℞ Dabigatran Etexilate Capsules 75mg, 110mg, 150mg

DABIFIB® 75, 110, 150 डेबिफिब ७५, ११०, १५०

Dabigatran Etexilate 75mg
Each hard cellulose Capsule Contains
Dabigatran Etexilate Mesylate Equivalent to
Dabigatran Etexilate .... 75 mg
Excipients: Q.S & Approved colors used in capsule shell
Colours: Titanium Dioxide IP

Dabigatran Etexilate 110mg
Each hard cellulose Capsule Contains
Dabigatran Etexilate Mesylate Equivalent to
Dabigatran Etexilate .... 110 mg
Excipients: Q.S & Approved colors used in capsule shell
Colours: Titanium Dioxide IP

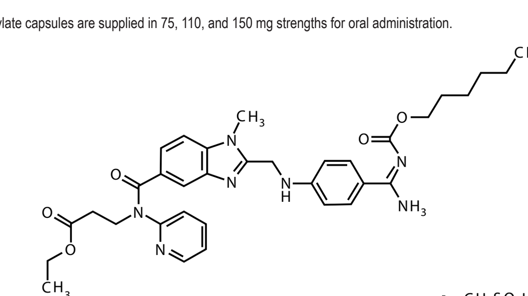
Dabigatran Etexilate 150mg
Each hard cellulose Capsule Contains
Dabigatran Etexilate Mesylate Equivalent to
Dabigatran Etexilate .... 150 mg
Excipients: Q.S & Approved colors used in capsule shell
Colours: Titanium Dioxide IP

DRUG DESCRIPTION

The chemical name for dabigatran etexilate mesylate, a direct thrombin inhibitor, is β-Alanine, N-[[2-[[[4-[[[(hexyloxy) carbonyl] amino] iminomethyl] phenyl] amino] methyl]-1-methyl-1H-benzimidazol-5-yl] carbonyl]-N-2-pyridinyl-, ethyl ester, methanesulfonate.

The empirical formula is $C_{34}H_{41}N_7O_5 \times CH_4O_3S$ and the molecular weight is 723.86 (mesylate salt), 627.75 (free base). The structural formula is:

Dabigatran etexilate mesylate is a yellow-white to yellow colored powder. It is freely soluble in methanol, soluble in ethanol and practically insoluble in ethyl acetate.
Dabigatran etexilate mesylate capsules are supplied in 75, 110, and 150 mg strengths for oral administration.



DOSAGE FORM AND STRENGTHS

Hard Capsules; 75mg, 110mg and 150 mg

INDICATIONS

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation: Dabigatran etexilate mesylate is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Treatment of Deep Venous Thrombosis and Pulmonary Embolism: Dabigatran etexilate mesylate is indicated for the treatment of deep venous thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5-10 days.

Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism: Dabigatran etexilate mesylate is indicated to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism in patients who have been previously treated.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery: Dabigatran etexilate mesylate is indicated for the prophylaxis of deep vein thrombosis and pulmonary embolism, in patients who have undergone hip replacement surgery.

DOSAGE AND METHOD OF ADMINISTRATION

Recommended Dose

Indication	Dosage
Reduction in Risk of Stroke and Systemic Embolism in Non-valvular AF	CrCl >30 mL/min: 150 mg twice daily CrCl 15 to 30 mL/min: 75 mg twice daily CrCl <15 mL/min or on dialysis: Dosing recommendations cannot be provided
	CrCl 30 to 50 mL/min with concomitant use of P-gp inhibitors: Reduce dose to 75 mg twice daily if given with P-gp inhibitors dronedarone or systemic ketoconazole. CrCl <30 mL/min with concomitant use of P-gp inhibitors: Avoid co-administration
Treatment of DVT and PE **Reduction in the Risk of Recurrence of DVT and PE**	CrCl >30 mL/min: 150 mg twice daily CrCl ≤30 mL/min or on dialysis: Dosing recommendations cannot be provided
	CrCl <50 mL/min with concomitant use of P-gp inhibitors: Avoid co-administration
Prophylaxis of DVT and PE Following Hip Replacement Surgery	CrCl >30 mL/min: 110 mg for first day, then 220 mg once daily CrCl ≤30 mL/min or on dialysis: Dosing recommendations cannot be provided
	CrCl <50 mL/min with concomitant use of P-gp inhibitors: Avoid co-administration

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
For patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose of Dabigatran etexilate mesylate is 150 mg taken orally, twice daily. For patients with severe renal impairment (CrCl 15-30 mL/min), the recommended dose of Dabigatran etexilate mesylate is 75 mg twice daily. Dosing recommendations for patients with a CrCl <15 mL/min or on dialysis cannot be provided.
Treatment of Deep Venous Thrombosis and Pulmonary Embolism
For patients with CrCl >30 mL/min, the recommended dose of Dabigatran etexilate mesylate is 150 mg taken orally, twice daily, after 5-10 days of parenteral anticoagulation. Dosing recommendations for patients with a CrCl ≤30 mL/min or on dialysis cannot be provided.
Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
For patients with CrCl >30 mL/min, the recommended dose of Dabigatran etexilate mesylate is 150 mg taken orally, twice daily after previous treatment. Dosing recommendations for patients with a CrCl ≤30 mL/min or on dialysis cannot be provided.
Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
For patients with CrCl >30 mL/min, the recommended dose of Dabigatran etexilate mesylate is 110 mg taken orally 1-4 hours after surgery and after hemostasis has been achieved, then 220 mg taken once daily for 28-35 days. If Dabigatran etexilate mesylate is not started on the day of surgery, after hemostasis has been achieved initiate treatment with 220 mg once daily. Dosing recommendations for patients with a CrCl ≤30 mL/min or on dialysis cannot be provided.

Dosing Adjustments
Assess renal function prior to initiation of treatment with Dabigatran etexilate mesylate. Periodically assess renal function as clinically indicated (i.e., more frequently in clinical situations that may be associated with a decline in renal function) and adjust therapy accordingly. Discontinue Dabigatran etexilate mesylate in patients who develop acute renal failure while on Dabigatran etexilate mesylate and consider alternative anticoagulant therapy.
Generally, the extent of anticoagulation does not need to be assessed. When necessary, use aPTT or ECT, and not INR, to assess for anticoagulant activity in patients on Dabigatran etexilate mesylate.

Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
In patients with moderate renal impairment (CrCl 30-50 mL/min), concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole can be expected to produce dabigatran exposure similar to that observed in severe renal impairment. Reduce the dose of Dabigatran etexilate mesylate to 75 mg twice daily.
Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
Dosing recommendations for patients with CrCl ≤30 mL/min cannot be provided. Avoid use of concomitant P-gp inhibitors in patients with CrCl <50 mL/min.
Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
Dosing recommendations for patients with CrCl ≤30 mL/min or on dialysis cannot be provided. Avoid use of concomitant P-gp inhibitors in patients with CrCl <50 mL/min.

Instructions to Patients
Instruct patients to swallow the capsules whole. Dabigatran etexilate mesylate should be taken with a full glass of water. Breaking, chewing, or emptying the contents of the capsule can result in increased exposure.
If a dose of Dabigatran etexilate mesylate is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of Dabigatran etexilate mesylate should not be doubled to make up for a missed dose.

Converting from or to Warfarin
When converting patients from warfarin therapy to Dabigatran etexilate mesylate, discontinue warfarin and start Dabigatran etexilate mesylate when the INR is below 2.0.
When converting from Dabigatran etexilate mesylate to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:
- For CrCl e50 mL/min, start warfarin 3 days before discontinuing Dabigatran etexilate mesylate.
- For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing Dabigatran etexilate mesylate.
- For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing Dabigatran etexilate mesylate.
- For CrCl <15 mL/min, no recommendations can be made.

Because Dabigatran etexilate mesylate can increase INR, the INR will better reflect warfarin's effect only after Dabigatran etexilate mesylate has been stopped for at least 2 days.

Converting from or to Parenteral Anticoagulants
For patients currently receiving a parenteral anticoagulant, start Dabigatran etexilate mesylate 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).
For patients currently taking Dabigatran etexilate mesylate, wait 12 hours (CrCl ≥30 mL/min) or 24 hours (CrCl <30 mL/min) after the last dose of Dabigatran etexilate mesylate before initiating treatment with a parenteral anticoagulant.

Discontinuation for Surgery and Other Interventions
If possible, discontinue Dabigatran etexilate mesylate 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding. Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required.
If surgery cannot be delayed, there is an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention. Use a specific reversal agent (idarucizumab) in case of emergency surgery or urgent procedures when reversal of the anticoagulant effect of dabigatran is needed. Refer to the idarucizumab prescribing information for additional information. Restart Dabigatran etexilate mesylate as soon as medically appropriate.

USE IN SPECIAL POPULATION

Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women.
Dabigatran has been shown to decrease the number of implantations when male and female rats were treated at a dosage of 70 mg/kg (about 2.6 to 3.0 times the human exposure at maximum recommended human dose [MRHD] of 300 mg/day based on area under the curve [AUC] comparisons) prior to mating and up to implantation (gestation Day 6). Treatment of pregnant rats after implantation with dabigatran at the same dose increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition. Although dabigatran increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat, it did not induce major malformations in rats or rabbits.

Labor and Delivery
Safety and effectiveness of Dabigatran etexilate mesylate during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using Dabigatran etexilate mesylate in this setting.
Death of offspring and mother rats during labor in association with uterine bleeding occurred during treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with dabigatran at a dose of 70 mg/kg (about 2.6 times the human exposure at MRHD of 300 mg/day based on AUC comparisons).

Nursing Mothers
It is not known whether dabigatran is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Dabigatran etexilate mesylate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of Dabigatran etexilate mesylate in pediatric patients have not been established.

Geriatric Use
The risk of stroke and bleeding increases with age, but the risk-benefit profile is favorable in all age groups.

Renal Impairment
Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
No dose adjustment of Dabigatran etexilate mesylate is recommended in patients with mild or moderate renal impairment. Reduce the dose of Dabigatran etexilate mesylate in patients with severe renal impairment (CrCl 15-30 mL/min). Dosing recommendations for patients with CrCl <15 mL/min or on dialysis cannot be provided.
Adjust dose appropriately in patients with renal impairment receiving concomitant P-gp inhibitors.
Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
Dosing recommendations for patients with CrCl ≤30 mL/min or on dialysis cannot be provided. Avoid use of Dabigatran etexilate mesylate with concomitant P-gp inhibitors in patients.
Dosing recommendations for patients with CrCl ≤30 mL/min or on dialysis cannot be provided. Avoid use of Dabigatran etexilate mesylate with concomitant P-gp inhibitors in patients with CrCl <50 mL/min.
Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
Dosing recommendations for patients with CrCl <30 mL/min or on dialysis cannot be provided.
Avoid use of Dabigatran etexilate mesylate with concomitant P-gp inhibitors in patients with CrCl <50 mL/min.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to Dabigatran etexilate mesylate (e.g., anaphylactic reaction or anaphylactic shock).
- 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 of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone.
- Prosthetic heart valves requiring anticoagulant treatment.

WARNINGS AND PRECAUTIONS

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 mesylate is not recommended in this population.

Increased Risk of Thrombotic Events after Premature Discontinuation
Premature discontinuation of any oral anticoagulant, including Dabigatran etexilate mesylate, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If Dabigatran etexilate mesylate is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant and restart Dabigatran etexilate mesylate as soon as medically appropriate.

Risk of Bleeding
Dabigatran etexilate mesylate increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue Dabigatran etexilate mesylate in patients with active pathological bleeding.

Risk factors for bleeding include the concomitant use of other drugs that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs). Dabigatran etexilate mesylate's anticoagulant activity and half-life are increased in patients with renal impairment.
Reversal of Anticoagulant Effect:
A specific reversal agent (idarucizumab) for dabigatran is available when reversal of the anticoagulant effect of dabigatran is needed:
- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding Hemodialysis can remove dabigatran; however the clinical experience supporting the use of hemodialysis as a treatment for bleeding is limited. Prothrombin complex concentrates, or recombinant Factor VIIa may be considered but their use has not been evaluated in clinical trials. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of dabigatran. Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used.

Spinal/Epidural Anesthesia or Puncture
When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis. To reduce the potential risk of bleeding associated with the concurrent use of dabigatran and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of dabigatran. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of dabigatran is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves
The use of Dabigatran etexilate mesylate is contraindicated in patients with mechanical prosthetic valves. The use of Dabigatran etexilate mesylate for the prophylaxis of thromboembolic events in patients with atrial fibrillation in the setting of other forms of valvular heart disease, including the presence of a bioprosthetic heart valve, has not been studied and is not recommended.

Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure
The concomitant use of Dabigatran etexilate mesylate with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided.
P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran.
Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.
Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation
Reduce the dose of Dabigatran etexilate mesylate to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered with Dabigatran etexilate mesylate in patients with moderate renal impairment (CrCl 30-50 mL/min). Avoid use of Dabigatran etexilate mesylate and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min),
Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
Avoid use of Dabigatran etexilate mesylate and concomitant P-gp inhibitors in patients with CrCl <50 mL/min.
Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
Avoid use of Dabigatran etexilate mesylate and concomitant P-gp inhibitors in patients with CrCl <50 mL/min.

DRUG INTERACTIONS

The concomitant use of Dabigatran etexilate mesylate with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided.
P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran.
Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.
In patients with moderate renal impairment (CrCl 30-50 mL/min), reduce the dose of Dabigatran etexilate mesylate to 75 mg twice daily when administered concomitantly with the P-gp inhibitors dronedarone or systemic ketoconazole. The use of the P-gp inhibitors verapamil, amiodarone, quinidine, clarithromycin, and ticagrelor does not require a dose adjustment of Dabigatran etexilate mesylate. These results should not be extrapolated to other P-gp inhibitors.
The concomitant use of Dabigatran etexilate mesylate and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided.

Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism
Avoid use of Dabigatran etexilate mesylate and P-gp inhibitors in patients with CrCl <50 mL/min.

Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Following Hip Replacement Surgery
In patients with CrCl ≥50 mL/min who have concomitant administration of P-gp inhibitors such as dronedarone or systemic ketoconazole, it may be helpful to separate the timing of administration of dabigatran and the P-gp inhibitor by several hours. The concomitant use of Dabigatran etexilate mesylate and P-gp inhibitors in patients with CrCl <50 mL/min should be avoided.

UNDESIRABLE EFFECTS

The following serious adverse reactions are described elsewhere in the labeling:
- Increased Risk of Thrombotic Events after Premature Discontinuation
- Risk of Bleeding
- Spinal/Epidural Anesthesia or Puncture
- Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves

The most serious adverse reactions reported with Dabigatran etexilate were related to bleeding
A total of 10,795 patients were treated in 6 actively controlled VTE prevention trials with at least one dose of the medicinal product. Of these 6,684 were treated with 150 mg or 220 mg daily of Dabigatran etexilate mesylate.
In the pivotal study investigating the prevention of stroke and SEE in patients with atrial fibrillation, a total of 12,042 patients were treated with dabigatran etexilate. Of these 6,059 were treated with 150 mg twice daily of dabigatran etexilate, while 5,983 received doses of 110 mg twice daily.
In the 2 active controlled DVT/PE treatment trials, RE-COVER and RE-COVER II, a total of 2,553 patients were included in the safety analysis for dabigatran etexilate. All patients received doses of 150 mg twice daily of dabigatran etexilate. Adverse drug reactions for both treatments, dabigatran etexilate and warfarin, are counted from the first intake of dabigatran etexilate or warfarin after the parenteral therapy has been discontinued (oral only treatment period). This includes all adverse drug reactions which occurred during dabigatran therapy. All adverse drug reactions, which occurred during warfarin therapy, are included except for those during the overlap period between warfarin and parenteral therapy.
A total of 2,114 patients were treated in the active controlled DVT/PE prevention trial, RE-MEDY, and in the placebo-controlled DVT/PE prevention trial, RE-SONATE. All patients received doses of 150 mg twice daily of dabigatran etexilate.
In total, about 9 % of patients treated for elective hip or knee surgery (short-term treatment for up to 42 days), 22 % of patient with atrial fibrillation treated for the prevention of stroke and SEE (long-term treatment for up to 3 years), 14 % of patient treated for DVT/PE and 15 % of patients treated for DVT/PE prevention experienced adverse reactions.
The most commonly reported adverse reactions are bleedings occurring in total in approximately 14 % of patients treated short-term for elective hip or knee replacement surgery, 16.6 % in patients with atrial fibrillation treated long-term for the prevention of stroke and SEE, and in 14.4 % of patients treated for DVT/PE. Furthermore, bleeding occurred in 19.4% of patients in the DVT/PE prevention trial RE-MEDY and in 10.5% of patient in the DVT/PE prevention trial RE-SONATE.
Since the patient populations treated in the three indications are not comparable and bleeding events are distributed over several System Organ Classes (SOC), a summary description of major and any bleeding are broken down by indication and given in tables (Table: Number (%) of patients experiencing the adverse reaction bleeding and Table: Bleeding events in a study testing the prevention of thromboembolic stroke and SEE in patients with atrial fibrillation) below.
Although low 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
Below Table shows the adverse reactions identified from the primary VTE prevention studies after hip or knee replacement surgery, the study in the prevention of thromboembolic stroke, and SEE in patients with atrial fibrillation and the studies in DVT/PE treatment and in DVT/PE prevention. They are ranked under headings of 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: Adverse reactions

SOC / Preferred term.	Primary VTE prevention after hip or knee replacement surgery	Stroke and SEE prevention in patients with atrial fibrillation	DVT/PE treatment and DVT/PE prevention
Blood and lymphatic system disorders			
Anaemia	Uncommon	Common	Uncommon
Haemoglobin decreased	Common	Uncommon	Not known
Thrombocytopenia	Rare	Uncommon	Rare
Haematocrit decreased	Uncommon	Rare	Not known
Immune system disorder			
Drug hypersensitivity	Uncommon	Uncommon	Uncommon
Rash	Rare	Uncommon	Uncommon
Pruritus	Rare	Uncommon	Uncommon
Anaphylactic reaction	Rare	Rare	Rare
Angioedema	Rare	Rare	Rare
Urticaria	Rare	Rare	Rare
Bronchospasm	Not known	Not known	Not known
Nervous system disorders			
Intracranial haemorrhage	Rare	Uncommon	Rare
Vascular disorders			
Haematoma	Uncommon	Uncommon	Uncommon
Haemorrhage	Rare	Uncommon	Uncommon
Wound haemorrhage	Uncommon	-	
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Uncommon	Common	Common
Haemoptysis	Rare	Uncommon	Uncommon
Gastrointestinal disorders			
Gastrointestinal haemorrhage	Uncommon	Common	Common
Abdominal pain	Rare	Common	Uncommon
Diarrhoea	Uncommon	Common	Uncommon
Dyspepsia	Rare	Common	Common
Nausea	Uncommon	Common	Uncommon
Rectal haemorrhage	Uncommon	Uncommon	Common
Haemorrhoidal haemorrhage	Uncommon	Uncommon	Uncommon
Gastrointestinal ulcer, including oesophageal ulcer	Rare	Uncommon	Uncommon
Gastroesophagitis	Rare	Uncommon	Uncommon
Gastroesophageal reflux disease	Rare	Uncommon	Uncommon
Vomiting	Uncommon	Uncommon	Uncommon
Dysphagia	Rare	Uncommon	Rare
Hepatobiliary disorders			
Hepatic function abnormal/ Liver function Test abnormal	Common	Uncommon	Uncommon
Alanine aminotransferase increased	Uncommon	Uncommon	Uncommon
Aspartate aminotransferase increased	Uncommon	Uncommon	Uncommon
Hepatic enzyme increased	Uncommon	Rare	Uncommon
Hyperbilirubinaemia	Uncommon	Rare	Not known
Skin and subcutaneous tissue disorder			
Skin haemorrhage	Uncommon	Common	Common
Musculoskeletal and connective tissue disorders			
Haemarthrosis	Uncommon	Rare	Uncommon
Renal and urinary disorders			
Genitourological haemorrhage, including haematuria	Uncommon	Common	Common
General disorders and administration site conditions			
Injection site haemorrhage	Rare	Rare	Rare
Catheter site haemorrhage	Rare	Rare	Rare
Bloody discharge	Rare	-	
Injury, poisoning and procedural complications			
Traumatic haemorrhage	Uncommon	Rare	Uncommon
Incision site haemorrhage	Rare	Rare	Rare
Post procedural haematoma	Uncommon	-	-
Post procedural haemorrhage	Uncommon	-	-
Anaemia postoperative	Rare	-	-
Post procedural discharge	Uncommon	-	-
Wound secretion	Uncommon	-	-
Surgical and medical procedures			
Wound drainage	Rare	-	-
Post procedural drainage	Rare	-	-

Primary Prevention of Venous Thromboembolism in Orthopaedic Surgery (pVTEp orthopaedic surgery)
Bleeding
The below table shows the number (%) of patients experiencing the adverse reaction bleeding during the treatment period in the VTE prevention in the two pivotal clinical trials, according to dose
Table: Number (%) of patients experiencing the adverse reaction bleeding

	Dabigatran etexilate 150 mg once daily N (%)	Dabigatran etexilate 220 mg once daily 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)

The definition of the adverse reaction major bleeding in the RE-NOVATE and RE-MODEL studies were as follows:
- Fatal bleeding
- Clinically overt bleeding in excess of what was expected and associated with ≥ 20 g/L (corresponds to 1.24 mmol/L) fall in haemoglobin in excess of what was expected
- clinically overt bleeding in excess of what was expected and leading to transfusion of ≥ 2 units packed cells or whole blood in excess of what was expected
- Symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding
- bleeding requiring treatment cessation
- bleeding leading to re-operation

Objective testing was required for a retroperitoneal bleed (ultrasound or Computer Tomography (CT) scan) and for an intracranial and intraspinal bleed (CT scan or Magnetic Resonance Imaging).
Prevention of stroke and SEE in adult patients with NVAF with one or more risk factors
Bleeding
The below table shows bleeding events broken down to major and any bleeding in the pivotal study testing the prevention of thromboembolic stroke and SEE in patients with atrial fibrillation.
Table: Bleeding events in a study testing the prevention of thromboembolic stroke and SEE in patients with atrial fibrillation

	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
Major bleeding	347 (2.92 %)	409 (3.40 %)	426 (3.61 %)
Intracranial bleeding	27 (0.23 %)	39 (0.32 %)	91 (0.77 %)
GI bleeding	134 (1.13 %)	192 (1.60 %)	128 (1.09 %)
Fatal bleeding	26 (0.22 %)	30 (0.25 %)	42 (0.36 %)
Minor bleeding	1,566 (13.16 %)	1,787 (14.85 %)	1,931 (16.37 %)
Any bleeding	1,759 (14.78 %)	1,997 (16.60 %)	2,169 (18.39 %)

Major bleeding was defined to fulfil one or more of the following criteria:
Bleeding associated with a reduction in haemoglobin of at least 20 g/L 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 haemoglobin of at least 50 g/L; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic medicinal products; a bleed that necessitated surgical intervention.
Subjects randomized to dabigatran etexilate 110 mg twice daily or 150 mg twice daily had a significantly lower risk for life-threatening bleeds and intracranial bleeding compared to warfarin [p < 0.05]. Both dose strengths of dabigatran etexilate had also a statistically significant lower total bleed rate. Subjects randomized to dabigatran etexilate 110 mg twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81 [p=0.0027]). Subjects randomized to dabigatran etexilate 150 mg twice daily had a significantly higher risk for major GI bleeds compared with warfarin (hazard ratio 1.48 [p=0.0005]. This effect was seen primarily in patients ≥ 75 years.
The clinical benefit of dabigatran with regard to stroke and SEE prevention and decreased risk of ICH compared to warfarin is preserved across individual subgroups, e.g. renal impairment, age, concomitant medication use such as anti-platelets or P-gp inhibitors. While certain patient subgroups are at an increased risk of major bleeding when treated with an anticoagulant, the excess bleeding risk for dabigatran is due to GI bleeding, typically seen within the first 3-6 months following initiation of dabigatran etexilate therapy.
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (DVT/PE treatment)
Below Table shows bleeding events in the pooled pivotal studies RE-COVER and RE-COVER II testing the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). In the pooled studies the primary safety endpoints of major bleeding, major or clinically relevant bleeding and any bleeding were significantly lower than warfarin at a nominal alpha level of 5 %.
Table: Bleeding events in the studies RE-COVER and RE-COVER II testing the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)

	Dabigatran etexilate 150 mg twice daily	Warfarin	Hazard ratio vs. warfarin (95% confidence interval)
Patients included in safety analysis	2,456	2,462	
Major bleeding events	24 (1.0 %)	40 (1.6 %)	0.60 (0.36, 0.99)
Intracranial Bleeding	2 (0.1 %)	4 (0.2 %)	0.50 (0.09, 2.74)
Major GI bleeding	10 (0.4 %)	12 (0.5 %)	0.83 (0.36, 1.93)
Life-threatening bleed	4 (0.2 %)	6 (0.2 %)	0.66 (0.19, 2.36)
Major bleeding events/clinically relevant bleeds	109 (4.4 %)	189 (7.7 %)	0.56 (0.45, 0.71)
Any bleeding	354 (14.4 %)	503 (20.4 %)	0.67 (0.59, 0.77)
Any GI bleeding	70 (2.9 %)	55 (2.2 %)	1.27 (0.90, 1.82)

Bleeding events for both treatments are counted from the first intake of dabigatran etexilate or warfarin after the parenteral therapy has been discontinued (oral only treatment period). This includes all bleeding events, which occurred during dabigatran etexilate therapy. All bleeding events which occurred during warfarin therapy are included except for those during the overlap period between warfarin and parenteral therapy.
The definition of major bleeding events (MBEs) followed the recommendations of the International Society on Thrombosis and Haemostasis. A bleeding event was categorized 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 a 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

Below Table shows bleeding events in pivotal study RE-MEDY testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). Some bleeding events (MBEs/CRBEs; any bleeding) were significantly lower at a nominal alpha level of 5% in patients receiving dabigatran etexilate as compared with those receiving warfarin.
Table: Bleeding events in study RE-MEDY testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)

	Dabigatran etexilate 150 mg twice daily	Warfarin	Hazard ratio vs warfarin (95% Confidence Interval)
Treated patients	1,430	1,426	
Major bleeding events	13 (0.9 %)	25 (1.8 %)	0.54 (0.25, 1.16)
Intracranial bleeding	2 (0.1 %)	4 (0.3 %)	Not calculable*
Major GI bleeding	4 (0.3%)	8 (0.5%)	Not calculable*
Life-threatening bleed	1 (0.1 %)	3 (0.2 %))	Not calculable*
Major bleeding event /clinically relevant bleeds	80 (5.6 %)	145 (10.2 %)	0.55 (0.41, 0.72)
Any bleeding	278 (19.4 %)	373 (26.2 %)	0.71 (0.61, 0.83)
Any GI bleeds	45 (3.1%)	32 (2.2%)	1.39 (0.87, 2.20)

*HR not estimable as there is no event in either one cohort/treatment
The definition of MBEs followed the recommendations of the International Society on Thrombosis and Haemostasis as described under RE-COVER and RE-COVER II.
Below Table shows bleeding events in pivotal study RE-SONATE testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). The rate of the combination of MBEs/CRBEs and the rate of any bleeding was significantly lower at a nominal alpha level of 5 % in patients receiving placebo as compared with those receiving dabigatran etexilate.
Table: Bleeding events in study RE-SONATE testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)

	Dabigatran etexilate 150 mg twice daily	Placebo	Hazard ratio vs placebo (95% confidence interval)
Treated patients	684	659	
Major bleeding events	(0.3 %)	0	Not calculable*
Intracranial bleeding	0	0	Not calculable*
Major GI bleeding	2 (0.3%)	0	Not calculable*
Life-threatening bleeds	0	0	Not calculable*
Major bleeding event/clinical relevant bleeds	36 (5.3 %)	13 (2.0 %)	2.69 (1.43, 5.07)
Any bleeding	72 (10.5 %)	40 (6.1 %)	1.77 (1.20, 2.61)
Any GI bleeds	5 (0.7%)	2 (0.3%)	2.38 (0.46, 12.27)

*HR not estimable as there is no event in either one treatment
The definition of MBEs followed the recommendations of the International Society on Thrombosis and Haemostasis as described under RE-COVER and RE-COVER II.
Myocardial infarction
Prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation with one or more risk factors (SPAF)
In the RE-LY study, in comparison to warfarin the annual myocardial infarction rate for dabigatran etexilate was increased from 0.64 % (warfarin) to 0.82 % (dabigatran etexilate 110 mg twice daily) / 0.81 % (dabigatran etexilate 150 mg twice daily).
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (DVT/PE)
In the three active controlled studies, a higher rate of MI was reported in patients who received dabigatran etexilate than in those who received warfarin: 0.4% vs. 0.2% in the short-term RE-COVER and RE-COVER II studies; and 0.8 % vs. 0.1% in the long-term RE-MEDY trial. The increase was statistically significant in this study (p=0.022).
In the RE-SONATE study, which compared dabigatran etexilate to placebo, the rate of MI was 0.1% for patients who received dabigatran etexilate and 0.2 % for patients who received placebo.
Paediatric population (DVT/PE)
In the clinical study 1160.88 in total, 9 adolescent patients (age 12 to < 18 years) with diagnosis of primary VTE received an initial oral dose of dabigatran etexilate of 1.71 (± 10 %) mg/kg bodyweight. Based on dabigatran concentrations as determined by the diluted thrombin time test and clinical assessment, the dose was adjusted to the target dose of 2.14 (± 10%) mg/kg bodyweight of dabigatran etexilate. On treatment 2 (22.1 %) patients experienced mild related adverse events (gastroesophageal reflux / abdominal pain; abdominal discomfort) and 1 (11.1 %) patient experienced a not related serious adverse event (recurrent VTE of the leg) in the post treatment period > 3 days after stop of dabigatran etexilate.

OVERDOSAGE

Accidental overdose may lead to hemorrhagic complications. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with Dabigatran etexilate mesylate, and investigate the source of bleeding. A specific reversal agent (idarucizumab) is available.
Dabigatran is primarily eliminated by the kidneys with a low plasma protein binding of approximately 35%. Hemodialysis can remove dabigatran; however, data supporting this approach are limited. Using a high-flux dialyzer, blood flow rate of 200 mL/min, and dialysate flow rate of 700 mL/min, approximately 49% of total dabigatran can be cleared from plasma over 4 hours. At the same dialysate flow rate, approximately 57% can be cleared using a dialyzer blood flow rate of 300 mL/min, with no appreciable increase in clearance observed at higher blood flow rates. Upon cessation of hemodialysis, a redistribution effect of approximately 7% to 15% is seen. The effect of dialysis on dabigatran's plasma concentration would be expected to vary based on patient specific characteristics. Measurement of aPTT or ECT may help guide therapy.
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 should be given according to the physician's judgement.

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antithrombotic, 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-catalyzed 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 also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

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-catalyzed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. The absolute bioavailability of dabigatran following oral administration of Dabigatran etexilate mesylate was approximately 6.5 %.
After oral administration of Dabigatran etexilate mesylate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterized 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.
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. Therefore, patients should be advised not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages).
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.
C_{max} and the area under the plasma concentration-time curve were dose proportional. 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 below (Table: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function).
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.
Special populations
Renal insufficiency
In phase I studies the exposure (AUC) of dabigatran after the oral administration of Dabigatran etexilate mesylate is approximately 2.7-fold higher in volunteers with moderate renal insufficiency (CrCL between 30-50 mL/min) than in those without renal insufficiency.
In a small number of volunteers with severe renal insufficiency (CrCL 10-30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency.
Table: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function.

glomerular filtration rate (CrCL,) [mL/min]	gMean (gCV %; range) half-life [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 randomized 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 n Doses of dabigatran etexilate 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 mesylate treatment. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. Depending on the clinical situation appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescriber's discretion.
For situations when rapid reversal of the anticoagulant effect of Dabigatran etexilate mesylate is required the specific reversal agent (Praxbind, idarucizumab) antagonizing the pharmacodynamics effect of Dabigatran etexilate mesylate is available.
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 drugs have been used. All symptomatic treatment should be given according to the physician's judgment.
Depending on local availability, a consultation of a coagulation expert should be considered in case of major bleedings.
As protein binding is low, dabigatran can be dialyzed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies.
g/ml (gCV of 70.6 %) measured two hours after the administration of the last dose.
Clearance of dabigatran by hemodialysis was investigated in 7 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 drug 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.
The median CrCL in RE-LY was 68.4 mL/min. Almost half (45.8 %) of the RE-LY patients had a CrCL > 50-< 80 mL/min. Patients with moderate renal impairment (CrCL between 30-50 mL/min) had on average 2.29-fold and 1.81-fold higher pre- and post-dose dabigatran plasma concentrations, respectively, when compared with patients without renal impairment (CrCL ≥ 80 mL/min).
The median CrCL in the RE-COVER study was 100.4 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 and 50 mL/min). Patients with mild and moderate renal impairment had at steady state an average 1.8-fold and 3.6-fold higher pre-dose dabigatran plasma concentrations compared with patients with CrCL > 80 mL/min, respectively. Similar values for CrCL were found in RE-COVER II.
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 and 50 mL/min in in the RE-MEDY and RE-SONATE studies.
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 subjects with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls.
Body weight
The dabigatran trough concentrations were about 20 % lower in 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. Limited clinical data in 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. In atrial fibrillation patients females had on average 30 % higher trough and post-dose concentrations. No dose adjustment is required.
Ethnic origin
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding dabigatran pharmacokinetics and pharmacodynamics.
Pharmacokinetic interactions
The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-gp. Therefore concomitant use of P-gp transporter inhibitors (amiodarone, verapamil, clarithromycin, quinidine, dronedarone, ticagrelor and ketoconazole) and inducers (rifampicin) had been investigated.
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).

INCOMPATABILITIES

Not applicable

PACKAGING INFORMATION

Alu / Alu Desiccant Blister Pack

STORAGE AND HANDLING INSTRUCTIONS

Protect from moisture, Store below 30°C.

Keep away from children.

Manufactured by:
MSN Laboratories Private Limited,
Formulation Division,
Unit-II, Sy.No. 1277, 1319 to 1324,
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