# *Averodab 75 mg*

# *Hard Gelatin Capsules*

## Clinical particulars

## Therapeutic indications

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

## Posology and method of administration

## Posology

*Primary Prevention of Venous Thromboembolism in Orthopaedic Surgery (pVTEp orthopaedic surgery)*

*Patients following elective knee replacement surgery*

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

*Patients following elective hip replacement surgery* The recommended dose of dabigatran is 220 mg once daily. Treatment should be initiated orally within 1–4 hours of completed surgery with a single dose of 110 mg and continuing with 220 mg once daily thereafter for a total of 28-35 days. For the following groups the recommended daily dose of dabigatran is 150 mg taken once daily as 2 capsules of 75 mg.

Treatment should be initiated orally within 1-4 hours of completed surgery with a single capsule of 75 mg and continuing with 2 capsules once daily thereafter for a total of 10 days (knee replacement surgery) or 28-35 days (hip replacement surgery):

• Patients with moderate renal impairment (creatinine clearance, CrCL 30-50 mL/min) .

• Patients who receive concomitant verapamil, amiodarone, quinidine .

• Patients aged 75 or above for both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Assessment of renal function (*pVTEp orthopaedic surgery*):

In all patients:

• Renal function should be assessed by calculating the creatine 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)

The method used to estimate renal function (CrCL in mL/min) during The clinical development of dabigatran was the Cockgroft Gault method. The formula is as follows:

For creatinine in µmol/L

$$\frac{1.23\times(140-Age\ (years))\times weight(kg)(\times 0.85\ if\ female)}{\text{Serum creatinine ( µmol/L )}}$$

For creatinine in mg/dL :

$$\frac{(140 - Age\ (years)) \times weight\ (kg)(\times 0.85\ if\ female)}{72 \times \text{Serum creatinine (mg/ dL)}}$$

This method is recommended when assessing patients' CrCL prior to and during Averodab treatment.

Special populations

*Renal impairment (pVTEp orthopaedic surgery)*

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

In patients with moderate renal impairment (CrCL 3050 mL/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg .

*Concomitant use of Averodab with mild to moderate Pglycoprotein (Pgp) inhibitors, i.e. amiodarone, quinidine or verapamil (pVTEp orthopaedic surgery)*

Dosing should be reduced to 150 mg taken once daily as 2 capsules of 75 mg Averodab in patients who receive concomitantly dabigatran etexilate and amiodarone, quinidine or verapamil . In this situation Averodab and these medicinal products should be taken at the same time.

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

*Elderly (pVTEp orthopaedic surgery)*

In elderly patients (> 75 years) there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg .

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). While on treatment the renal function should also be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc.

*Hepatic impairment (pVTEp orthopaedic surgery)*

Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials investigating the VTE prevention following elective hip or knee replacement surgery. 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 .

*Weight (pVTEp orthopaedic surgery)*

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

*Gender (pVTEp orthopaedic surgery)*

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

*Switching (pVTEp orthopaedic surgery)*

*Averodab treatment to parenteral anticoagulant*

It is recommended to wait 24 hours after the last dose before switching from Averodab 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)) .

*Paediatric population (pVTEp orthopaedic surgery)*
There is no relevant use of Averodab in the paediatric population in the indication: primary prevention of venous thromboembolic events in patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

*Missed dose (pVTEp orthopaedic surgery)*
It is recommended to continue with the remaining daily doses of dabigatran etexilate at the same time of the next day.
No double dose should be taken to make up for missed individual doses.

*Method of administration (pVTEp orthopaedic surgery)*
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 in controlled clinical trials investigating the VTE prevention following elective hip or knee replacement surgery. 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 .
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. 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. Table 1: Factors which may increase the haemorrhagic risk.

| Pharmacodynamic and kinetic factors | Age ≥ 75 years |
|---|---|
| Factors increasing dabigatran plasma levels | <u>Major:</u><br>• Moderate renal impairment (30-50 mL/min CrCL)<br>• P-gp inhibitor co-medication (some P-gp inhibitors are contraindicated,)<br><u>Minor:</u><br>• Low body weight (< 50 kg) |
| Pharmacodynamic interactions | • ASA<br>• NSAID<br>• Clopidogrel<br>• SSRIs or SNRIs<br>• Other drugs which may impair haemostasis |
| Diseases / procedures with special haemorrhagic risks | • Congenital or acquired coagulation disorders<br>• Thrombocytopenia or functional platelet defects<br>• Recent biopsy, major trauma<br>• Bacterial endocarditis<br>• 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) | |
|---|---|

| | |
|---|---|
| dTT [ng/mL] | > 67 |
| ECT [x-fold upper limit of normal] | No data |
| aPTT [x-fold upper limit of normal] | > 1.3 |
| INR | Should not be performed |

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

## 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 .
UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter .
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 ,ss and C ,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 monotreatments. With a loading dose of 300 mg or 600 mg clopidogrel, dabigatran AUC ,ss and C ,ss were increased by about 30-40 %
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.
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 coadministration was applied. Based on logistic regression analysis, coadministration 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 shortterm perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use 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 halflives > 12 hours, close observation for signs of bleeding is recommended.
LMWH: The concomitant use of LMWHs, such as enoxaparin and dabigatran etexilate has not been specifically investigated. After switching from 3day treatment of once daily 40 mg enoxaparin s.c., 24 hours after the last dose of enoxaparin the exposure to dabigatran was slightly lower than that after administration of dabigatran etexilate (single dose of 220 mg) alone. A higher antiFXa/ FIIa activity was observed after dabigatran etexilate administration with enoxaparin pretreatment compared to that after treatment with dabigatran etexilate alone. This is considered to be due to the carryover effect of enoxaparin treatment, and regarded as not clinically relevant. Other dabigatran related anticoagulation tests were not changed significantly by the pretreatment of enoxaparin.

Interaction linked to dabigatran etexilate and dabigatran metabolic profile

Dabigatran etexilate and dabigatran are not metabolized by the cytochrome P450 system and have no invitro 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 dabigatran was co-administered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and $C_{max}$ were increased by about 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 .

Patients treated for prevention of VTEs after hip or knee replacement surgery, dosing should be reduced to 150 mg taken once daily as 2 capsules of 75 mg Averodab if they receive concomitantly dabigatran etexilate and 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 $C_{max,ss}$ were increased on average by 53 % and 56 %, respectively with concomitant quinidine .

Patients treated for prevention of VTEs after hip or knee replacement surgery, dosing should be reduced to 150 mg taken once daily as 2 capsules of 75 mg Averodab if they receive concomitantly dabigatran etexilate and 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 $C_{max}$ 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 $C_{max}$ by about 180 % and AUC by about 150 %). The effect was progressively decreased with administration of an extended release formulation (increased of $C_{max}$by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increased of $C_{max}$ by about 60 % and AUC by about 50 %).
Therefore, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with verapamil. In patients with normal renal function after the hip or knee replacement surgery, receiving dabigatran etexilate and verapamil concomitantly, the dose of Averodab should be reduced to 150 mg taken once daily as 2 capsules of 75 mg . In patients with moderate renal impairment and concomitantly treated with dabigatran etexilate and verapamil, a dose reduction of Averodab to 75 mg daily should be considered . 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 $C_{max}$ 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 $C_{max}$ 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 $C_{max}$were increased by 1.73-fold and 1.95-fold (+73% and 95 %), respectively. After multiple doses of ticagrelor 90 mg b.i.d. the increase of dabigatran exposure is 1.56-fold and 1.46-fold (+56% and 46%) for $C_{max}$ and AUC, respectively.
Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran $AUC_{\tau}$,ss and Cmax,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 Cmax,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 Cmax,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 Averodab 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 Averodab in clinical trials, and concomitant PPI treatment did not appear to reduce the efficacy of Averodab.
Ranitidine: Ranitidine administration together with Averodab 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.

## Effects on ability to drive and use machines

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

## Undesirable effects

Summary of the safety profile
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.
The most commonly reported adverse reactions are bleedings occurring in total in approximately 14 % of patients; the frequency of major bleeds (including wound site bleedings) is less than 2 %.
Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Tabulated list of adverse reactions

Table 4 shows the adverse reactions ranked under headings of System Organ Classes (SOC) and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 4: Adverse reactions

| SOC / Preferred term. | |
|---|---|
| Blood and lymphatic system disorders | |
| Haemoglobin decreased | Common |
| Anaemia | Uncommon |
| Haematocrit decreased | Uncommon |
| Thrombocytopenia | Rare |
| Immune system disorder | |
| Drug hypersensitivity | Uncommon |
| Anaphylactic reaction | Rare |
| Angioedema | Rare |
| Urticaria | Rare |
| Rash | Rare |
| Pruritus | Rare |
| Bronchospasm | Not known |
| Nervous system disorders | |
| Intracranial haemorrhage | Rare |
| Vascular disorders | |
| Haematoma | Uncommon |
| Wound haemorrhage | Uncommon |
| Haemorrhage | Rare |
| Respiratory, thoracic and mediastinal disorders | |
| Epistaxis | Uncommon |
| Haemoptysis | Rare |
| Gastrointestinal disorders | |
| Gastrointestinal haemorrhage | Uncommon |
| Rectal haemorrhage | Uncommon |
| Haemorrhoidal haemorrhage | Uncommon |
| Diarrhoea | Uncommon |
| Nausea | Uncommon |
| Vomiting | Uncommon |
| Gastrointestinal ulcer, including oesophageal ulcer | Rare |
| Gastroesophagitis | Rare |
| Gastroesophageal reflux disease | Rare |
| Abdominal pain | Rare |
| Dyspepsia | Rare |
| Dysphagia | Rare |
| Hepatobiliary disorders | |

| | |
|---|---|
| Hepatic function abnormal/ Liver function Test abnormal | Common |
| Alanine aminotransferase increased | Uncommon |
| Aspartate aminotransferase increased | Uncommon |
| Hepatic enzyme increased | Uncommon |
| Hyperbilirubinaemia | Uncommon |
| Skin and subcutaneous tissue disorder | |
| Skin haemorrhage | Uncommon |
| Musculoskeletal and connective tissue disorders | |
| Haemarthrosis | Uncommon |
| Renal and urinary disorders | |
| Genitourological haemorrhage, including haematuria | Uncommon |
| General disorders and administration site conditions | |
| Injection site haemorrhage | Rare |
| Catheter site haemorrhage | Rare |
| Bloody discharge | Rare |
| Injury, poisoning and procedural complications | |
| Traumatic haemorrhage | Uncommon |
| Post procedural haematoma | Uncommon |
| Post procedural haemorrhage | Uncommon |
| Post procedural discharge | Uncommon |
| Wound secretion | Uncommon |
| Incision site haemorrhage | Rare |
| Anaemia postoperative | Rare |
| Surgical and medical procedures | |
| Wound drainage | Rare |
| Post procedural drainage | Rare |

## Bleeding

The table 5 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 5: Number (%) of patients experiencing the adverse reaction bleeding Overdose.

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

The definition of the adverse reaction major bleeding in the RENOVATE and REMODEL 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 reoperation
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).

**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 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 .

## 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 of Averodab was approximately 6.5 %.
After oral administration of Averodab 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.

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 9.
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 Averodab 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 9: 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 endstage 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.
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.

*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

## List of excipients

Active ingredients:
Dabigatran etexilate mesylate 86.48 (eq. to 75 mg Dabigatran etexilate)
Inactive ingredients:
Microcrystalline Cellulose
Povidone (PVP K30)
Starcap 1500 (Corn Starch + Pregelatinized starch )
Anhydrous citric acid
Sodium lauryl sulphate
Colloidal Anhydrous Silica

**Storage Conditions :**
Store at temperature not exceeding 30 ° C in dry place
**Nature and contents of container**
Carton box containing (Al foil/ opaque white PVDC) strip of 10 hard gelatin capsules + inner leaflet

Manufactured by: Averroes Pharma for pharmaceutical industries

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