to be exercised in case concomitant use (see sections 4.2 and 4.4)	
Verapamil	When dabigatran etexilate (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 sections 4.2 and 4.4).

	The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to the dabigatran etexilate intake (increase of C_{max} by about 2.8-fold and AUC by about 2.5-fold). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 1.9-fold and AUC by about 1.7-fold) or administration of multiple doses of verapamil (increase of C_{max} by about 1.6-fold and AUC by about 1.5-fold). There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 1.1-fold and AUC by about 1.2-fold). This is explained by completed dabigatran absorption after 2 hours.
Amiodarone	When dabigatran etexilate was co-administered 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 C_{max} were increased by about 1.6-fold and 1.5-fold, respectively. In view of the long half-life of amiodarone the potential for an interaction may exist for weeks after discontinuation of amiodarone (see sections 4.2 and 4.4).
Quinidine	Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1,000 mg. Dabigatran etexilate was given twice daily 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 1.53-fold and 1.56-fold, respectively with concomitant quinidine (see sections 4.2 and 4.4).
Clarithromycin	When clarithromycin (500 mg twice daily) was administered together with dabigatran etexilate in healthy volunteers, increase of AUC by about 1.19-fold and C_{max} by about 1.15-fold was observed.
Ticagrelor	When a single dose of 75 mg dabigatran etexilate was coadministered 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, respectively. After multiple doses of ticagrelor 90 mg b.i.d. the increase of dabigatran exposure is 1.56-fold and 1.46-fold 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 $C_{max,ss}$ by

	1.49-fold and 1.65-fold, 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, respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose. Concomitant administration of 90 mg ticagrelor b.i.d. (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.
Posaconazole	Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when dabigatran etexilate is co-administered with posaconazole.
P-gp inducers	
Concomitant use should be avoided.	
e.g. rifampicin, St. John´s wort (Hypericum perforatum), carbamazepine, or phenytoin	Concomitant administration is expected to result in decreased dabigatran concentrations. Pre-dosing of the probe inducer rifampicin at a dose of 600 mg once daily 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.
Protease inhibitors such as ritonavir	
Concomitant use not recommended	
e.g. ritonavir and its combinations with other protease inhibitors	These affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with dabigatran etexilate.
P-gp substrate	
Digoxin	In a study performed with 24 healthy subjects, when dabigatran etexilate was co-administered with digoxin, no changes on digoxin and no clinically relevant changes on

	dabigatran exposure have been observed.

Anticoagulants and antiplatelet aggregation medicinal products

There is no or only limited experience with the following treatments which may increase the risk of bleeding when used concomitantly with dabigatran etexilate: anticoagulants such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic medicinal products, and vitamin K antagonists, rivaroxaban or other oral anticoagulants (see section 4.3), and antiplatelet aggregation medicinal products such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran, and sulfinpyrazone (see section 4.4).

UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter or during catheter ablation for atrial fibrillation (see section 4.3).

Table 8: Interactions with anticoagulants and antiplatelet aggregation medicinal products

NSAIDs	NSAIDs given for short-term analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in a phase III clinical trial comparing dabigatran to warfarin for stroke prevention in atrial fibrillation patients (RE-LY), NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran etexilate and warfarin.
Clopidogrel	In young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ and the coagulation measures for dabigatran effect or the inhibition of platelet aggregation as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300 mg or 600 mg clopidogrel, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased by about 30-40 % (see section 4.4) .
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 (see section 4.4).
LMWH	The concomitant use of LMWHs, such as enoxaparin and dabigatran etexilate has not been specifically investigated. After switching from 3-day treatment of once daily 40 mg enoxaparin s.c., 24 hours after the last dose of enoxaparin the exposure to dabigatran was

	slightly lower than that after administration of dabigatran etexilate (single dose of 220 mg) alone. A higher anti-FXa/FIIa activity was observed after dabigatran etexilate administration with enoxaparin pre-treatment compared to that after treatment with dabigatran etexilate alone. This is considered to be due to the carry-over effect of enoxaparin treatment, and regarded as not clinically relevant. Other dabigatran related anti-coagulation tests were not changed significantly by the pre-treatment of enoxaparin.

Other interactions

Table 9: Other interactions

Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)	
SSRIs, SNRIs	SSRIs and SNRIs increased the risk of bleeding in all treatment groups of a phase III clinical trial comparing dabigatran to warfarin for stroke prevention in atrial fibrillation patients (RE-LY).
Substances influencing gastric pH	
Pantoprazole	When Dabigatran etexilate was co-administered with pantoprazole, a decrease in the dabigatran AUC of approximately 30% was observed. Pantoprazole and other proton-pump inhibitors (PPI) were co-administered with Dabigatran etexilate in clinical trials, and concomitant PPI treatment did not appear to reduce the efficacy of Dabigatran etexilate.
Ranitidine	Ranitidine administration together with dabigatran etexilate had no clinically relevant effect on the extent of absorption of dabigatran.

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and have no *in vitro* effects on human cytochrome P450 enzymes. Therefore, related medicinal product interactions are not expected with dabigatran.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should avoid pregnancy during treatment with Dabigatran etexilate capsules.

Pregnancy

There is limited amount of data from the use of Dabigatran etexilate capsules in pregnant women.

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Dabigatran etexilate capsules should not be used during pregnancy unless clearly necessary.

Breast-feeding

There are no clinical data of the effect of dabigatran on infants during breast-feeding.

Breast-feeding should be discontinued during treatment with Dabigatran etexilate capsules.

Fertility

No human data available.

In animal studies an effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (representing a 5-fold higher plasma exposure level compared to patients). No other effects on female fertility were observed. There was no influence on male fertility. At doses that were toxic to the mothers (representing a 5- to 10-fold higher plasma exposure level to patients), a decrease in foetal body weight and embryofoetal viability along with an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients).

4.7 Effects on ability to drive and use machines

Dabigatran etexilate has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Dabigatran etexilate has been evaluated in clinical trials overall in approximately 64,000 patients; thereof approximately 35,000 patients were treated with dabigatran etexilate.

In actively controlled VTE prevention trials 6,684 patients were treated with 150 mg or 220 mg dabigatran etexilate daily.

The most commonly reported events are bleedings occurring in approximately 14 % of patients; the frequency of major bleeds (including wound site bleedings) is less than 2 %.

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.

Tabulated list of adverse reactions

Table 10 shows the adverse reactions ranked under headings of System Organ Classes (SOC) and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 10: Adverse reactions

SOC / Preferred term	Frequency
Blood and lymphatic system disorders	
Haemoglobin decreased	Common
Anaemia	Uncommon
Haematocrit decreased	Uncommon
Thrombocytopenia	Rare
Neutropenia	Not known
Agranulocytosis	Not known
Immune system disorder	
Drug hypersensitivity	Uncommon
Anaphylactic reaction	Rare
Angioedema	Rare
Urticaria	Rare
Rash	Rare
Pruritus	Rare

Bronchospasm	Not known
Nervous system disorders	
Intracranial haemorrhage	Rare
Vascular disorders	
Haematoma	Uncommon
Wound haemorrhage	Uncommon
Haemorrhage	Rare
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Uncommon
Haemoptysis	Rare
Gastrointestinal disorders	
Gastrointestinal haemorrhage	Uncommon
Rectal haemorrhage	Uncommon
Haemorrhoidal haemorrhage	Uncommon
Diarrhoea	Uncommon
Nausea	Uncommon
Vomiting	Uncommon
Gastrointestinal ulcer, including oesophageal ulcer	Rare
Gastroesophagitis	Rare
Gastroesophageal reflux disease	Rare
Abdominal pain	Rare
Dyspepsia	Rare
Dysphagia	Rare
Hepatobiliary disorders	
Hepatic function abnormal/ Liver function Test abnormal	Common
Alanine aminotransferase increased	Uncommon
Aspartate aminotransferase increased	Uncommon

Hepatic enzyme increased	Uncommon
Hyperbilirubinaemia	Uncommon
Skin and subcutaneous tissue disorder	
Skin haemorrhage	Uncommon
Alopecia	Not known
Musculoskeletal and connective tissue disorders	
Haemarthrosis	Uncommon
Renal and urinary disorders	
Genitourological haemorrhage, including haematuria	Uncommon
General disorders and administration site conditions	
Injection site haemorrhage	Rare
Catheter site haemorrhage	Rare
Bloody discharge	Rare
Injury, poisoning and procedural complications	
Traumatic haemorrhage	Uncommon
Post procedural haematoma	Uncommon
Post procedural haemorrhage	Uncommon
Post procedural discharge	Uncommon
Wound secretion	Uncommon
Incision site haemorrhage	Rare
Anaemia postoperative	Rare
Surgical and medical procedures	
Wound drainage	Rare
Post procedural drainage	Rare

Description of selected adverse reactions

Bleeding reactions

Due to the pharmacological mode of action, the use of dabigatran etexilate may be associated with an increased risk of occult or overt bleeding from any tissue or organ. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. In the clinical studies mucosal bleedings (e.g. gastrointestinal, genitourinary) were seen more frequently during long term dabigatran etexilate treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit is of value to detect occult bleeding. The risk of bleedings may be increased in certain patient groups e.g. those patients with moderate renal impairment and/or on concomitant treatment affecting haemostasis or strong P-gp inhibitors (see section 4.4 Haemorrhagic risk). Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock.

Known bleeding complications such as compartment syndrome and acute renal failure due to hypoperfusion have been reported for dabigatran etexilate. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient. For adult patients, a specific reversal agent for dabigatran, idarucizumab, is available in case of uncontrollable bleeding (see Section 4.9).

The table 11 shows the number (%) of patients experiencing the adverse reaction bleeding during the treatment period in the indication primary VTE prevention after hip or knee replacement surgery in the two pivotal clinical trials, according to dose.

Table 11: Number (%) of patients experiencing the adverse reaction bleeding

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Treated	1,866 (100.0)	1,825 (100.0)	1,848 (100.0)
Major bleeding	24 (1.3)	33 (1.8)	27 (1.5)
Any bleeding	258 (13.8)	251 (13.8)	247 (13.4)

Agranulocytosis and neutropenia

Agranulocytosis and neutropenia have been reported very rarely during post approval use of dabigatran etexilate. Because adverse reactions are reported in the postmarketing surveillance setting from a population of uncertain size, it is not possible to reliably determine their frequency. The

reporting rate was estimated as 7 events per 1 million patient years for agranulocytosis and as 5 events per 1 million patient years for neutropenia.

Paediatric population

The safety of dabigatran etexilate in the treatment of VTE and prevention of recurrent VTE in paediatric patients was studied in two phase III trials (DIVERSITY and 1160.108). In total, 328 paediatric patients had been treated with dabigatran etexilate. The patients received age and weight adjusted doses of an age-appropriate formulation of dabigatran etexilate.

Overall, the safety profile in children is expected to be the same as in adults.

In total, 26% of paediatric patients treated with dabigatran etexilate for VTE and for prevention of recurrent VTE experienced adverse reactions.

Tabulated list of adverse reactions

Table 12 shows the adverse reactions identified from the studies in the treatment of VTE and prevention of recurrent VTE in paediatric patients. They are ranked under headings of System Organ Class (SOC) and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 12: Adverse reactions

	Frequency
SOC / Preferred term.	treatment of VTE and prevention of recurrent VTE in paediatric patients
Blood and lymphatic system disorders	
Anaemia	Common
Haemoglobin decreased	Uncommon
Thrombocytopenia	Common
Haematocrit decreased	Uncommon
Neutropenia	Uncommon
Agranulocytosis	Not known

Immune system disorder	
Drug hypersensitivity	Uncommon
Rash	Common
Pruritus	Uncommon
Anaphylactic reaction	Not known
Angioedema	Not known
Urticaria	Common
Bronchospasm	Not known
Nervous system disorders	
Intracranial haemorrhage	Uncommon
Vascular disorders	
Haematoma	Common
Haemorrhage	Not known
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Common
Haemoptysis	Uncommon
Gastrointestinal disorders	
Gastrointestinal haemorrhage	Uncommon
Abdominal pain	Uncommon
Diarrhoea	Common
Dyspepsia	Common
Nausea	Common
Rectal haemorrhage	Uncommon
Haemorrhoidal haemorrhage	Not known
Gastrointestinal ulcer, including oesophageal ulcer	Not known
Gastroesophagitis	Uncommon

Gastroesophageal reflux disease	Common
Vomiting	Common
Dysphagia	Uncommon
Hepatobiliary disorders	
Hepatic function abnormal/ Liver function Test abnormal	Not known
Alanine aminotransferase increased	Uncommon
Aspartate aminotransferase increased	Uncommon
Hepatic enzyme increased	Common
Hyperbilirubinaemia	Uncommon
Skin and subcutaneous tissue disorder	
Skin haemorrhage	Uncommon
Alopecia	Common
Musculoskeletal and connective tissue disorders	
Haemarthrosis	Not known
Renal and urinary disorders	
Genitourological haemorrhage, including haematuria	Uncommon
General disorders and administration site conditions	
Injection site haemorrhage	Not known
Catheter site haemorrhage	Not known
Injury, poisoning and procedural complications	
Traumatic haemorrhage	Uncommon
Incision site haemorrhage	Not known

Bleeding reactions

In the two phase III trials in the indication treatment of VTE and prevention of recurrent VTE in paediatric patients, a total of 7 patients (2.1%) had a major bleeding event, 5 patients (1.5%) a clinically relevant non-major bleeding event and 75 patients (22.9%) a minor bleeding event. The

frequency of bleeding events was overall higher in the oldest age group (12 to <18 years: 28.6%) than in the younger age groups (birth to <2 years: 23.3%; 2 to <12 years: 16.2%). Major or severe bleeding, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

4.9 Overdose

Dabigatran etexilate doses beyond those recommended, expose the patient to increased risk of bleeding.

In case of an overdose suspicion, coagulation tests can help to determine a bleeding risk. A calibrated quantitative dTT test or repetitive dTT measurements allow prediction of the time by when certain dabigatran levels will be reached, also in case additional measures e.g. dialysis have been initiated.

Excessive anticoagulation may require interruption of dabigatran etexilate treatment. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies.

Management of bleeding complications

In the event of haemorrhagic complications, dabigatran etexilate treatment must be discontinued and the source of bleeding investigated. Depending on the clinical situation appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescriber's discretion.

For adult patients in situations when rapid reversal of the anticoagulant effect of dabigatran is required the specific reversal agent (idarucizumab) antagonizing the pharmacodynamic effect of dabigatran is available. The efficacy and safety of idarucizumab have not been established in paediatric patients.

Coagulation factor concentrates (activated or non-activated) or recombinant Factor VIIa may be taken into account. There is some experimental evidence to support the role of these medicinal products in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following administration of suggested coagulation factor concentrates. Caution should be exercised when interpreting these tests. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet medicinal products have been used. All symptomatic treatment should be given according to the physician's judgement.

Depending on local availability, a consultation of a coagulation expert should be considered in case of major bleedings.

5.CLINICAL PHARMACOLOGY

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, direct thrombin inhibitors,

ATC code: B01AE07.

Mechanism 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.

Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Pharmacodynamic effects

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 clear correlation between plasma dabigatran concentration and degree of anticoagulant effect based on phase II studies. Dabigatran prolongs the thrombin time (TT), ECT, and aPTT.

The calibrated quantitative diluted TT (dTT) test provides an estimation of dabigatran plasma concentration that can be compared to the expected dabigatran plasma concentrations. When the calibrated dTT assay delivers a dabigatran plasma concentration result at or below the limit of quantification, an additional coagulation assay such as TT, ECT or aPTT should be considered.

The ECT can provide a direct measure of the activity of direct thrombin inhibitors.

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. However, the aPTT test has limited sensitivity and is not suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of

dabigatran. Although high aPTT values should be interpreted with caution, a high aPTT value indicates that the patient is anticoagulated.

In general, it can be assumed that these measures of anti-coagulant activity may reflect dabigatran levels and can provide guidance for the assessment of bleeding risk, i.e. exceeding the 90th percentile of dabigatran trough levels or a coagulation assay such as aPTT measured at trough (for aPTT thresholds see section 4.4, table 4) is considered to be associated with an increased risk of bleeding.

Primary prevention of VTE in orthopaedic surgery

Steady state (after day 3) geometric mean dabigatran peak plasma concentration, measured around 2 hours after 220 mg dabigatran etexilate administration, was 70.8 ng/mL, with a range of 35.2-162 ng/mL (25th-75th percentile range). The dabigatran geometric mean trough concentration, measured at the end of the dosing interval (i.e. 24 hours after a 220 mg dabigatran dose), was on average 22.0 ng/mL, with a range of 13.0-35.7 ng/mL (25th-75th percentile range).

In a dedicated study exclusively in patients with moderate renal impairment (creatinine clearance, CrCL 30-50 mL/min) treated with dabigatran etexilate 150 mg QD, the dabigatran geometric mean trough concentration, measured at the end of the dosing interval, was on average 47.5 ng/mL, with a range of 29.6 - 72.2 ng/mL (25th-75th percentile range).

In patients treated for prevention of VTEs after hip or knee replacement surgery with 220 mg dabigatran etexilate once daily,

• the 90th percentile of dabigatran plasma concentrations was 67 ng/mL, measured at trough (20-28 hours after the previous dose) (see section 4.4 and 4.9),

• the 90th percentile of aPTT at trough (20-28 hours after the previous dose) was 51 seconds, which would be 1.3-fold upper limit of normal.

The ECT was not measured in patients treated for prevention of VTEs after hip or knee replacement surgery with 220 mg dabigatran etexilate once daily.

Clinical efficacy and safety

Ethnic origin

No clinically relevant ethnic differences among Caucasians, African-American, Hispanic, Japanese or Chinese patients were observed.

Clinical trials in VTE prophylaxis following major joint replacement surgery

In 2 large randomised, parallel group, double-blind, dose-confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received 75 mg or 110 mg dabigatran etexilate within 1-4 hours of surgery followed by 150 mg or 220 mg once daily thereafter, haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and daily thereafter.

In the RE-MODEL trial (knee replacement) treatment was for 6-10 days and in the RE-NOVATE trial (hip replacement) for 28-35 days. Totals of 2,076 patients (knee) and 3,494 (hip) were treated respectively.

Composite of total VTE (including pulmonary embolism (PE), proximal and distal deep vein thrombosis (DVT), whatever symptomatic or asymptomatic detected by routine venography) and all-cause mortality constituted the primary end-point for both studies. Composite of major VTE (including PE and proximal DVT, whatever symptomatic or asymptomatic detected by routine venography) and VTE-related mortality constituted a secondary end-point and is considered of better clinical relevance.

Results of both studies showed that the antithrombotic effect of 220 mg and 150 mg dabigatran etexilate were statistically non-inferior to that of enoxaparin on total VTE and all-cause mortality. The point estimate for incidence of major VTE and VTE related mortality for the 150 mg dose was slightly worse than enoxaparin (table 13). Better results were seen with the 220 mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 13).

The clinical studies have been conducted in a patient population with a mean age >65 years.

There were no differences in the phase 3 clinical studies for efficacy and safety data between men and women.

In the studied patient population of RE-MODEL and RE-NOVATE (5,539 patients treated), 51 % suffered from concomitant hypertension, 9 % from concomitant diabetes, 9 % from concomitant coronary artery disease and 20 % had a history of venous insufficiency. None of these diseases showed an impact on the effects of dabigatran on VTE-prevention or bleeding rates.

Data for the major VTE and VTE-related mortality endpoint were homogeneous with regards to the primary efficacy endpoint and are shown in table 13.

Data for the total VTE and all cause mortality endpoint are shown in table 14.

Data for adjudicated major bleeding endpoints are shown in table 15 below.

Table 13: Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
N	909	888	917
Incidences (%)	28 (3.1)	38 (4.3)	36 (3.9)
Risk ratio over enoxaparin	0.78	1.09	
95 % CI	0.48, 1.27	0.70, 1.70	
RE-MODEL (knee)			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk ratio over enoxaparin	0.73	1.08	
95 % CI	0.36, 1.47	0.58, 2.01	

Table 14: Analysis of total VTE and all cause mortality during the treatment period in the RE-NOVATE and the RE-MODEL orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
N	880	874	897
Incidences (%)	53 (6.0)	75 (8.6)	60 (6.7)
Risk ratio over enoxaparin	0.9	1.28	

95 % CI	(0.63, 1.29)	(0.93, 1.78)	
RE-MODEL (knee)			
N	503	526	512
Incidences (%)	183 (36.4)	213 (40.5)	193 (37.7)
Risk ratio over enoxaparin	0.97	1.07	
95 % CI	(0.82, 1.13)	(0.92, 1.25)	

Table 15: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
Treated patients N	1,146	1,163	1,154
Number of MBE N(%)	23 (2.0)	15 (1.3)	18 (1.6)
RE-MODEL (knee)			
Treated patients N	679	703	694
Number of MBE N(%)	10 (1.5)	9 (1.3)	9 (1.3)

Clinical trials for the prevention of thromboembolism in patients with prosthetic heart valves

A phase II study examined dabigatran etexilate and warfarin in a total of 252 patients with recent mechanical valve replacement surgery (i.e. within the current hospital stay) and in patients who received a mechanical heart valve replacement more than three months ago. More thromboembolic events (mainly strokes and symptomatic/asymptomatic prosthetic valve thrombosis) and more bleeding events were observed with dabigatran etexilate than with warfarin. In the early post-operative patients, major bleeding manifested predominantly as haemorrhagic pericardial effusions, specifically in patients who started dabigatran etexilate early (i.e. on Day 3) after heart valve replacement surgery.

Paediatric population

Clinical trials in VTE prophylaxis following major joint replacement surgery

The European Medicines Agency has waived the obligation to submit the results of studies with Dabigatran etexilate in all subsets of the paediatric population in prevention of thromboembolic events for the indication of primary prevention of VTE in patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Treatment of VTE and prevention of recurrent VTE in paediatric patients

The DIVERSITY study was conducted to demonstrate the efficacy and safety of dabigatran etexilate compared to standard of care (SOC) for the treatment of VTE in paediatric patients from birth to less than 18 years of age. The study was designed as an open-label, randomised, parallel-group, non-inferiority study. Patients enrolled were randomised according to a 2:1 scheme to either an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate (doses adjusted for age and weight) or SOC comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux (1 patient 12 years old). The primary endpoint was a composite endpoint of patients with complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality related to VTE. Exclusion criteria included active meningitis, encephalitis and intracranial abscess.

In total, 267 patients had been randomised. Of those, 176 patients were treated with dabigatran etexilate and 90 patients according to SOC (1 randomised patient was not treated). 168 patients were 12 to less than 18 years old, 64 patients 2 to less than 12 years, and 35 patients were younger than 2 years.

Of the 267 randomised patients, 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The corresponding rate difference demonstrated non-inferiority of dabigatran etexilate to SOC. Consistent results were also generally observed across subgroups: there were no significant differences in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors. For the 3 different age strata, the proportions of patients that met the primary efficacy endpoint in the dabigatran etexilate and SOC groups, respectively, were 13/22 (59.1%) and 7/13 (53.8%) for patients from birth to <2 years, 21/43 (48.8%) and 12/21 (57.1%) for patients aged 2 to <12 years, and 47/112 (42.0%) and 19/56 (33.9%) for patients aged 12 to <18 years.

Adjudicated major bleeds were reported for 4 patients (2.3%) in the dabigatran etexilate group and 2 patients (2.2%) in the SOC group. There was no statistically significant difference in the time to first major bleeding event. Thirty-eight patients (21.6%) in the dabigatran etexilate arm and 22 patients (24.4%) in the SOC arm had any adjudicated bleeding event, most of them categorised as minor. The combined endpoint of adjudicated major bleeding event (MBE) or clinically relevant non-major (CRNM) bleeding (on treatment) was reported for 6 (3.4%) patients in the dabigatran etexilate group and 3 (3.3%) patients in the SOC group.

An open label, single arm safety prospective cohort, multi-centre, phase III study (1160.108) was conducted to assess the safety of dabigatran etexilate for the prevention of recurrent VTE in paediatric patients from birth to less than 18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were allowed to be included in the study. Eligible patients received age and weight adjusted doses of an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events and the mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months. Outcome events were adjudicated by an independent blinded adjudication committee.

Overall, 214 patients entered the study; among them 162 patients in age stratum 1 (from 12 to less than 18 years of age), 43 patients in age stratum 2 (from 2 to less than 12 years of age) and 9 patients in age stratum 3 (from birth to less than 2 years of age). During the on-treatment period, 3 patients (1.4%) had an adjudication-confirmed recurrent VTE within the first 12 months after treatment start. Adjudication-confirmed bleeding events during the on-treatment period were reported for 48 patients (22.5%) within the first 12 months. The majority of the bleeding events were minor. In 3 patients (1.4%), an adjudication-confirmed major bleeding event occurred within the first 12 months. For 3 patients (1.4%), adjudication-confirmed CRNM bleeding was reported within the first 12 months. No on-treatment deaths occurred. During the on-treatment period, 3 patients (1.4%) developed post-thrombotic syndrome (PTS) or had worsening of PTS within the first 12 months.

5.2 Pharmacokinetic properties

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. The absolute bioavailability of dabigatran following oral administration of Dabigatran etexilate capsules was approximately 6.5 %.

After oral administration of Dabigatran etexilate capsules in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with C_{max} attained within 0.5 and 2.0 hours post administration.

Absorption

A study evaluating post-operative absorption of dabigatran etexilate, 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 in a postoperative period due to contributing factors such as anaesthesia, gastrointestinal paresis, and surgical effects independent of the oral medicinal product formulation. 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 dabigatran is rapid with peak plasma concentrations attained 2 hours after medicinal product administration.

Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours.

C_{max} and AUC were dose proportional.

The oral bioavailability may be increased by 75 % after a single dose and 37 % at steady state compared to the reference capsule formulation when the pellets are taken without the Hydroxypropylmethylcellulose (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.

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

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.

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

Plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 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. Half-life is prolonged if renal function is impaired as shown in table 16.

Special populations

Renal insufficiency

In phase I studies the exposure (AUC) of dabigatran after the oral administration of dabigatran etexilate is approximately 2.7-fold higher in adult volunteers with moderate renal insufficiency (CrCL between 30 and 50 mL/min) than in those without renal insufficiency.

In a small number of adult 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 sections 4.2, 4.3 and 4.4).

Table 16: 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)

Additionally, dabigatran exposure (at trough and peak) was assessed in a prospective open label randomised pharmacokinetic study in NVAF patients with severe renal impairment (defined as creatinine clearance [CrCl] 15-30 mL/min) receiving dabigatran etexilate 75 mg twice daily.

This regimen resulted in a geometric mean trough concentration of 155 ng/ml (gCV of 76.9 %), measured immediately before administration of the next dose and in a geometric mean peak concentration of 202 ng/ml (gCV of 70.6 %) measured two hours after the administration of the last dose.

Clearance of dabigatran by haemodialysis was investigated in 7 adult patients with end-stage renal disease (ESRD) without atrial fibrillation. Dialysis was conducted with 700 mL/min dialysate flow rate, four hour duration and a blood flow rate of either 200 mL/min or 350-390 mL/min. This resulted in a removal of 50 % to 60 % of dabigatran concentrations, respectively. The amount of substance cleared by dialysis is proportional to the blood flow rate up to a blood flow rate of 300 mL/min. The anticoagulant activity of dabigatran decreased with decreasing plasma concentrations and the PK/PD relationship was not affected by the procedure.

Elderly patients

Specific pharmacokinetic phase I studies with elderly subjects showed an increase of 40 to 60 % in the AUC and of more than 25 % in C_{max} compared to young subjects.

The effect by age on exposure to dabigatran was confirmed in the RE-LY study with an about 31 % higher trough concentration for subjects ≥ 75 years and by about 22 % lower trough level for subjects <65 years compared to subjects between 65 and 75 years.

Hepatic impairment

No change in dabigatran exposure was seen in 12 adult subjects with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls.

Body weight

The dabigatran trough concentrations were about 20 % lower in adult patients with a body weight >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 (see sections 4.2 and 4.4). Limited clinical data in adult patients <50 kg are available.

Gender

Active substance exposure in the primary VTE prevention studies was about 40 % to 50 % higher in female patients and no dose adjustment is recommended.

Ethnic origin

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding dabigatran pharmacokinetics and pharmacodynamics.

Paediatric population

Oral administration of dabigatran etexilate according to the protocol defined dosing algorithm resulted in exposure within the range observed in adults with DVT / PE. Based on the pooled analysis of pharmacokinetic data of studies DIVERSITY and 1160.108, the observed geometric mean trough exposures were 53.9 ng/mL, 63.0 ng/mL and 99.1 ng/mL in 0 to <2-year-old, 2 to <12-year-old and 12 to <18-year-old paediatric VTE patients, respectively.

Pharmacokinetic interactions

In vitro interaction studies did not show any inhibition or induction of the principal isoenzymes of cytochrome P450. This has been confirmed by *in vivo* studies with healthy volunteers, who did not show any interaction between this treatment and the following active substances: atorvastatin (CYP3A4), digoxin (P-gp transporter interaction) and diclofenac (CYP2C9).

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Effects observed in the repeated dose toxicity studies were due to the exaggerated pharmacodynamic effect of dabigatran.

An effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (5-fold the plasma exposure level in patients). At doses that were toxic to the mothers (5- to 10-fold the plasma exposure level in patients), a decrease in foetal body weight and viability along with an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients).

In a juvenile toxicity study conducted in Han Wistar rats, mortality was associated with bleeding events at similar exposures, at which bleeding was seen in adult animals. In both adult and juvenile rats, mortality is considered to be related to the exaggerated pharmacological activity of dabigatran in association with the exertion of mechanical forces during dosing and handling. Data of the juvenile toxicity study did neither indicate an increased sensitivity in toxicity, nor any toxicity specific to juvenile animals.

In lifetime toxicology studies in rats and mice, there was no evidence for a tumorigenic potential of dabigatran up to maximum doses of 200 mg/kg.

Dabigatran, the active moiety of dabigatran etexilate mesilate, is persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:

Tartaric Acid, Hypromellose, Talc, Sugar Spheres, Isopropyl alcohol, Methylene Chloride, Hydroxypropyl cellulose, Empty Hard HMPC capsule shells.

Empty Hard HMPC capsule shells composition

FDA/E172 Red Iron Oxide, FDA/E172 Yellow Iron Oxide, FD&C Blue #1, FD&C Red #40, Titanium Dioxide, Water, Hypromellose, Black SW-9008/SW-9009 Printing Ink.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Stored below 30º C and protect from moisture.

6.5 Nature and contents of pack's

10' Blister Pack

6.6 Instructions for use, handling and disposal

Not applicable.

7. SUPPLIER

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LAGOS

8. Registration Number

Not applicable

9. Date of Publication of this Package Insert

Not applicable