PROFESSIONAL INFORMATION

DABIKLOT RANGE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DABIKLOT 75 mg hard capsules

DABIKLOT 110 mg hard capsules

DABIKLOT 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DABIKLOT 75 mg: Each capsule contains 75 mg dabigatran etexilate (as mesilate salt).

DABIKLOT 110 mg: Each capsule contains 110 mg dabigatran etexilate (as mesilate salt).

DABIKLOT 150 mg: Each capsule contains 150 mg dabigatran etexilate (as mesilate salt).

DABIKLOT capsules are sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard capsules.

DABIKLOT 75 mg: Size “2” capsules with a white opaque cap and body, containing white to light yellow coloured pellets. The white opaque cap is imprinted "MD" and the white opaque body imprinted "75", both with black ink.

DABIKLOT 110 mg: Size “1” capsules with a white opaque cap and body, containing white to light yellow coloured pellets. The white opaque cap is imprinted "MD" and the white opaque body imprinted "110", both with black ink.

DABIKLOT 150 mg: Size “0” capsules with a white opaque cap and body, containing white to light yellow coloured pellets. The white opaque cap is imprinted "MD" and the white opaque body imprinted "150", both with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Reduction of the risk of a stroke and systemic embolism in patients with atrial fibrillation.

Treatment of acute and prevention of 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 DABIKLOT is 220 mg once daily taken as 2 capsules of 110 mg. There is an increased risk of bleeding in patients with moderate renal impairment. In these patients, the recommended dose of DABIKLOT is 150 mg once daily.

VTE prevention following knee replacement surgery:

Treatment with DABIKLOT should be initiated orally within 1 - 4 hours of completed surgery with a single capsule (110 mg), 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, it should be initiated with 2 capsules once daily.

There is an increased risk of bleeding in patients with moderate renal impairment. In these patients, DABIKLOT 75 mg capsules should be used instead of the 110 mg capsules.

VTE prevention following hip replacement surgery:

Treatment with DABIKLOT should be initiated orally within 1 - 4 hours of completed surgery, with a single capsule (110 mg), 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, treatment should be initiated with 2 capsules once daily.

There is an increased risk for bleeding in patients with moderate renal impairment. In these patients, DABIKLOT 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 DABIKLOT is 300 mg taken orally, as two 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 DABIKLOT 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 DABIKLOT is 300 mg taken orally, as 150 mg capsules twice daily. Depending on the individual patient's risk factors, therapy could be continued life-long.

Special populations

Renal impairment:

Patients with severe renal impairment (i.e. CrCl < 30 mL/min) should be excluded from treatment. Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment.

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

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) renal function should be assessed during treatment.

DABIKLOT can by 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:

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

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

In patients with moderate renal impairment (CrCl 30 - 50 mL/min), no dose adjustment is necessary however, renal function should be assessed at least once a year. Patients should be treated with a daily dose of 300 mg DABIKLOT, 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 DABIKLOT, taken orally as 150 mg capsules twice daily.

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

Renal function should be assessed at least once a year in patients with moderate renal impairment (CrCl 30 - 50 mL/min).

In patients with renal function over CrCl 30 mL/min, no dose adjustment is necessary. A daily dose of 300 mg DABIKLOT, taken orally as 150 mg capsules twice daily is recommended.

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 level (CrCl) prior to initiation of treatment with DABIKLOT 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 DABIKLOT 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 dosage in Renal impairment above).

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 DABIKLOT taken once daily as 2 capsules of 110 mg.

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

Patients aged 80 years or above should be treated with a daily dose of 220 mg DABIKLOT, 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 DABIKLOT, taken orally as 150 mg capsules twice daily.

Weight:

No dose adjustment is necessary.

Concomitant use of DABIKLOT 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:

DABIKLOT dosing should be reduced to 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive 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 DABIKLOT. Simultaneous initiation of treatment with DABIKLOT and verapamil should also be avoided.

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 DABIKLOT, 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 DABIKLOT, 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: age (≥ 75 years), moderate renal impairment (CrCl 30 - 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 DABIKLOT 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, DABIKLOT should only be given in these patients if the expected benefit outweighs bleeding risks.

Switching from DABIKLOT 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 DABIKLOT to a parenteral anticoagulant.

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

Before switching to a parenteral anticoagulant, wait 12 hours after the last dose of DABIKLOT.

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

Before switching to a parenteral anticoagulant, wait 12 hours after the last dose of DABIKLOT.

Switching from parenteral anticoagulant treatment to DABIKLOT:

DABIKLOT 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 unfractionated heparin (UFH)).

Switching from warfarin to DABIKLOT:

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

The warfarin should be stopped. As soon as the INR is < 2,0, DABIKLOT can be administered.

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

The warfarin should be stopped. As soon as the INR is < 2,0, DABIKLOT can be administered.

Switching from DABIKLOT 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 DABIKLOT
- CrCl ≥ 30 - < 50 mL/min, start warfarin 2 days before discontinuing DABIKLOT

Cardioversion:

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

While being cardioverted, patients can remain on DABIKLOT.

Paediatric population

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

Catheter ablation for atrial fibrillation

Catheter ablation can be conducted in non-valvular atrial fibrillation patients on 150 mg twice daily, DABIKLOT treatment does not need to be interrupted. There are no clinical data on contribution of 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 PCI with stenting can be treated with DABIKLOT in combination with antiplatelets after haemostasis is achieved.

Method of administration

DABIKLOT can be taken with or without food. DABIKLOT should be taken with a glass of water, to facilitate delivery to the stomach. Do not open the capsule.

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 DABIKLOT 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 DABIKLOT 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 DABIKLOT 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 DABIKLOT 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)

*for more details see the table in sections 4.4 and 5.2

4.3 Contraindications

- hypersensitivity to dabigatran etexilate or to any of the ingredients of DABIKLOT
- patients with severe renal impairment (CrCl < 30 mL/min) (see section 4.2)
- 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) or liver disease expected to have any impact on survival
- 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, ciclosporin, itraconazole, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir (see section 4.5)
- concomitant treatment with any of the following: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, 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 DABIKLOT and vitamin K antagonists (e.g. warfarin) can be administered together, but only for a few days during switching from DABIKLOT to vitamin K antagonist treatment
- in patients with suspected infective endocarditis
- in patients with prosthetic heart valve replacement requiring anticoagulant treatment.

4.4 Special warnings and precautions for use

Haemorrhagic risk:

DABIKLOT should be used with caution in a condition with an increased risk of bleeding or with concomitant use of medicines affecting haemostasis by inhibition of platelet aggregation.
Bleeding can occur at any site during therapy with DABIKLOT.

An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.
For situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran, as in DABIKLOT, is required, the specific reversal agent (Praxbind, idarucizumab) is available (see section 4.9).

In clinical trials, dabigatran, as in DABIKLOT, was associated with higher rates of major gastrointestinal (GI) bleeding. An increased risk was seen in the elderly (≥ 75 years) for the 150 mg twice daily dose regimen. Further risk factors comprise co-medication with platelet aggregation inhibitors such as clopidogrel and acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory medicines (NSAIDs), as well as the presence of esophagitis, gastritis or gastroesophageal reflux.

Caution is advised as tests to monitor coagulation are not available.
There is no correlation between plasma dabigatran concentration and degree of anticoagulant effect. However, this can only be partially measured by a combination of activated partial thromboplastin time 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 DABIKLOT.

DABIKLOT treatment cannot be therapeutically monitored by coagulation tests. The INR test is unreliable in patients on DABIKLOT 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

DABIKLOT activity. DABIKLOT related anticoagulation can be assessed by ECT or TT. If ECT or TT is not available, the aPTT test provides an approximation of DABIKLOT anticoagulant activity. However, in patients who are bleeding, aPTT tests may help determine an excess of anticoagulant activity.

Precautions and management of the haemorrhagic risk:

For the management of bleeding complications, see section 4.9.

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 (CrCl) prior to initiation of treatment with DABIKLOT to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30 mL/min).

Patients who develop acute renal failure should discontinue DABIKLOT.

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 1 hour should elapse before the administration of the first dose of DABIKLOT (see section 4.3). These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

Surgery and interventions:

Patients on DABIKLOT therapy who undergo surgery or invasive procedures are at increased risk for bleeding. As a result, surgical interventions may require the temporary discontinuation of DABIKLOT (see section 5.2*).*

Pre-operative phase:

DABIKLOT may be stopped temporarily in advance of invasive or surgical procedures due to an increased risk of bleeding.

If possible, DABIKLOT 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, stopping DABIKLOT 2 - 4 days before surgery should be considered. Clearance of DABIKLOT in patients with renal insufficiency may take longer. This should be considered in advance of any procedures (see sections 4.2 - table summarising discontinuation rules – and 5.2).

DABIKLOT is contraindicated in patients with severe renal dysfunction (CrCl < 30 mL/min) (see section 4.3) but, should this occur, DABIKLOT treatment should be stopped at least 5 days before any major surgery.

If an acute intervention is required, DABIKLOT 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.

For cardioversion see section 4.2.

Post-procedural period:

Resume/start treatment as soon as possible provided the clinical situation allows and after complete haemostasis is achieved.

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 (see sections 4.4 and 5.1).

Close clinical surveillance

Close observation for signs of bleeding or anaemia is recommended throughout the treatment period, especially if risk factors are combined.

Amiodarone: DABIKLOT exposure in healthy subjects was increased by 60 % in the presence of amiodarone.

The concomitant use of DABIKLOT 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 agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, vitamin K antagonists, and the P-gp inhibitors itraconazole, tacrolimus, ciclosporin, verapamil, amiodarone, quinidine, clarithromycin, ritonavir, tipranavir, nelfinavir and saquinavir.

The concomitant use of dronedarone increases exposure of DABIKLOT and is not recommended (see section 4.5).

A major bleeding risk may be significantly increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs).

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

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

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 thrombin 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) is 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:

DABIKLOT, when given concomitantly with NSAIDs for short-term peri-operative analgesia, has been shown not to be associated with increased bleeding risk.

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 DABIKLOT with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John's Wart (*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 DABIKLOT 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.

Myocardial Infarction (MI):

In the phase III study RE-LY (SPAF) the overall rate of MI was 0,82; 0,81 and 0,64 % / year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29 % and 27 % compared to warfarin. Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left ventricular ejection fraction < 40 %, and patients with moderate renal dysfunction. Furthermore, a higher risk of MI was seen in patients concomitantly taking ASA plus clopidogrel or clopidogrel alone.

In the three active-controlled DVT/PE phase III studies, a higher rate of MI was reported in patients who received dabigatran etexilate than in those who received warfarin: 0,4 % vs. 0,2 % in the short-term RECOVER and RE-COVER II studies; and 0,8 % vs. 0,1 % in the long-term RE-MEDY trial. The increase was statistically significant in this study (p=0,022).

In the RE-SONATE study, which compared dabigatran etexilate to placebo, the rate of MI was 0,1 % for patients who received dabigatran etexilate and 0,2 % for patients who received placebo

Active Cancer Patients (DVT/PE)

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

4.5 Interaction with other medicines and other forms of interaction

The concomitant use of DABIKLOT 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).

DABIKLOT is not metabolised by the cytochrome P450 system, *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 DABIKLOT. This has been confirmed by *in vivo* studies in healthy volunteers, who did not show any interaction between dabigatran etexilate and either of the following: atorvastatin (CYP3A4), digoxin (P-gp transporter interaction) and diclofenac (CYP2C9).

Atorvastatin: When co-administered with atorvastatin (a CYP3A4 substrate), exposure of atorvastatin, atorvastatin metabolites and those of DABIKLOT were unchanged, indicating a lack of interaction.

Diclofenac: When co-administered with diclofenac (a CYP2C9 substrate), pharmacokinetic properties of both medicines remained unchanged, indicating a lack of interaction between DABIKLOT 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 DABIKLOT plasma concentrations (see section 4.2).

Concomitant use contraindicated (see section 4.3):

Ketoconazole:

Systemic ketoconazole increased total dabigatran (as in DABIKLOT) $AUC_{0-\infty}$ 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.

Dronedarone:

When dabigatran (as in DABIKLOT) 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 twice daily, 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 hours after dabigatran, the decreases in dabigatran $AUC_{0-\infty}$ were 1,3-fold and 1,6-fold, respectively (see section 4.4).

Itraconazole, ciclosporin:

Based on *in vitro* results a similar effect as with ketoconazole may be expected.

Glecaprevir /pibrentasvir:

The concomitant use of dabigatran etexilate (as in DABIKLOT) with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasvir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.

Concomitant use not recommended:

Tacrolimus

Tacrolimus has been found *in vitro* to have a similar level of inhibitory effect on P-gp as that seen with itraconazole and ciclosporin. Dabigatran etexilate has not been clinically studied together with

tacrolimus. However, limited clinical data with another P-gp substrate (everolimus) suggest that the inhibition of P-gp with tacrolimus is weaker than that observed with strong P-gp inhibitors.

Cautions to be exercised in case concomitant use (see sections 4.2 and 4.4):

Verapamil:

When dabigatran etexilate 150 mg (as in DABIKLOT) 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 exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to DABIKLOT intake (increase in 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 DABIKLOT (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.

Amiodarone:

DABIKLOT 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:

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

Quinidine:

Quinidine was given as a 200 mg dose every 2nd hour up to a total dose of 1 000 mg Dabigatran (as in DABIKLOT) was given twice daily over 3 consecutive days, on the 3rd day either with or without

quinidine. Dabigatran $AUC_{t,ss}$ 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 is administered together with DABIKLOT no clinically relevant pharmacokinetic (PK)-interaction is observed (increase of C_{max} by about 15 % and AUC by about 19 %).

Ticagrelor:

When a single dose of 75 mg dabigatran (as in DABIKLOT) 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 (in steady state) increased the dabigatran $AUC_{-t\ ss}$ and by $C_{max\ ss}$ by 1,49-fold and 1,65-fold (±49 % and 65 %) respectively compared with dabigatran given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran (in steady state) the increase of dabigatran $AUC_{-t\ ss}$ and $C_{max\ ss}$ was reduced to 1,27-fold and 1,23-fold (±27 % and 23 %) respectively compared with dabigatran given alone. Concomitant administration of 90 mg ticagrelor twice daily (maintenance dose) with 110 mg dabigatran increased the adjusted dabigatran $AUC_{-t\ ss}$ and $C_{max\ ss}$ 1,26-fold and 1,29-fold respectively compared with dabigatran given alone.

Posaconazole:

Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when DABIKLOT is co-administered with posaconazole.

P-GP INDUCERS:

Concomitant use should be avoided:

Rifampicin, St. John´s wort (*Hypericum perforatum*), carbamazepine, or phenytoin:

Concomitant administration is expected to result in decreased dabigatran concentrations.

Pre-dosing of the probe inducer rifampicin at a dose of 600 mg once daily for 7 days decreased total dabigatran peak and total exposure by

65,5 % and 67 %, respectively. The inducing effect was diminished resulting in dabigatran exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days. The concomitant use with P-gp inducers (e.g. rifampicin) reduces exposure to DABIKLOT and should be avoided (see section 4.4).

Protease inhibitors such as ritonavir

Concomitant use not recommended:

Ritonavir and its combinations with other protease inhibitors

These affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with DABIKLOT.

P-glycoprotein substrate

Digoxin:

When DABIKLOT was co-administered with digoxin, a P-gp substrate, no changes in digoxin and no clinically relevant changes in dabigatran exposure have been observed. Neither dabigatran nor the prod-drug dabigatran etexilate is a clinically relevant P-gp inhibitor.

PLATELET-INHIBITORS:

Acetylsalicylic acid (ASA):

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

In clinical studies, it was observed that ASA or clopidogrel co-medication with DABIKLOT 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 in warfarin.

NSAIDs:

NSAIDs given for short-term analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran etexilate and warfarin.

Clopidogrel:

In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran 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 $AUC_{t,ss}$ and $C_{max,ss}$ were increased by about 1,3- to 1,4-fold (+ 30 - 40 %). (See above subsection on ASA and section 4.3).

Low molecular weight heparins (LMWH):

The concomitant use of LMWHs, such as enoxaparin and dabigatran etexilate has not been specifically investigated. After switching from 3-day treatment of once daily 40 mg enoxaparin s.c., 24 hours after the last dose of enoxaparin the exposure to dabigatran was slightly lower than that after administration of dabigatran etexilate (single dose of 220 mg) alone. A higher anti-FXa/FIIa activity was observed after dabigatran etexilate administration with enoxaparin pre-treatment compared to that after treatment with dabigatran etexilate alone. This is considered to be due to the carry-over effect of enoxaparin treatment, and regarded as not clinically relevant. Other dabigatran related anti-coagulation tests were not changed significantly by the pre-treatment of enoxaparin.

Other interactions

Selective serotonin re-uptake inhibitors (SSRIs) or Selective Serotonin Norepinephrine Re-Uptake Inhibitors (SNRIs):

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

SUBSTANCES INFLUENCING GASTRIC pH

Pantoprazole

Pantoprazole and other proton-pump inhibitors (PPI) were co-administered with DABIKLOT in clinical trials, and concomitant PPI treatment did not appear to reduce the efficacy of DABIKLOT.

Ranitidine

Ranitidine administration together with DABIKLOT had no clinically relevant effect on the extent of absorption of dabigatran.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should avoid pregnancy during treatment with DABIKLOT.

Pregnancy

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

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

DABIKLOT should not be used during pregnancy.

Breastfeeding

There are no clinical data of the effect of dabigatran on infants during breastfeeding.

Breastfeeding should be discontinued during treatment with DABIKLOT.

Fertility

No human data available.

4.7 Effects on ability to drive and use machines:

DABIKLOT has no or negligible influence on the ability to drive and use machines. No studies of the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

a). Summary of the safety profile

Undesirable effects, 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 table below. A second table, with indication-specific undesirable effects, is also provided.

Bleeding

Bleeding is the most relevant side effect of DABIKLOT. 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 active 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.

Undesirable effects identified independent from indication, including:

- risk reduction of thromboembolic stroke and systemic embolism in patients with atrial fibrillation (SPAF) at dosages of 110 or 150 mg taken twice daily
- treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) (aVTEt) at dosage of 150 mg taken twice daily
- prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) (sVTEp) at dosage of 150 mg taken twice daily, and
- primary VTE prevention (pVTEp) studies after hip and knee replacement surgery at dosages of 220 or 150 mg taken once daily:

b). Tabulated summary of adverse reactions

System Organ Class & Side effect	**Frequency**			
	SPAF	**pVTEp**	**aVTEt**	**sVTEp**
Blood and lymphatic system disorders				
Anaemia	Frequent	Less frequent	Less frequent	Less frequent

Thrombocytopenia	Less frequent	Less frequent	Less frequent	Less frequent
Haemoglobin decreased	Less frequent	Frequent	Frequency unknown	Frequency unknown
Haematocrit decreased	Less frequent	Less frequent	Frequency unknown	Frequency unknown
Neutropenia	Frequency unknown	Frequency unknown	Frequency unknown	Frequency unknown
Agranulocytosis	Frequency unknown	Frequency unknown	Frequency unknown	Frequency unknown
Immune system disorders				
Hypersensitivity	Less frequent	Less frequent	Less frequent	Less frequent
Bronchospasm	Frequency unknown	Frequency unknown	Frequency unknown	Frequency unknown
Anaphylactic reaction	Frequency unknown	Frequency unknown	Frequency unknown	Frequency unknown
Angioedema	Frequency unknown	Frequency unknown	Frequency unknown	Frequency unknown
Nervous system disorders				
Intercranial 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

Wound haemorrhage	-	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	Frequent	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
Rectal haemorrhage	Frequent	Less frequent	Less frequent	Less frequent
Haemorrhoidal haemorrhage	Less frequent	Less frequent	Less frequent	Less frequent
Hepato-biliary disorders				
Abnormal hepatic function	Less frequent	Frequent	Less frequent	Less frequent
Liver function test abnormal	Less frequent	Frequent	Less frequent	Less frequent
Alanine aminotransferase increased	Less frequent	Less frequent	Less frequent	Less frequent
Aspartate aminotransferase increased	Less frequent	Less frequent	Less frequent	Less frequent
Hepatic enzyme increased	Less frequent	Less frequent	Less frequent	Less frequent
Hyperbilirubinaemia	Less frequent	Less frequent	Frequency unknown	Frequency unknown
Skin and subcutaneous tissue disorders				
Skin haemorrhage	Frequent	Less frequent	Frequent	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
Alopecia	Frequency unknown	Frequency unknown	Frequency unknown	Frequency unknown
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 administrative 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 and poisoning				
Traumatic haemorrhage	Less frequent	Less frequent	Less frequent	Less frequent
Anaemia postoperative	-	Less frequent	-	-
Surgical and medical procedures				
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:

System Organ Class	Frequency	Side effects
Vascular disorders	Less frequent	Wound haemorrhage
General disorders and administrative site conditions	Less frequent	Bloody discharge
Injury and poisoning	Less frequent	Post procedural haematoma, post procedural haemorrhage, post procedural discharge, wound secretion
Surgical and medical procedures	Less frequent	Wound drainage, post procedural drainage

c). Description of selected adverse reactions

Bleeding reactions

Due to the pharmacological mode of action, the use of DABIKLOT 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 VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/ haematocrit is of value to detect occult bleeding. The risk of bleedings may be increased in certain patient groups e.g. those patients with moderate renal impairmentand/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 DABIKLOT. Therefore, the possibility of haemorrhage is to beconsidered in evaluating the condition in any anticoagulated patient. A specific reversal agent for dabigatran, idarucizumab, is available in case of uncontrollable bleeding (see section 4.9).

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the links: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/ or https://www.sahpra.org.za/Publications/Index/8.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product

4.9 OVERDOSE

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

A specific reversal agent antagonising the pharmacodynamics effect of DABIKLOT 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 the bleeding investigated. Since DABIKLOT 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 are some experimental evidence to support the role of these agents in reversing the anticoagulant effect of DABIKLOT 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, DABIKLOT is dialysable, however there is limited clinical experience in using dialysis in this setting (see section 5.2, Special populations, Renal insufficiency)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents, direct thrombin inhibitors

ATC code: B01AE07

Pharmacological classification: A 8.2 Anticoagulant.

Mechanism of action

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. 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. At recommended prophylactic doses of dabigatran etexilate, dabigatran may prolong the activated partial thromboplastin time (aPTT), and the INR but these tests are not representative of the activity of dabigatran and are unsuitable as measures of anticoagulant activity.

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 a 0,5 and 2,0 hours post administration.
The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate was approximately 6,5 %.

Absorption:

Post-operative absorption of dabigatran etexilate, 1 - 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 least 7 - 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. 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).

Distribution:

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

Biotransformation:

Metabolism and excretion of dabigatran were studied following a single intravenous dose of 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 - 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-O, 2-O, 3-0, 4-O acylglucuronide exist, each accounts for less than 10 % of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.

Elimination:

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 -14 hours was observed. The half-life was independent of dose. Half-life is prolonged if renal function is impaired.

Pharmacokinetics in special patient groups

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 (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 (see sections 4.2, 4.3 and 4.4).

Half-life of a total dabigatran in healthy subjects and subjects with impaired renal function:

Glomerular filtration rate (CrCl)	gMean (gCV %; range) half-life
[mL/min]	[h]
> 80	13,4 (25,7 %; 11,0 - 21,6)
> 50 - ≤ 80	15,3 (42,7 %; 11,7 - 34,1)
> 30 - ≤ 50	18,4 (18,5 %;13,3 - 23,0)
≤ 30	27,2 (15,3 %; 21,6 - 35,0)

Clearance of dabigatran by haemodialysis 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 - 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 - < 80mL/min. Patients with moderate renal impairment (CrCl between 30 - 50 mL/min) had on average 2,29-fold and 1,81-fold higher pre- and post-dose dabigatran plasma concentrations, respectively, when compared with patients without renal impairment (CrCl ≥ 80 mL/min).

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 - 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 patients studied had a CrCl > 50 - < 80 mL/min, and 4,1 % and 4,8 % had a CrCl between 30 - 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 1 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 - 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 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 50 - 100 kg. The majority (80,8 %) of the subjects were in the ≥ 50kg 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.

Ethnic origin:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Croscarmellose sodium

Hydroxypropyl cellulose

Hydroxypropyl methylcellulose

Magnesium Stearate

Talc

Tartaric acid pellets (for pH-adjustment)

Hard capsules (Size 0, 1 and 2)

Hypromellose

Titanium dioxide

Black Printing ink:

Black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C, protect from light and moisture.

6.5 Nature and contents of container

Aluminium-LDPE-Nitrocellulose/aluminum blister. 30 or 60 tablets are packed in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

DABIKLOT 75 mg: A55/8.2/0325

DABIKLOT 110 mg: A55/8.2/0326

DABIKLOT 150 mg: A55/8.2/0327

9. DATE OF FIRST AUTHORISATION

December 2023