SCHEDULING STATUS

S4

1. NAME OF THE MEDICINAL PRODUCT

DABIGATRAN 75 DRL Capsules

DABIGATRAN 110 DRL Capsules

DABIGATRAN 150 DRL Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DABIGATRAN 75 DRL: Each capsule contains 75 mg of dabigatran etexilate (as mesilate salt).

DABIGATRAN 110 DRL: Each capsule contains 110 mg of dabigatran etexilate (as mesilate salt).

DABIGATRAN 150 DRL: Each capsule contains 150 mg of dabigatran etexilate (as mesilate salt).

DABIGATRAN DRL is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DABIGATRAN 75 DRL: Size "2" capsule with a white opaque caps imprinted "MD" and white opaque body imprinted "75" with black ink, containing a blend of white to light yellow coloured pellets and light yellow coloured granulate.

DABIGATRAN 110 DRL: Size "1" capsule having white opaque caps imprinted "MD" and white opaque body imprinted "110" with black ink, containing a blend of white to light yellow coloured pellets and light yellow coloured granulate.

DABIGATRAN 150 DRL: Size "0" capsule having white opaque caps imprinted "MD" and white opaque body imprinted "150" with black ink, containing a blend of white to light yellow coloured pellets and light yellow coloured granulate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE).

4.2 Posology and method of administration

Posology

Adults:

Prevention of venous thromboembolism (VTE) in patients following hip and knee replacement surgery:

The recommended dose of DABIGATRAN DRL is 220 mg once daily taken as 2 capsules of 110 mg.

Patients with moderate renal impairment have an increased risk for bleeding. For those patients the recommended dose of DABIGATRAN DRL is 150 mg once daily (see also "Renal impairment" below).

VTE prevention following knee replacement surgery:

Treatment with DABIGATRAN DRL should be initiated orally within 1 to 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 10 days. 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.

Patients with moderate renal impairment have an increased risk for bleeding:

For those patients the DABIGATRAN DRL 75 mg capsules

should be used instead of the 110 mg capsules**.**

VTE prevention following hip replacement surgery:

Treatment with DABIGATRAN DRL should be initiated orally within 1 to 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 28 days. 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.

Patients with moderate renal impairment have an increased risk for bleeding. For those patients the DABIGATRAN DRL 75 mg capsules should be used instead of the 110 mg capsules.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

The recommended daily dose of DABIGATRAN DRL is 300 mg taken orally as 150 mg capsules twice daily. Therapy should be continued life-long.

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

The recommended daily dose of DABIGATRAN DRL is 300 mg taken orally as 150 mg capsules twice daily following treatment with a parenteral anticoagulant for at least 5 days. Therapy should be continued for up to 6 months.

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

The recommended daily dose of DABIGATRAN DRL is 300 mg taken orally as 150 mg capsules twice daily. Therapy could be continued life-long depending on the individual patient's risk factors.

Children:

DABIGATRAN DRL has not been investigated in patients< 18 years of age. Treatment of children with DABIGATRAN DRL is not recommended.

Renal impairment:

Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with DABIGATRAN DRL to exclude patients for treatment with severe renal impairment (i.e., CrCl < 30 mL/min).

There are no data to support use in patients with severe renal impairment (CrCl < 30 mL/min); treatment in this population with DABIGATRAN DRL is not recommended (see section 4.3).

While on treatment renal function should be assessed in certain clinical situations when it is suspected that the renal function

could decline or deteriorate (such as hypovolaemia, dehydration, and with certain co-medications that may decrease renal function such as with initiation of chemotherapeutics, or amphotericin B or under chronic treatment with NSAIDs).

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

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery:

Dosing should be reduced to 150 mg DABIGATRAN DRL taken once daily as 2 capsules of 75 mg in patients with moderate renal impairment (CrCl 30 to 50 mL/min).

Treatment with DABIGATRAN DRL should be initiated orally within 1 to 4 hours of completed surgery with a single capsule of 75 mg and continuing with 2 capsules of 75 mg once daily thereafter for a total of 10 days (following knee replacement surgery) or 28 days (following hip replacement surgery). For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

In patients with moderate renal impairment (CrCl 30 to 50 mL/min) the renal function should be assessed at least once a year.

No dose adjustment is necessary. Patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

No dose adjustment is necessary in patients with renal function

over CrCl 30 mL/min. Patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

In patients with moderate renal impairment (CrCl 30 to 50 mL/min) the renal function should be assessed at least once a year.

No dose adjustment is necessary in patients with renal function over CrCl 30 mL/min. Patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Elderly

Pharmacokinetic studies in older subjects demonstrate an increase in dabigatran exposure in those patients with age-related decline of renal function. As renal impairment may be frequent in the elderly (> 75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with DABIGATRAN DRL to exclude patients for treatment 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 DABIGATRAN DRL or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolaemia, dehydration, and with certain co-medications that may decrease renal function such as with initiation of chemotherapeutics, or amphotericin B or under chronic treatment with NSAIDs) (see also section 4.2, For use in Renal impairment).

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery:

No dose adjustment is necessary, patients should be treated with 220 mg DABIGATRAN DRL

taken once daily as 2 capsules of 110 mg.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

Patients aged 80 years or above should be treated with a daily dose of 220 mg taken orally as 110 mg capsules twice daily.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

No dose adjustment is necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Weight:

No dose adjustment is necessary.

Concomitant use of DABIGATRAN DRL with strong P-glycoprotein Inhibitors, i.e., amiodarone, quinidine or verapamil*:*

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery: Dosing should be
reduced to DABIGATRAN DRL 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive DABIGATRAN DRL and amiodarone, quinidine or verapamil (see section 4.5).

Treatment initiation with verapamil should be avoided in patients who have undergone hip and knee replacement surgery who are already treated with DABIGATRAN DRL.

Simultaneous initiation of treatment with DABIGATRAN DRL and verapamil should also be avoided.

Treatment with DABIGATRAN DRL should be initiated orally within 1 to 4 hours of completed surgery with a single capsule of 75 mg and continuing with 2 capsules of 75 mg once daily thereafter for a total of 10 days (following knee replacement surgery) or 28 days (following hip replacement surgery). For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be

initiated with 2 capsules once daily.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

No dose adjustment is necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

No dose adjustment is necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg capsules twice daily.

Patients at risk of bleeding:

The presence of the following factors is associated with an increased risk of bleeding: e.g., age ≥ 75 years, moderate renal impairment (CrCl 30 to 50 mL/min), concomitant treatment with strong P-gp inhibitors (see section 4.5), antiplatelet medicines or previous gastrointestinal bleed (see sections 4.3 and 4.4).

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

For patients with one or more than one of these risk factors, a reduced daily dose of 220 mg given as 110 mg twice daily may be considered at the discretion of the doctor.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

No dose adjustment is necessary for patients with single risk factors.

Only limited clinical data are available for patients with multiple risk factors. Therefore, DABIGATRAN DRL should only be given in these patients if the expected benefit outweighs bleeding risks.

Switching from DABIGATRAN DRL treatment to a parenteral anticoagulant:

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery:

Wait 24 hours after the last dose before switching from DABIGATRAN DRL to a parenteral

anticoagulant.

T*o reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:*

Wait 12 hours after the last dose before switching from DABIGATRAN DRL to a parenteral anticoagulant.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

Wait 12 hours after the last dose before switching from DABIGATRAN DRL to a parenteral anticoagulant.

Switching from parenteral anticoagulant treatment to DABIGATRAN DRL:

DABIGATRAN DRL should be given within 2 hours prior to the time that

the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g., intravenous UFH).

Switching from warfarin to DABIGATRAN DRL:

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

The warfarin should be stopped. DABIGATRAN DRL can be given as soon as the INR is < 2,0.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

The warfarin should be stopped. DABIGATRAN DRL can be given as soon as the INR is < 2,0.

Switching from DABIGATRAN DRL to warfarin:

The starting time of warfarin should be adjusted according to the patient's CrCl as follows:

- CrCl ≥ 50 mL/min, start warfarin 3 days before discontinuing DABIGATRAN DRL.
- CrCl ≥30 - < 50 mL/min, start warfarin 2 days before discontinuing DABIGATRAN DRL.

Cardioversion:

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation: Patients can

stay on DABIGATRAN DRL while being cardioverted.

Catheter ablation for atrial fibrillation:

Catheter ablation can be conducted in non-valvular atrial fibrillation patients on 150 mg twice daily DABIGATRAN DRL treatment. DABIGATRAN DRL treatment does not need to be interrupted. There are no clinical data on continuation of DABIGATRAN DRL treatment during catheter ablation in those non-valvular atrial fibrillation patients receiving 110 mg twice daily.

Percutaneous coronary intervention (PCI) with stenting:

Patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with DABIGATRAN DRL in combination with antiplatelets after haemostasis is achieved.

Missed dose:

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery:

Patients should continue with their remaining daily doses of DABIGATRAN DRL at the same time on the next day and not take a double dose to make up for missed individual doses.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

A forgotten DABIGATRAN DRL dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose, the missed dose should be omitted. Patients should not take a double dose to make up for missed individual doses.

Treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE): A forgotten DABIGATRAN DRL dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose, the missed dose should be omitted. Patients should not take a double dose to make up for missed individual doses.

Discontinuation rules before invasive or surgical procedures:

Renal function (CrCl in mL/min)	Estimated half-life (hours)	Stop DABIGATRAN DRL before elective surgery

		High risk of bleeding or major surgery	Standard risk
≥ 80	~ 13*	2 days before	24 hours before
≥ 50 to < 80	~ 15*	2 to 3 days before	1 to 2 days before
≥ 30 to < 50	~ 18*	4 days before	2 to 3 days before (> 48 hours)

*for more details see the table in Pharmacokinetic properties (section 5.2) and WARNINGS AND SPECIAL PRECAUTIONS (section 4.4).

Method of administration

DABIGATRAN DRL for oral use.

DABIGATRAN DRL can be taken with or without food. DABIGATRAN DRL should be taken with a glass of water, to facilitate delivery to the stomach. Do not open the capsule. If gastrointestinal symptoms develop it is recommended to take DABIGATRAN DRL with a meal and/or a proton pump inhibitor such as pantoprazole.

4.3 Contraindications

- Known hypersensitivity to dabigatran or dabigatran etexilate or to one of the excipients of DABIGATRAN DRL
- Patients with severe renal impairment (CrCl < 30 ml/min)
- Haemorrhagic manifestations, patients with a bleeding diathesis, or patients with spontaneous or pharmacological impairment of haemostasis
- Moderate to severe hepatic impairment (Child-Pugh B/C)
- Organ lesions at risk of clinically significant bleeding, including haemorrhagic stroke within

the last 6 months

- Patients with an indwelling spinal or epidural catheter and during the first hour after removal (see section 4.4)
- Prolonged co-administration with heparins or warfarin
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir (see section 4.5)
- The following treatments should not be administered concomitantly with DABIGATRAN DRL: unfractionated heparins and heparin
  derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic medicines, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, ticagrelor, dextran, sulfinpyrazone and Vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter and that DABIGATRAN DRL and Vitamin K antagonists (e.g., warfarin) can be administered together, but only for a few days during switching from DABIGATRAN DRL to Vitamin K antagonist treatment
- In patients with suspected infective endocarditis
- Prosthetic heart valve replacement

4.4 Special warnings and precautions for use

Haemorrhagic risk:

DABIGATRAN DRL increases the risk of bleeding and can cause significant and sometimes fatal bleeding.

DABIGATRAN DRL should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with DABIGATRAN DRL. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site. In

the case of haemorrhagic complications treatment must be discontinued and the source of bleeding investigated. For situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effects of dabigatran is required, the specific reversal agent idarucizumab is available. Careful clinical monitoring including renal function testing is required in certain clinical situations.

Caution is advised as tests to monitor coagulation are not available.

There is a correlation between plasma dabigatran concentration and degree of anticoagulant effect. However, this can only be partially measured by a combination of aPTT, prothrombin time (PT, expressed as INR), thromboplastin time and ecarin clotting time tests, no single one of which provides a complete assessment of the anticoagulant effect of DABIGATRAN DRL.

DABIGATRAN DRL treatment cannot be therapeutically monitored by coagulation tests. The INR test is unreliable in patients on DABIGATRAN DRL and false positive INR elevations have been reported. Therefore, INR tests should not be performed. Tests of anticoagulant activity such as thrombin time (TT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) are available to detect excessive DABIGATRAN DRL activity. DABIGATRAN DRL related anticoagulation can be assessed by ECT or TT.

If ECT or TT ls not available, the aPTT test provides an approximation of DABIGATRAN DRL's anticoagulant activity. However, in patients who are bleeding a PTT tests may help determine an excess of anticoagulant activity.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

In atrial fibrillation patients treated with 150 mg twice daily an aPTT of greater than 2,0 to 3,0-fold of normal range at trough was associated with an increased risk of bleeding.

Renal impairment:

Renal function should be assessed by calculating the creatinine clearance (CrCI) prior to initiation

of treatment with DABIGATRAN DRL to exclude patients for treatment with severe renal impairment (i.e., CrCl < 30 mL/min).

Patients who develop acute renal failure should discontinue DABIGATRAN DRL.

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 DABIGATRAN DRL is not recommended in this population. Hepatic impairment or liver disease expected to have any impact on survival is contraindicated (see section 4.3).

Surgery and interventions:

Patients on DABIGATRAN DRL who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of DABIGATRAN DRL (see also section 5.2).

Patients can stay on DABIGATRAN DRL while being cardioverted. DABIGATRAN DRL treatment (150 mg twice daily) does not need to be interrupted in patients undergoing catheter ablation for atrial fibrillation (see section 4.2).

In case of emergency surgery or urgent procedures when rapid reversal of the anticoagulation effect is required the specific reversal agent idarucizumab to DABIGATRAN DRL is available.

Reversing DABIGATRAN DRL therapy exposes patients to the thrombotic risk of their underlying disease.

DABIGATRAN DRL treatment can be re-initiated 24 hours after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved.

Pre-operative phase:

Due to an increased risk of bleeding DABIGATRAN DRL may be stopped temporarily in advance of invasive or surgical procedures.

Emergency surgery or urgent procedure:

The specific reversal agent idarucizumab of DABIGATRAN DRL is available for the rapid reversal of the anticoagulation effect (see Surgery and Interventions).

Acute surgery/intervention:

DABIGATRAN DRL should be temporarily discontinued. An acute surgery/intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed there may be an increase in the risk of bleeding. Neuraxial blocks are not recommended for within 24 hours after discontinuation of DABIGATRAN DRL Refer to Haemorrhagic risk above for information regarding correlation between plasma dabigatran concentration and degree of anticoagulant effect.

Elective surgery/intervention/spinal anaesthesia/epidural anaesthesia/lumbar puncture:

If possible, DABIGATRAN DRL should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding, or in major surgery where complete haemostasis may be required, consider stopping DABIGATRAN DRL 2 to 4 days before surgery. Clearance of DABIGATRAN DRL in patients with renal insufficiency may take longer. This should be considered in advance of any procedures (see Pharmacokinetic properties and the table summarising discontinuation rules under section 4.2).

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 1

hour should elapse before the administration of the first dose of DABIGATRAN DRL. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

DABIGATRAN DRL is contra-indicated in patients with severe renal dysfunction (CrCl < 30 ml/min) but, should this occur, then DABIGATRAN DRL should be stopped at least 5 days before major surgery.

If an acute intervention is required, DABIGATRAN DRL 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 there may be an increase in the risk of bleeding. This risk of bleeding should be weighed together with the urgency of intervention.

Post-procedural period:

Resume treatment after complete haemostasis is achieved***.***

Amiodarone:

DABIGATRAN DRL exposure in healthy subjects was increased by 60 % in the presence of amiodarone.

The concomitant use of DABIGATRAN DRL with the following treatments has not been studied and may increase the risk of bleeding:

unfractionated heparins (except at doses necessary to maintain patency of a central venous or arterial catheter) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic medicines, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, Vitamin K antagonists, and the P-gp inhibitors itraconazole, tacrolimus, ciclosporin, ritonavir, tipranavir, nelfinavir and saquinavir.

The concomitant use of DABIGATRAN DRL with the fixed-dose combination of the P-gp inhibitors

glecaprevir/pibrentasevir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.

The concomitant use of dronedarone increases exposure of DABIGATRAN DRL and is not recommended. See section 4.5.

Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake Inhibitors (SNRIs).

Use of fibrinolytic medicines for the treatment of acute ischaemic stroke:

The use of fibrinolytic medicines for the treatment of acute ischaemic stroke may be considered if the patient presents with a thrombi time (TT), or ecarin clotting time (ECT), or activated partial thromboplastin time (aPTT) not exceeding the upper limit of normal (ULN) according to the local reference range.

In situations where there is an increased haemorrhagic risk (e.g**.,** recent biopsy or major trauma, bacterial endocarditis) close observation (looking for signs of bleeding or anaemia) fs generally required.

If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool, or testing for a drop in haemoglobin Is suggested.

Prevention of venous thromboembolic events in patients who have undergone hip and knee replacement surgery:

NSAIDs given for short-term peri-operative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction

with DABIGATRAN DRL.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

Co-administration of anti-platelet (including aspirin, clopidogrel and ticagrelor) and NSAID therapies increase the risk of bleeding.

Specifically, with concomitant Intake of antiplatelets or strong P-gp Inhibitors in patients aged ≥

75 years, the risk of major bleeding, including gastrointestinal bleeding, increases. If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool, or testing for a drop in haemoglobin is suggested.

Interaction with P-gp inducers:

The concomitant use of DABIGATRAN DRL with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John's Wort (*Hypericum perforatum)* or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution (see section 4.5).

Patients with antiphospholipid syndrome:

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

Patients on a controlled sodium diet:

Each DABIGATRAN DRL 75/110/150 capsule contains 0,24/0,35/0,48 mg of sodium respectively. This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of interaction

The concomitant use of DABIGATRAN DRL with treatments that act on haemostasis or coagulation including Vitamin K antagonists and anti-platelet medicines can markedly increase the risk of bleeding (see sections 4.3 and 4.4).

DABIGATRAN DRL is not metabolised by the cytochrome P450 system and *in vitro* interaction studies did not show any inhibition or induction of the principal isoenzymes of cytochrome P450.Therefore related interactions are not expected with DABIGATRAN DRL. This has been

confirmed by in vivo studies with healthy volunteers, who did not show any interaction between this treatment and the following medicines: atorvastatin (CYP3A4), digoxin (P-gp transporter interaction) and diclofenac (CYP2C9).

Atorvastatin:

When DABIGATRAN DRL was co-administered with atorvastatin, a CYP3A4 substrate, exposure of atorvastatin, atorvastatin metabolites and of DABIGATRAN DRL were unchanged indicating a lack of interaction.

Diclofenac:

When DABIGATRAN DRL was co-administered with diclofenac, a CYP2C9 substrate, pharmacokinetic properties of both medicines remained unchanged indicating a lack of interaction between DABIGATRAN DRL and diclofenac.

P-gp Inhibitor/inducer interactions:

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

P-glycoprotein inhibitors:

Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, systemic ketoconazole, dronedarone, ticagrelor and clarithromycin) is expected to result in increased DABIGATRAN DRL plasma concentrations (see section 4.2).

Concomitant administration of systemic ketoconazole is contra-indicated.

Amiodarone:

DABIGATRAN DRL exposure in healthy subjects was increased by 1,6-fold (+ 60 %) in the presence of amiodarone.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

DABIGATRAN DRL concentrations were increased by no more than 14 % and no increased risk of bleeding was observed.

Dronedarone:

When DABIGATRAN DRL and dronedarone were given at the same time total DABIGATRAN DRL $AUC_{0-\infty}$ 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 twice dally, 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 DRL were not affected by dronedarone. When single and multiple doses of dronedarone were given 2 hours after DABIGATRAN DRL, the decreases in dabigatran $AUC_{0-\infty}$ were 1,3-fold and 1,6-fold, respectively (see section 4.4).

Verapamil:

When DABIGATRAN DRL (150 mg) was co-administered with oral verapamil, the C_{max} and AUC of dabigatran were increased but the magnitude of this change differs, depending on timing of administration and formulation of verapamil.

The greatest elevation of DABIGATRAN DRL exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to DABIGATRAN DRL 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 (increase of C_{max} by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increase of C_{max} by about 60 % and AUC by about 50 %). This can be explained by the induction of P-gp in the gut by chronic verapamil treatment.

There was no meaningful interaction observed when verapamil was given 2 hours after DABIGATRAN DRL (increase of C_{max} by about 10 % and AUC by about 20 %). This is explained by completed dabigatran absorption after 2 hours (see section 4.2).

No data are available for the parenteral application of verapamil; based on the mechanism of the

interaction, no meaningful interaction is expected.

Quinidine:

Quinidine was given as a 200 mg dose every 2nd hour up to a total dose of 1 000 mg. DABIGATRAN DRL was given twice dally. over 3 consecutive days, on the 3rd day either with or without quinidine. DABIGATRAN DRL $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased on average by 1,5-fold (+ 53 % and 56 %), respectively, with concomitant quinidine.

Clarithromycin:

When clarithromycin 500 mg twice daily was administered together with DABIGATRAN DRL no clinically relevant pharmacokinetic (PK)-interaction was observed (increase of C_{max} by about 15 % and AUC by about 19 %).

Ketoconazole:

Systemic ketoconazole increased total DABIGATRAN DRL $AUC_{0-\infty}$ and C_{max} values by about 2,4-fold (+ 138 % and 135 %, respectively), after a single dose of 400 mg, and 2,5-fold (+ 153 % and 149 %, respectively), after multiple dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole (see section 4.3).

Ticagrelor:

When a single dose of 75 mg DABIGATRAN DRL was co-administered 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 twice daily the increase of dabigatran exposure after a single dose is reduced to 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 DRL (in steady state) increased the dabigatran AUC τ,ss and by Cmax,ss by 1,49 fold and 1,65 fold (+ 49 % and 65 %), respectively, compared with DABIGATRAN DRL given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg DABIGATRAN DRL (in steady state), the increase of dabigatran AUC τ,ss and Cmax,ss was reduced to 1,27 fold and 1,23 fold

(+ 27 % and 23 %), respectively, compared with DABIGATRAN DRL given alone. Concomitant administration of 90 mg ticagrelor twice daily (maintenance dose) with 110 mg DABIGATRAN DRL increased the adjusted dabigatran AUC τ,ss and Cmax,ss 1,26 fold and 1,29 fold, respectively, compared with DABIGATRAN DRL given alone.

P-glycoprotein substrate:

Digoxin: When DABIGATRAN DRL was co-administered with digoxin, a P-gp substrate, no changes in digoxin and no clinically relevant changes in DABIGATRAN DRL exposure have been observed.

Neither dabigatran nor the pro-drug dabigatran etexilate is a clinically relevant P-gp inhibitor.

P-glycoprotein inducers:

Rifampicin: Pre-dosing of the probe inducer rifampicin at a dose of 600 mg once daily for 7 days decreased total DABIGATRAN DRL peak and total exposure by 65,5 and 67 %, respectively. The inducing effect was diminished resulting in DABIGATRAN DRL exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days.

The concomitant use with P-gp inducers (e.g., rifampicin) reduces exposure to DABIGATRAN DRL and should be avoided (see section 4.4).

Platelet-inhibitors:

Acetylsalicylic add (ASA):

The effect of concomitant administration of dabigatran and acetylsalicylic acid (ASA) on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomised ASA co-administration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran twice daily may increase the risk for any bleeding from 12 % to 18 % and 24 % with 81 mg and 325 mg ASA, respectively.

From the data gathered in the phase III study, it was observed that ASA or clopidogrel co-medication with dabigatran at dosages of 110 or 150 mg twice daily may increase the risk of

major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was, however, also observed for warfarin.

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

NSAIDs increased the risk of bleeding.

Clopidogrel:

In a phase I study in young healthy male volunteers, the concomitant administration of DABIGATRAN DRL and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. However, with a loading dose of 300 or 600 mg clopidogrel, DABIGATRAN DRL $AUC_{T, ss}$ and $C_{max, ss}$ were increased by about 1,3 to 1,4-fold (+ 30 to 40 %). (See above subsection on ASA). (See section 4.3).

Selective serotonin re-uptake inhibitors (SSRIs):

SSRIs increased the risk of bleeding (see section 4.4).

Gastric pH-elevating medicines:

The changes in DABIGATRAN DRL exposure determined by population pharmacokinetic analysis caused by proton pump inhibitors and antacids were not considered clinically relevant because the magnitude of the effects were minor (fractional decrease in bioavailability not significant for antacids and 14,6 % for PPIs).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should avoid pregnancy during treatment with DABIGATRAN DRL.

Pregnancy

There is limited amount of data from the use of DABIGATRAN DRL in pregnant women.

Studies in animals have shown reproductive toxicity.

The potential risk for humans is unknown.

DABIGATRAN DRL should not be used during pregnancy unless clearly necessary.

Lactation

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

Breast-feeding should be discontinued during treatment with DABIGATRAN DRL.

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 others (representing a 5- to 10-fold higher plasma exposure level to patients), a decrease in foetal body weight and embryofoetal viability along with an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients).

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

Summary of the safety profile

Bleeding:

Bleeding is the most relevant side effect of dabigatran.

Depending on the indication, bleeding of any type or severity occurred in approximately 14 % of patients treated short-term for elective hip or knee replacement surgery, in long-term treatment in

nearly 16,5 % of patients with atrial fibrillation treated for the reduction of risk of stroke and systemic embolism and in 14,4 % of patients with acute DVT and/or PE. In the recurrent DVT/PE trials 19,4 % and 10,5 % of patients experienced any bleeding in the active controlled and placebo controlled studies, respectively.

Major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Side effects in general:

Adverse drug reactions are classified by System Organ Class and Medical Dictionary for Regulatory Activities (MedDRA) preferred terms reported from any treatment group per population of all controlled studies are shown in the listings below. A second list with indication-specific side effects is also provided.

Side effects identified independent from indication, i.e., including:

- Risk reduction of thromboembolic stroke and systemic embolism in patients with atrial fibrillation (SPAF) with dabigatran dosages of 110 or 150 mg taken twice daily.
- Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) (aVTEt) with a dabigatran dosage of 150 mg taken twice daily.
- Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) (sVTEp) with a dabigatran dosage of 150 mg taken twice daily.
- Primary VTE prevention (pVTEp) studies after hip and knee replacement surgery with dabigatran dosages of 220 or 150 mg taken once daily.

MedDRA preferred term:	**Frequency in SPAF:**	**Frequency in pVTEp:**	**Frequency in aVTEt:**	**Frequency in sVTEp:**
Blood and the lymphatic system disorders:				

Anaemia	Frequent	Less frequent	Less frequent	Less frequent
Thrombocytopenia	Less frequent	Less frequent	Less frequent	Less frequent
Neutropenia	Not known	Not known	Not known	Not known
Agranulocytosis	Not known	Not known	Not known	Not known
Immune system disorders:				
Hypersensitivity	Less frequent	Less frequent	Less frequent	Less frequent
Pruritis	Less frequent	Less frequent	Less frequent	Less frequent
Rash	Less frequent	Less frequent	Less frequent	Less frequent
Urticaria	Less frequent	Less frequent	Less frequent	Less frequent
Bronchospasm	Not known	Not known	Not known	Not known
Anaphylactic reaction	Not known	Not known	Not known	Not known
Angioedema	Less frequent	Less frequent	Less frequent	Less frequent
Nervous system disorders:				
Intracranial haemorrhage	Less frequent	Less frequent	Less frequent	Less frequent
Vascular disorders:				
Haematoma	Less frequent	Less frequent	Less frequent	Less frequent
Haemorrhage	Less frequent	Less frequent	Less frequent	Less frequent
Respiratory, thoracic and mediastinal disorders:				
Epistaxis	Frequent	Less frequent	Frequent	Frequent
Haemoptysis	Less frequent	Less frequent	Less frequent	Less frequent
Gastrointestinal disorders:				
Gastrointestinal haemorrhage	Frequent	Less frequent	Less frequent	Less frequent
Abdominal pain	Frequent	Less frequent	Less frequent	Less frequent

Diarrhoea	Frequent	Less frequent	Less frequent	Less frequent
Dyspepsia	Frequent	Less frequent	Frequent	Frequent
Dysphagia	Less frequent	Less frequent	Less frequent	Less frequent
Gastrointestinal ulcer, including oesophageal ulcer	Less frequent	Less frequent	Less frequent	Less frequent
Gastro-oesophagitis	Less frequent	Less frequent	Less frequent	Less frequent
Gastro-oesophageal reflux disease	Less frequent	Less frequent	Less frequent	Less frequent
Nausea	Frequent	Less frequent	Less frequent	Less frequent
Vomiting	Less frequent	Less frequent	Less frequent	Less frequent
Hepatobiliary disorders:				
Abnormal hepatic function	Less frequent	Frequent	Less frequent	Less frequent
Skin and subcutaneous tissue disorders:				
Skin haemorrhage	Frequent	Less frequent	Frequent	Frequent
Alopecia	Not known	Not known	Not known	Not known
Musculoskeletal, connective tissue and bone disorders:				
Haemarthrosis	Less frequent	Less frequent	Less frequent	Less frequent
Renal and urinary disorders:				
Urogenital haemorrhage	Frequent	Less frequent	Frequent	Frequent
Haematuria	Frequent	Less frequent	Frequent	Frequent
General disorders and administration site conditions:				

Injection site haemorrhage	Less frequent	Less frequent	Less frequent	Less frequent
Catheter site haemorrhage	Less frequent	Less frequent	Less frequent	Less frequent
Injury, poisoning and procedural complications:				
Traumatic haemorrhage	Less frequent	Less frequent	Less frequent	Less frequent
Incision site haemorrhage	Less frequent	Less frequent	Less frequent	Less frequent

Other side effects identified specifically from the studies in the indication primary VTE prevention after hip and knee replacement surgery:

Vascular disorders:

Less frequent: wound haemorrhage

General disorders and administration site conditions:

Less frequent: bloody discharge

Injury, poisoning and procedural complications:

Less frequent: post procedural haematoma, post procedural haemorrhage, post procedural discharge, wound secretion, post operative anaemia

Surgical and medical procedures:

Less frequent: wound drainage, post procedural drainage

Description of selected adverse reactions

Bleeding reactions

Due to the pharmacological mode of action, the use of dabigatran may be associated with an increased risk of occult or overt bleeding from any tissue or organ. The signs, symptoms, and

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

Known bleeding complications such as compartment syndrome and acute renal failure due to hypoperfusion have been reported for dabigatran. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Agranulocytosis and neutropenia

Agranulocytosis and neutropenia have been reported very rarely during post approval use of dabigatran. Because adverse reactions are reported in the post-marketing surveillance setting from a population of uncertain size, it is not possible to reliably determine their frequency. The reporting rate was estimated as 7 events per 1 million patient years for agranulocytosis and as 5 events per 1 million patient years for neutropenia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdose following administration of DABIGATRAN DRL may lead to haemorrhagic complications due to its pharmacodynamic properties.

A specific reversal agent antagonising the pharmacodynamic effect of DABIGATRAN DRL is available, namely idarucizumab (see section, 4.4, Haemorrhagic risk; Surgery and interventions, Pre-operative phase). In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since DABIGATRAN DRL is excreted predominantly by the renal route adequate diuresis must be maintained.

Depending on the clinical situation appropriate standard treatment, e.g., surgical haemostasis as indicated and blood volume replacement, should be undertaken. In addition, consideration may be given to the use of fresh whole blood or fresh frozen plasma.

Coagulation factor concentration (activated or non-activated) or recombinant Factor VIIa may be considered. There is some experimental evidence to support the role of these medicines in reversing the anticoagulant effect of dabigatran, but their usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet medicines have been used. All symptomatic treatment has to be given according to the doctor's judgement.

As protein binding is low, DABIGATRAN DRL is dialysable, however there is limited clinical experience in using dialysis in this setting (see section 5.2, Pharmacokinetic properties, Special populations, Renal insufficiency).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 8.2 Anticoagulants

Pharmacotherapeutic group: Antithrombotic agents, direct thrombin inhibitors, ATC code: B01AE07.

Dabigatran etexilate is a small molecule pro-drug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and then converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a 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.
In vivo and *ex vivo* animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran etexilate after oral administration in various animal models of thrombosis.
There is a correlation between plasma dabigatran concentration and degree of anticoagulant effect. Prothrombin time (PT, expressed as International Normalised Ratio (INR)) is too insensitive to reliably detect anticoagulant activity of dabigatran and is therefore not recommended as a suitable tool for monitoring anticoagulant activity. Ecarin Clotting Time (ECT), Thrombin Time (TT) and diluted Thrombin Time (dTT) are sensitive assays that increase in direct proportion to dabigatran plasma concentration without any deviation from linearity at high plasma concentrations. However, ECT is not readily available in clinical practice. Activated Partial Thromboplastin Time (aPTT) increases in a non-linear manner to dabigatran concentration and is less proportional at higher dabigatran concentrations (see section 4.4, Haemorrhagic risk). ECT, TT and aPTT are not standardised or validated with dabigatran for commercial use. In cases of emergency, TT and aPTT are the most accessible qualitative methods for determining the

presence or absence of the anticoagulant effect of dabigatran.

Interpretation of coagulation assay results should consider time of DABIGATRAN DRL administration relative to time of blood sampling (see section 5.2, Pharmacokinetic properties).

In patients undergoing elective hip replacement surgery, greater test variability with aPTT and ECT was observed. The mechanisms for this variability immediately after surgery are unclear and aPTT and ECT levels measured in the first 2 to 3 days following surgery should be interpreted with caution.

Whilst DABIGATRAN DRL does not require routine laboratory anticoagulant monitoring, careful clinical monitoring including renal function testing is required in certain clinical situations (see sections 4.4, Haemorrhagic risk and section 4.2).

5.2 Pharmacokinetic properties

After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with peak concentration (C_{max}) attained within 0,5 and 2,0 hours post administration. C_{max} and the area under the plasma concentration-time curve (AUC) were dose proportional. After C_{max} plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of approximately 11 hours in healthy elderly subjects. After multiple doses a terminal half-life of about 12 to 14 hours was observed. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown in the table below.

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	1314 (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)

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate was approximately 6,5 %.

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

The oral bioavailability may be increased by 1,4 fold (+ 37 %) compared to the reference capsule formulation when the pellets are taken without the capsule shell. Hence, the integrity of the capsules should always be preserved in clinical use to avoid unintentionally Increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and take the pellets alone (e.g., sprinkled over food or into beverages) (see section 4.2).

Post-operative absorption of dabigatran etexilate, 1 to 3 hours following surgery Is relatively slow compared with that in healthy volunteers. Peak plasma concentrations are reached at 6 hours following administration, or at 7 to 9 hours following surgery. It is noted, however, that contributing factors such as anaesthesia, gastrointestinal paresis and surgical effects will mean that a proportion of patients will exhibit absorption delay independent of the oral medicine formulation. Slow and delayed absorption is usually only present on the day of surgery. On subsequent post-surgery days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after medicine administration.

Metabolism and excretion of dabigatran were studied following a single intravenous dose of radiolabelled 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 to 94 % of the administered dose by 168 hours post-dose.

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the pro-drug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction.

Dabigatran Is subject to conjugation forming pharmacologically active acylglucuronides. Four positional Isomers, 1-0, 2-0, 3-0, 4-0-acylglucuronlde 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.

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

Special populations:

Renal insufficiency:

The exposure (AUC) of dabigatran after the oral administration of dabigatran etexilate is approximately 2,7-fold higher in volunteers with moderate renal insufficiency (CrCI between 30 to 50 mL/min) than in those without renal insufficiency.

.

In a small number of volunteers with severe renal insufficiency (CrCI 10 to 30 ml/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see sections 4.2 and 4.3).

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

To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation:

Almost half (45,8 %) of the patients studied had a CrCl > 50 -< 80 mL/min. Patients with moderate renal impairment (CrCl between
30 to 50 ml/min) had on average 2,29-fold and 1,81-fold higher pre- and post- dose dabigatran plasma concentrations, respectively,
when compared with patients without renal impairment (CrCl ≥ 80 mL/min).

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

21,7 % of patients had mild renal impairment (CrCl >50-< 80 mL/min) and
4,5 % of patients had moderate renal impairment (CrCl between 30 to 50 mL/min). Patients with mild and moderate renal impairment had on average 1,7-fold and 3,4-fold higher steady state dabigatran trough concentrations, respectively, compared with patients with CrCl > 80 mL/min.

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

22,9 % and 22,5 % of the patients studied had a CrCl > 50 -< 80 mL/min, and 4,1 % and 4,8 % had a CrCl between 30 to 50 mL/min.

Hepatic insufficiency:

No change in dabigatran exposure was seen in 12 volunteers with moderate hepatic insufficiency (Child-Pugh B) compared to 12 controls in a phase I study. In clinical trials, patients with Child-Pugh classification B and C, or liver disease, expected to have any impact on survival, including hepatitis A, B or C, or with elevated enzymes ≥ 2 Upper Limit of Normal (ULN) were excluded.

Elderly patients:

Specific pharmacokinetic studies with elderly subjects showed an increase of 1,4 to 1,6-fold (+ 40 to 60 %) in the AUC and of more than 1,25-fold (+ 25 %) in C_{max} compared to young subjects. The $AUC_{T, ss}$ and $C_{max, ss}$ in male and female elderly subjects (> 65 years) were approximately.1,9-fold and 1,6-fold higher for elderly females compared to young females and 2,2 and 2,0-fold higher for elderly males than in male subjects of 18 to 40 years of age The observed

increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance.

The effect by age on exposure to dabigatran was confirmed in the reduction of risk of stroke in atrial fibrillation study with an about 1,3-fold (+ 31 %) higher trough concentration for subjects ≥ 75 years and by about 22 % lower trough level for subjects < 65 years compared to subjects of age between 65 and 75 years.

Body weight:

The dabigatran trough concentrations were about 20 % lower in patients with a BW > 100 kg compared with 50 to 100 kg. The majority (80,8 %) of the subjects were in the ≥ 50 kg and < 100 kg category with no clear difference detected.

Limited data in patients ≤ 50 kg are available.

Gender:

Dabigatran exposure in the primary VTE prevention studies was about 1,4 to 1,5- fold (+ 40 % to 50 %) higher in female patients.

In atrial fibrillation patients, females had on average 1,3-fold (+ 30 %) higher trough and post-dose concentrations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Croscarmellose sodium

Hydroxypropyl cellulose

Hypromellose

Magnesium stearate

Talc

Tartaric acid

Capsule shell

Hypromellose

Titanium dioxide

Black printing ink

Black Iron Oxide

Butyl Alcohol

Dehydrated Alcohol

Isopropyl Alcohol

Potassium Hydroxide

Propylene Glycol

Purified Water

Shellac

Strong Ammonia Solution

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original packaging in order to protect from moisture.

Keep out of reach of children.

6.5 Nature and contents of container

DABIGATRAN 75 and DABIGATRAN 110 DRL capsules: cartons containing 30 or 60 capsules, packed in aluminium blister strips of 10 capsules per strip.

DABIGATRAN 150 DRL capsules: cartons containing 30 or 60 capsules, packed in aluminium blister strips of 10 capsules per strip.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBERS

DABIGATRAN 75 DRL: 56/8.2/0695

DABIGATRAN 110 DRL: 56/8.2/0696

DABIGATRAN 150 DRL: 56/8.2/0697

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 February 2024

10. DATE OF REVISION OF TEXT

11 June 2024