Averodab 150 mg

Dabigatran etexilate

Hard Gelatin Capsules

Each Hard gelatin Capsule contain
Dabigatran etexilate mesylate 172.965 mg (eq. to 150 mg Dabigatran etexilate).

Clinical particulars

Therapeutic indications
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Posology and method of administration
Posology (SPAF, DVT/PE)
Prevention of stroke and SEE in adult patients with NVAF with one or more risk factors (SPAF)
The recommended daily dose of Averodab is 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term.
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE)
The recommended daily dose of Averodab is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.
SPAF, DVT/PE
For the following groups the recommended daily dose of dabigatran etexilate is 220 mg taken as one 110 mg capsule twice daily:
• Patients aged 80 years or above
• Patients who receive concomitant verapamil
For the following groups the daily dose of dabigatran etexilate of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:
• Patients between 75-80 years
• Patients with moderate renal impairment
• Patients with gastritis, esophagitis or gastroesophageal reflux
• Other patients at increased risk of bleeding
For DVT/PE the recommendation for the use of dabigatran etexilate 220 mg taken as one 110 mg capsule twice daily is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting.
See further down .
In case of intolerability to dabigatran, patients should be instructed to immediately consult their treating physician in order to be switched to alternate acceptable treatment options for prevention of stroke and SEE associated with atrial fibrillation or for DVT/PE.
Elderly (SPAF, DVT/PE)
Patients between 75-80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. A dose of dabigatran etexilate 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high .
Patients aged 80 years or above should be treated with a daily dose of dabigatran etexilate 220 mg taken as one 110 mg capsule twice daily due to the increased risk of bleeding in this population.

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

Patients at risk of bleeding (SPAF, DVT/PE)

Patients with an increased bleeding risk should be closely monitored clinically (looking for signs of bleeding or anaemia). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a dose of dabigatran etexilate 220 mg taken as one 110 mg capsule twice daily is recommended. When clinically relevant bleeding occurs, treatment should be interrupted.

For subjects with gastritis, esophagitis, or gastroesophageal reflux, the dose of dabigatran etexilate 220 mg taken as one 110 mg capsule twice daily may be considered due to the elevated risk of major gastro-intestinal bleeding .

Assessment of renal function (SPAF, DVT/PE)

In all patients:

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

• 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)

Additional requirements in patients with mild to moderate renal impairment and in patients aged over 75 years:

• Renal function should be assessed during treatment with Averodab at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products)

The method used to estimate renal function (CrCL in mL/min) during the clinical development of Averodab was the Cockgroft-Gault method .

Special populations

Renal impairment (SPAF, DVT/PE)

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

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

Concomitant use of Averodab with mild to moderate P-glycoprotein (P-gp) inhibitors, i.e. amiodarone, quinidine or verapamil (SPAF, DVT/PE)

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

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

Weight (SPAF, DVT/PE)

Given the available clinical and kinetic data, no dose adjustment is necessary, but close clinical surveillance is recommended in patients with a body weight < 50 kg .

Gender (SPAF, DVT/PE)

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

Hepatic impairment (SPAF, DVT/PE)

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

Switching (SPAF, DVT/PE)

Averodab treatment to parenteral anticoagulant

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

Parenteral anticoagulants to Averodab

Discontinue the parenteral anticoagulant and start dabigatran etexilate 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)) .

Averodab treatment to Vitamin K antagonists (VKA)

Adjust the starting time of the VKA based on CrCL as follows:

• CrCL ≥ 50 mL/min, start VKA 3 days before discontinuing dabigatran etexilate

• CrCL ≥ 30-< 50 mL/min, start VKA 2 days before discontinuing dabigatran etexilate

Because Averodab can increase INR, the INR will better reflect VKA's effect only after Averodab has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

VKA to Averodab

The VKA should be stopped. Dabigatran etexilate can be given as soon as the International Normalized Ratio (INR) is < 2.0.

Cardioversion (SPAF, DVT/PE)

Patients can stay on dabigatran etexilate while being cardioverted.

Paediatric population (SPAF)

There is no relevant use of Averodab in the paediatric population in the indication: prevention of stroke and systemic embolism in patients with NVAF.

Paediatric population (DVT/PE)

The safety and efficacy of Averodab in children from birth to less than 18 years of age have not yet been established. Currently available data are listed in the following sections, but no recommendation on a posology can be made.

Missed dose *(SPAF, DVT/PE)*

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 on, the missed dose should be omitted.

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

Method of administration *(SPAF, DVT/PE)*

Averodab can be taken with or without food. Averodab 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 .

Contraindications

• Hypersensitivity to the active substance or to any of the excipients .

• Patients with severe renal impairment (CrCL < 30 mL/min)

• Active clinically significant bleeding

• Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities

• Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances 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 .

Special warnings and precautions for use

Hepatic impairment

Patients with elevated liver enzymes > 2 ULN were excluded from the main trials. No treatment experience is available for this subpopulation of patients, and therefore the use of Averodab is not recommended in this population.

Haemorrhagic risk

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

Factors, such as decreased renal function (30-50 mL/min CrCL), age ≥ 75 years, low body weight < 50 kg, or mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, quinidine or verapamil) are associated with increased dabigatran plasma levels.
The concomitant use of ticagrelor increases the exposure to dabigatran and may show pharmacodynamic interaction, which may result in an increased risk of bleeding .
In a study of prevention of stroke and SEE in adult patients with NVAF, dabigatran etexilate was associated with higher rates of major gastrointestinal (GI) bleeding which was statistically significant for dabigatran etexilate 150 mg twice daily. This increased risk was seen in the elderly (≥ 75 years). Use of acetylsalicylic acid (ASA), clopidogrel or non steroidal antiinflammatory drug (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux increase the risk of GI bleeding. In these atrial fibrillation patients a dosage of dabigatran etexilate 220 mg given as 110 mg capsule twice daily should be considered and posology recommendation be followed . The administration of a PPI can be considered to prevent GI bleeding.
Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs) .
Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if risk factors are combined .
Table 1 summarises factors which may increase the haemorrhagic risk please also refer to contraindication section. Table 1: Factors which may increase the haemorrhagic risk.

Pharmacodynamic and kinetic factors	Age ≥ 75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (30-50 mL/min CrCL) • P-gp inhibitor co-medication (some P-gp inhibitors are contraindicated, see section 4.3 and 4.5) Minor: • Low body weight (< 50 kg)
Pharmacodynamic interactions	• ASA • NSAID • Clopidogrel • SSRIs or SNRIs • Other drugs 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

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. Averodab should only be given if the benefit outweighs bleeding risks.
Averodab does not in general require routine anticoagulant monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. The INR test is unreliable in patients on Averodab and false positive INR elevations have been reported. Therefore INR tests should not be performed. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardised, and results should be interpreted with caution .
Table 2 shows coagulation test thresholds at trough that may be associated with an increased risk of bleeding .
Table 2: Coagulation test thresholds at trough that may be associated with an increased risk of bleeding.

Test (trough value)	Indication
	SPAF and DVT/PE
dTT [ng/mL]	> 200
ECT [x-fold upper limit of normal]	> 3
aPTT [x-fold upper limit of normal]	> 2
INR	Should not be performed

Patients who develop acute renal failure must discontinue Averodab .

Limited data is available in patients < 50 kg .
When severe bleedings occur treatment must be discontinued and the source of bleeding investigated .
Medicinal products that may enhance the risk of haemorrhage should not be administered concomitantly or should be administered with caution with Averodab .
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 ULN according to the local reference range.
Interaction with P-gp inducers
Concomitant administration of P-gp inducers (such as rifampicin, St. John`s wort (Hypericum perforatum), carbamazepine, or phenytoin) is expected to result in decreased dabigatran plasma concentrations, and should be avoided .
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.
Preoperative phase
Table 3 summarises discontinuation rules before invasive or surgical procedures.
Table 3: Discontinuation rules before invasive or surgical procedures

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

If an acute intervention is required, 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 .
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 moderate renal impairment (CrCL 30-50 mL/min), 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 available in these patients and therefore they should be treated with caution.
Myocardial Infarction (SPAF)
In the phase III study RE-LY the overall rate of myocardial infarction (MI) was 0.82, 0.81, and 0.64 % / year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29 % and 27 % compared to warfarin. Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left ventricular ejection fraction < 40 %, and patients with moderate renal dysfunction. Furthermore a higher risk of MI was seen in patients concomitantly taking ASA plus clopidogrel or clopidogrel alone.
Myocardial Infarction (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 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

Active Cancer Patients (DVT/PE)

The efficacy and safety have not been established for DVT/PE patients with active cancer.

Interaction with other medicinal products and other forms of interaction

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 Averodab: 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 and platelet aggregation medicinal products such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran and sulfinpyrazone .From the limited data collected in the phase III study RE LY in patients with atrial fibrillation it was observed that the concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate and warfarin by approximately 2.5-fold, mainly related to situations when switching from one anticoagulant to another .

UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter .

From the data collected in the phase III study RE-LY in patients with atrial fibrillation , it was observed that the concomitant use of antiplatelets ASA or clopidogrel approximately doubles major bleeding rates with both dabigatran etexilate and warfarin.

Clopidogrel: In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran AUC τ,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 τ,ss and Cmax,ss were increased by about 30-40 % (see warning and precautions) (see also subsection on ASA below).

ASA: The effect of concomitant administration of dabigatran etexilate and ASA on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomized ASA co-administration was applied. Based on logistic regression analysis, 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 .

NSAIDs: NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50% on both dabigatran etexilate and warfarin. Therefore, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended (see warning and precautions).

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 dabigatran etexilate 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.

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.

Transporter interactions

P-gp inhibitors

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, ketoconazole, dronedarone, clarithromycin and ticagrelor) 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. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure .
The following strong P-gp inhibitors are contraindicated: systemic ketoconazole, cyclosporine, itraconazole and dronedarone . Concomitant treatment with tacrolimus is not recommended. Caution should be exercised with mild to moderate P-gp inhibitors (e.g. amiodarone, posaconazole, quinidine, verapamil and ticagrelor) .
Ketoconazole: Ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by 138 % and 135 %, respectively, after a single oral dose of 400 mg, and 153 % and 149 %, respectively, after multiple oral dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole .Concomitant treatment with systemic ketoconazole is contraindicated .
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 (+136 % and 125 %), respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold (+114 % and 87 %), respectively, after a single dose of 400 mg. The terminal half-life and renal clearance of dabigatran were not affected by dronedarone. When single and multiple doses of dronedarone were given 2 h after dabigatran etexilate, the increases in dabigatran $AUC_{0-\infty}$ were 1.3-fold and 1.6-fold, respectively. Concomitant treatment with dronedarone is contraindicated.
Amiodarone: When Averodab 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 Cmax were increased by about 60 % and 50 %, respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone . Close clinical surveillance is recommended when dabigatran etexilate is combined with amiodarone and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.
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 Cmax,ss were increased on average by 53 % and 56 %, respectively with concomitant quinidine . Close clinical surveillance is recommended when dabigatran etexilate is combined with quinidine and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.
Verapamil: When dabigatran etexilate (150 mg) was co-administered with oral verapamil, the Cmax and AUC of dabigatran were increased but magnitude of this change differs depending on timing of administration and formulation of verapamil .
The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of Cmax by about 180 % and AUC by about 150 %). The effect was progressively decreased with administration of an extended release formulation (increased of Cmaxby about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increased of Cmax by about 60 % and AUC by about 50 %).
Patients concomitantly receiving dabigatran etexilate and verapamil, the dose of Averodab should be reduced to dabigatran etexilate 220 mg taken as one 110 mg capsule twice daily . Close clinical surveillance is recommended when dabigatran etexilate is combined with verapamil and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.
There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increased of Cmax by about 10 % and AUC by about 20 %). This is explained by completed dabigatran absorption after 2 hours .
Clarithromycin: When clarithromycin (500 mg twice daily) was administered together with dabigatran etexilate in healthy volunteers, increase of AUC by about 19 % and Cmax by about 15 % was observed without any clinical safety concern. However, in patients receiving dabigatran, a clinically relevant interaction cannot be excluded when combined with clarithromycin. Therefore, a close monitoring should be exercised when dabigatran etexilate is combined with clarithromycin and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.
Ticagrelor: When a single dose of 75mg dabigatran etexilate was coadministered simultaneously with a loading dose of 180 mg ticagrelor, the dabigatran AUC and Cmaxwere increased by 1.73-fold and 1.95-fold (+73% and 95 %), respectively. After multiple doses of ticagrelor 90 mg b.i.d. the increase of dabigatran exposure is 1.56-fold and 1.46-fold (+56% and 46%) for Cmax and AUC, respectively.

Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ by 1.49-fold and 1.65-fold (+49% and 65%), respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ was reduced to 1.27-fold and 1.23-fold (+27% and 23%), respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose.
Concomitant administration of 90 mg ticagrelor BID (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.
The following potent P-gp inhibitors have not been clinically studied but from in vitro results a similar effect as with ketoconazole may be expected:
Itraconazole and cyclosporine, which are contra-indicated .
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. Based on these data concomitant treatment with tacrolimus is not recommended.
Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when Averodab is co-administered with posaconazole.
P-gp inducers
Concomitant administration of a P-gp inducer (such as rifampicin, St. John´s wort (Hypericum perforatum), carbamazepine, or phenytoin) is expected to result in decreased dabigatran concentrations and should be avoided .
Rifampicin: 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.
Other medicinal products affecting P-gp
Protease inhibitors including ritonavir and its combinations with other protease inhibitors affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with Averodab.
P-gp substrate
Digoxin: In a study performed with 24 healthy subjects, when Averodab was co-administered with digoxin, no changes on digoxin and no clinical relevant changes on dabigatran exposure have been observed.
Co-medication with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)
SSRIs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups.
Gastric pH
Pantoprazole: When dabigatran was co-administered with pantoprazole, a decrease in the dabigatran area under the plasma concentration-time curve of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors (PPI) were co-administered with dabigatran in clinical trials, and concomitant PPI treatment did not appear to reduce the efficacy of dabigatran.
Ranitidine: Ranitidine administration together with dabigatran had no clinically relevant effect on the extent of absorption of dabigatran.

Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should avoid pregnancy during treatment with dabigatran etexilate.
Pregnancy
There are limited amount of data from the use of dabigatran etexilate in pregnant women.
Studies in animals have shown reproductive toxicity . The potential risk for humans is unknown.
Averodab 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 Averodab.
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).

Effects on ability to drive and use machines

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

Undesirable effects

The most commonly reported adverse reactions are bleedings occurring in total in approximately 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.

Tabulated list of adverse reactions

Table 4 shows the adverse reactions identified with dabigatran from the study in prevention of thromboembolic stroke and SEE in patients with atrial fibrillation, the studies in DVT/PE treatment and in DVT/PE prevention. 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 4: Adverse reactions

	Stroke and SEE prevention in patients with atrial fibrillation	DVT/PE treatment and DVT/PE prevention
SOC / Preferred term.		
Blood and lymphatic system disorders		
Anaemia	Common	Uncommon
Haemoglobin decreased	Uncommon	Not known
Thrombocytopenia	Uncommon	Rare
Haematocrit decreased	Rare	Not known
Immune system disorder		
Drug hypersensitivity	Uncommon	Uncommon
Rash	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon
Anaphylactic reaction	Rare	Rare
Angioedema	Rare	Rare
Urticaria	Rare	Rare
Bronchospasm	Not known	Not known
Nervous system disorders		
Intracranial haemorrhage	Uncommon	Rare
Vascular disorders		
Haematoma	Uncommon	Uncommon
Haemorrhage	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Epistaxis	Common	Common
Haemoptysis	Uncommon	Uncommon
Gastrointestinal disorders		
Gastrointestinal haemorrhage	Common	Common
Abdominal pain	Common	Uncommon
Diarrhoea	Common	Uncommon
Dyspepsia	Common	Common
Nausea	Common	Uncommon

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

Bleeding

Prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation with one or more risk factors (SPAF)

Overdose

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 Averodab treatment. There is no specific antidote to dabigatran. 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. Appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescribers discretion.

Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX and X, may be considered. 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 reversing medicinal products. 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 judgement.

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 dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies .

Pharmacological properties

➢ Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic, direct thrombin inhibitors.

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 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-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. The absolute bioavailability of dabigatran following oral administration was approximately 6.5 %.

After oral administration of dabigatran 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, GI 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.

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 .

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 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 5: 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)

Clearance of dabigatran by haemodialysis 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.

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.

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

In atrial fibrillation patients females had on average 30 % higher trough and post-dose concentrations. 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.

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).

Pharmaceutical particulars

Pharmaceutical excipients :

Inactive ingredients:
Microcrystalline Cellulose
Povidone (PVP K30)
Starcap 1500 (Corn Starch + Pregelatinized starch)
Anhydrous citric acid
Sodium lauryl sulphate
Colloidal Anhydrous Silica
Capsule shell ingredients:

- Cap. Ingredients: (Gelatin (bovine origin), Titanium dioxide , Sunset yellow (C.I.N 15985) , Quanoline yellow (C.I.N 47005) , Erythrosine (C.I.N 45430).
- Body ingredients: (Gelatin (bovine origin), Titanium dioxide , Sunset yellow (C.I.N 15985) , Quanoline yellow (C.I.N 47005) , Erythrosine (C.I.N 45430).

Incompatibilities

Not applicable.

Storage Conditions :

Store at temperature not exceeding 30 ° C , in dry place .

Nature and contents of container

Carton box containing one strip of (hard Al foil/ opaque white PVDC) blister containing 10 hard gelatin capsules + inner leaflet.

Produced by: Averroes Pharma for Pharmaceutical Industries

Block No. (6048) 6th industrial zone - Sadat city - Egypt.