PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

Rothrom® 10 (Film-coated tablets)

Rothrom® 15 (Film-coated tablets)

Rothrom® 20 (Film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ROTHROM 10 film-coated tablet contains 10 mg rivaroxaban.

Each ROTHROM 15 film-coated tablet contains 15 mg rivaroxaban.

Each ROTHROM 20 film-coated tablet contains 20 mg rivaroxaban.

Excipients

Contains sugar (each ROTHROM 10, ROTHROM 15 and ROTHROM 20 film-coated tablet contains 48,475 mg, 45 mg and 60 mg lactose monohydrate respectively).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

ROTHROM 10: Approximately 6 mm, peach coloured, round, biconvex film-coated tablets marked with “10” on one side.

ROTHROM 15: Approximately 6 mm, light orange coloured, round, biconvex film-coated tablets marked with “15” on one side.

ROTHROM 20: Approximately 7 mm, orange coloured, round, biconvex film-coated tablets marked with “20” on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ROTHROM 10:

ROTHROM 10 film-coated tablets are indicated for:

- The prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.

ROTHROM 15 and ROTHROM 20:

ROTHROM 15 and ROTHROM 20 film-coated tablets are indicated for:

- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF).
- Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE).
- Treatment of pulmonary embolism (PE) and for the prevention of recurrent pulmonary embolism (PE) and deep vein thrombosis (DVT).

4.2. Posology and method of administration

There is no need for monitoring of coagulation parameters during treatment with ROTHROM film-coated tablets.

Posology:

ROTHROM 10:

For prevention of venous thromboembolism – Recommended dose and frequency of administration:

ROTHROM 10 film-coated tablets once daily for the prevention of venous thromboembolism (VTE) in major orthopaedic surgery.

The initial dose should be taken 6 – 10 hours after surgery provided that haemostasis has been established.

Missed dose:

If a dose is missed the patient should take ROTHROM 10 film-coated tablets immediately and continue on the following day with once daily intake as before.

For prevention of venous thromboembolism – Duration of treatment:

The duration of treatment depends on the type of major orthopaedic surgery.

After major hip surgery patients should be treated for 5 weeks. After major knee surgery patients should be treated for 2 weeks.

Special populations:

Elderly patients:

No dose adjustment is required for elderly patients

Paediatric patients (up to 18 years of age):

The safety and efficacy of ROTHROM 10 has not been established in paediatric patients. No clinical data is available

Hepatic impairment:

ROTHROM 10 is contraindicated in patients with significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk (see section 4.3).

No dose adjustment is necessary in patients with other hepatic diseases.

Limited clinical data in patients with moderate hepatic impairment indicate a significant increase in the pharmacological activity of rivaroxaban. No clinical data are available for patients with severe hepatic impairment.

Renal impairment:

No dose adjustment is required when ROTHROM 10 is administered to patients with mild (creatinine clearance 80 to 50 ml/min) or moderate (creatinine clearance < 50 – 30 ml/min) renal impairment.

Limited clinical data for patients with severe renal impairment (creatinine clearance < 30 to 15 ml/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore ROTHROM 10 must be used with caution in these patients (see section 4.4).

Ethnic differences:

No dose adjustment is required based on ethnic differences.

ROTHROM 15 and ROTHROM 20:

For SPAF – Recommended usual dose and frequency of administration:

The recommended dose is one ROTHROM 20 film-coated tablet once daily.

For patients with moderate renal impairment (creatinine clearance < 50 to 30 ml/min) the recommended dose is one ROTHROM 15 film-coated tablet once daily.

SPAF – Duration of treatment:

Therapy should be continued as long as risk factors and systemic embolism persist.

SPAF – Missed dose:

If a dose is missed the patient should take ROTHROM 15 and ROTHROM 20 film-coated tablets immediately and continue with the once daily intake as recommended on the following day.

The dose should not be doubled to make up for missed dose within the same day.

SPAF – Maximum daily dose:

The recommended maximum daily dose is one ROTHROM 20 film-coated tablet (20 mg rivaroxaban).

Special populations:

SPAF – Patients with hepatic impairment:

ROTHROM 15 and ROTHROM 20 are contraindicated in patients with or without coagulopathy (see section 4.3).

Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity.

No clinical data are available for patients with severe hepatic impairment (Child Pugh C) (see sections 4.3 and 5.2).

SPAF – Patients with renal impairment:

No dose adjustment is required if ROTHROM 20 is administered in patients with mild (creatinine clearance ≤ 80 to 50 ml/min) renal impairment. For patients with moderate (creatinine clearance < 50 to 30 ml/min) renal impairment the recommended dose is one ROTHROM 15 once daily.

Limited clinical data for patients with severe renal impairment (creatinine clearance < 30 to 15 ml/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore, ROTHROM 15 must be used with caution in these patients.

Use of ROTHROM 15 and ROTHROM 20 is not recommended with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

SPAF – Converting from warfarin to ROTHROM 15 or ROTHROM 20:

Warfarin treatment should be stopped and ROTHROM 15 or ROTHROM 20 therapy should be initiated when the INR is ≤ 3,0.

When converting patients from warfarin to ROTHROM 15 or ROTHROM 20, INR values will be falsely elevated after the intake of ROTHROM 15 or ROTHROM 20. The INR is not valid to measure the anticoagulant activity of ROTHROM 15 or ROTHROM 20, and therefore should not be used (see section 4.5).

SPAF – Converting from ROTHROM 15 or ROTHROM 20 to warfarin:

There is a potential for inadequate anticoagulation during the transition from ROTHROM 15 or ROTHROM 20 to warfarin.

Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant.

It should be noted that ROTHROM 15 and ROTHROM 20 can contribute to an elevated INR.

In patients converting from ROTHROM 15 or ROTHROM 20 to warfarin, warfarin should be given concurrently until the INR is ≥ 2,0. For the first two days of the conversion period, standard warfarin dosing should be used followed by warfarin dosing guided by INR testing.

While patients are on both ROTHROM 15 or ROTHROM 20 and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of ROTHROM 15 or ROTHROM 20).

Once ROTHROM 15 or ROTHROM 20 is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

SPAF – Converting from parenteral anticoagulant to ROTHROM 15 or ROTHROM 20:

For patients currently receiving a parenteral anticoagulant, start ROTHROM 15 or ROTHROM 20, 0 to 2 hours before the time of the next scheduled administration of the parenteral medicine (e.g. Low Molecular Weight Heparin-LMWH) or at the time of discontinuation of a continuously administered parenteral medicine (e.g. intravenous unfractionated heparin, IV-UFH).

SPAF – Converting from ROTHROM 15 or ROTHROM 20 to parenteral anticoagulants:

Discontinue ROTHROM 15 or ROTHROM 20 and give the first dose of parenteral anticoagulant at the time that the next ROTHROM 15 or ROTHROM 20 dose would have been taken.

SPAF – Children and adolescents (from birth to 18 years):

Safety and efficacy have not been established in children and adolescents below 18 years.

SPAF – Body weight:

No dose adjustment is required based on body weight (see section 5.2).

For DVT and PE treatment – Recommended usual dose and frequency of administration:

The recommended dose for the initial treatment of acute DVT and PE is one ROTHROM 15 film-coated tablet twice daily for the first three weeks followed by one ROTHROM 20 film-coated tablet once daily for the continued treatment and the prevention of recurrent DVT and PE.

DVT and PE treatment – Duration of treatment:

Therapy should be continued as long as the VTE risk persists.

DVT and PE treatment – Missed dose:

It is essential to adhere to the dosage schedule provided.

If a dose is missed during the ROTHROM 15 twice daily treatment phase the patient should take ROTHROM 15 immediately to ensure intake of 30 mg per day. In this case two ROTHROM 15 film-coated tablets may be taken at once.

The patient should continue with the regular one ROTHROM 15 twice daily intake as recommended on the following day.

If a dose is missed during the ROTHROM 20 once daily treatment phase the patient should take ROTHROM 20 immediately to ensure intake of 20 mg per day. The patient should continue with the regular one ROTHROM 20 once daily intake as recommended on the following day.

DVT and PE treatment – Maximum daily dose:

The recommended maximum daily dose is 30 mg during the first 3 weeks of treatment. In the following treatment phase the recommended maximum daily dose is 20 mg.

Special populations:

DVT and PE treatment – Patients with hepatic impairment:

ROTHROM film-coated tablets are contraindicated in patients with hepatic disease with or without coagulopathy (see section 4.3).

Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity.

No clinical data are available for patients with severe hepatic impairment (Child Pugh C) (see section 4.3 and 5.2).

DVT and PE treatment – Patients with renal impairment:

No dose adjustment is required if ROTHROM 15 and ROTHROM 20 is administered in patients with mild (creatinine clearance ≤ 80 to 50 ml/min) or moderate (creatinine clearance < 50 to 30 ml/min) renal impairment (see section 5.2).

Limited clinical data for patients with severe renal impairment (creatinine clearance < 30 to 15 ml/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore ROTHROM 15 and ROTHROM 20 must be used with caution in these patients.

Use of ROTHROM 15 and ROTHROM 20 are not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

DVT and PE treatment – Converting from warfarin to ROTHROM 15:

Warfarin treatment should be stopped and ROTHROM 15 therapy should be initiated once the INR is ≤ 2,5.

When converting patients from warfarin to ROTHROM 15, INR values will be falsely elevated after the intake of ROTHROM 15. The INR is not valid to measure the anticoagulant activity of ROTHROM 15, and therefore should not be used (see section 4.5).

DVT and PE treatment – Converting from ROTHROM 15 or ROTHROM 20 to warfarin:

There is a potential for inadequate anticoagulation during the transition from ROTHROM 15 or ROTHROM 20 to warfarin.

Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant.

It should be noted that ROTHROM 15 and ROTHROM 20 can contribute to an elevated INR.

In patients converting from ROTHROM 15 or ROTHROM 20 to warfarin, warfarin should be given concurrently until the INR is ≥ 2,0. For the first two days of the conversion period, standard warfarin dosing should be used followed by warfarin dosing guided by INR testing.

While patients are on both ROTHROM 15 or ROTHROM 20 and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of ROTHROM 15 or ROTHROM 20).

Once ROTHROM 15 or ROTHROM 20 is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

DVT and PE treatment – Converting from parenteral anticoagulants to ROTHROM 15:

For patients currently receiving a parenteral anticoagulant, start ROTHROM 15, 0 to 2 hours before the time of the next scheduled administration of the parenteral medicine (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicine (e.g. intravenous unfractionated heparin).

DVT and PE treatment – Converting from ROTHROM 15 or ROTHROM 20 to parenteral anticoagulants:

Discontinue ROTHROM 15 or ROTHROM 20 and give the first dose of parenteral anticoagulant at the time that the next ROTHROM 15 or ROTHROM 20 dose would have been taken.

DVT and PE treatment – Children and adolescents (from birth to 18 years):

Safety and efficacy have not been established in children and adolescents below 18 years.

DVT and PE treatment – Body weight:

No dose adjustment is required based on body weight (see section 5.2).

Method of administration:

For oral use.

ROTHROM 10 may be taken with or without food.

ROTHROM 15 and ROTHROM 20 should be taken with food.

4.3 Contraindications

ROTHROM film-coated tablets are contraindicated in:

- Hypersensitivity to rivaroxaban or any of the excipients of ROTHROM listed in section 6.1.
- Clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding).
- Hepatic disease with or without coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).
- Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent

brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Treatment with rivaroxaban in patients with persistent triple positive antiphospholipid syndrome (APS).
- Known existing inherited bleeding disorders.

4.4 Special warnings and precautions for use

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Patients with prosthetic valves:

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of ROTHROM have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that rivaroxaban provides adequate anticoagulation in this patient population. Treatment with rivaroxaban is not recommended for these patients.

Haemorrhagic risk:

As with other anticoagulants, patients taking ROTHROM are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. ROTHROM administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies with rivaroxaban, mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more

frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

In patients receiving ROTHROM for VTE prevention following elective hip or knee replacement surgery, this may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see sections 5.1).

Other haemorrhagic risk factors:

ROTHROM film-coated tablets should be used in caution with an increased bleeding risk such as:

- Congenital or acquired bleeding disorders
- Uncontrolled severe arterial hypertension
- Active ulcerative gastrointestinal disease
- Recent gastrointestinal ulcerations
- Other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- Vascular retinopathy

- Recent intracranial or intracerebral haemorrhage
- Intraspinal or intracerebral vascular abnormalities
- Shortly after brain, spinal or ophthalmological surgery
- Bronchiectasis or history of pulmonary bleeding.
- Impaired renal and hepatic function.

Care should be taken if patients are treated with concomitantly with medicines affecting haemostasis such as non-steroidal anti-inflammatory medicines (NSAIDS), acetylsalicylic acid and platelet aggregation inhibitors or other antithrombotics, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) (see section 4.5).
For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

Surgery and interventions:
If an invasive procedure or surgical intervention is required, ROTHROM film-coated tablets should be stopped at least 24 hours before the intervention, if possible and based on clinical judgement of the medical practitioner. If the procedure cannot be delayed the increased risk should be addressed against the urgency of the intervention.
ROTHROM film-coated tablets should be restarted after the invasive or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see section 5.2).

Neuraxial (epidural/spinal) anaesthesia:
When neuraxial (epidural/spinal) anaesthesia or spinal puncture is performed patients treated with antithrombotics for prevention of thromboembolic complications are at the risk for development of an epidural or spinal haematoma, which may result in long-term or permanent paralysis.
The risk of these events is further increased by use of indwelling epidural catheters or the concomitant use of medicines affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal punctures.

Patients should be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological deficits are noted, urgent diagnosis and treatment is necessary.
The medical practitioner should consider the potential benefit versus the risk before neuraxial intervention in patients who are anticoagulated or considered to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 15 mg or 20 mg rivaroxaban in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low.

However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known and should be weighed against the urgency of a diagnostic procedure. For the removal of an epidural catheter based on the general pharmacokinetic (PK) characteristics, at least 2x half-life, i.e. at least 18 hours in young adult patients and 26 hours in elderly patients should elapse after the last administration of ROTHROM film-coated tablets (see section 5.2).

ROTHROM film-coated tablets should be administered not before 6 hours after the removal of the catheter. If a traumatic puncture occurs, the administration of ROTHROM film-coated tablets should be delayed for 24 hours.

DVT and PE treatment – Renal impairment:

ROTHROM film-coated tablets is to be used with caution in patients with moderate renal impairment (creatinine clearance < 50 to 30 ml/min) receiving co-medications leading to increased rivaroxaban plasma concentrations (see section 4.5).

SPAF, DVT and PE treatment – Renal impairment:

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly elevated (1,6-fold on average) which may lead to an increased bleeding risk. Due to underlying disease these patients are at an increased risk of both bleeding and thrombosis.

Due to limited clinical data rivaroxaban should be used with caution in patients with creatinine clearance < 30 to 15 ml/min.

No clinical data are available for patients with severe renal impairment (creatinine clearance < 15 ml/min). Therefore, the use of ROTHROM film-coated tablets is not recommended in these patients (see sections 4.2, 5.1 and 5.2).

Patients with severe renal impairment or increased bleeding risk and patients receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors are to be carefully monitored for signs of bleeding complications after initiation of treatment (see section 4.5).

Concomitant medication:

ROTHROM film-coated tablets are not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These medications are strong inhibitors of both CYP 3A4 and P-gp. Therefore, these medications may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk (see section 4.5).

The azole anti-mycotic fluconazole, a moderate CYP 3A4 inhibitor, has however less effect on rivaroxaban exposure and can be co-administered (see section 4.5).

Women of childbearing potential:

ROTHROM film-coated tablets should be used in women of childbearing potential only with effective contraception (see section 4.6).

QTc prolongation:

No QTc prolongation effect was observed with rivaroxaban.

Patients with antiphospholipid syndrome (APS):

Treatment of patients with established APS is not recommended as evidence regarding safety and efficacy, including the benefit/harm balance of rivaroxaban (and DOACs with the same mechanism of action) in APS patients, is inconclusive. There is some evidence that treatment of persistently triple positive APS patients with rivaroxaban is associated with an increased risk of recurrent arterial thrombotic events compared with treatment of these patients with warfarin; a vitamin K antagonist (see section 4.3).

Patients with non-valvular atrial fibrillation who undergo PCI with stent placement:

Clinical data are available from an interventional study with the primary objective to assess safety in patients with non-valvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited (see sections 4.2 and 5.1). No data are available for such patients with a history of stroke/ transient ischaemic attack (TIA).

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy:

ROTHROM is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of ROTHROM have not been established in these clinical situations.

Patients with cancer:

Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during rivaroxaban therapy.

In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated (see section 4.3).

Elderly population:

Increasing age may increase haemorrhagic risk (see section 5.2).

Dermatological reactions:

Serious skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

Lactose intolerance:

ROTHROM contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ROTHROM.

4.5. Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions:

Rivaroxaban is cleared mainly via cytochrome P450-mediated (CYP 3A4, CYP 2J2) hepatic metabolism and renal excretion of the unchanged drug, involving the P-glycoprotein (P-gp) / breast cancer resistance protein (Bcrp) transporter systems (see section 5.2).

CYP inhibition:

Rivaroxaban does not inhibit CYP 3A4 or any major CYP isoforms.

CYP induction:

Rivaroxaban does not induce CYP 3A4 or any major CYP isoforms.

Effects on ROTHROM film-coated tablets:

The concomitant use of ROTHROM film-coated tablets with strong CYP 3A4 and P-gp inhibitors, may lead to both reduced hepatic and renal clearance and thus significantly increased systemic exposure.

Co-administration of ROTHROM film-coated tablets with azole-antimycotic ketoconazole (400 mg once daily) a strong CYP 3A4 and P-gp inhibitor, led to a 2,6-fold increase in mean rivaroxaban steady state AUC and a 1,7-fold increase in mean rivaroxaban C_{max}, with significant increases in its pharmacodynamic effects which may lead to an increased bleeding risk (see section 4.4).

Co-administration of ROTHROM film-coated tablets with the HIV protease inhibitor ritonavir (600 mg twice daily), a strong CYP 3A4 and P-gp-inhibitor, led to a 2,5-fold increase in mean rivaroxaban AUC and a 1,6-fold increase in mean rivaroxaban C_{max}, with significant increases in its pharmacodynamic effects which may lead to an increased bleeding risk. Data on the co-administration of rivaroxaban with HIV protease inhibitor ritonavir (100 mg twice daily) is not available.
Therefore, ROTHROM film-coated tablets are not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV-protease inhibitors (see section 4.4).
Other active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP 3A4 or P-gp, are expected to increase rivaroxaban plasma concentration to a lesser extent.

Clarithromycin (500 mg twice daily), considered a strong CYP 3A4 inhibitor and moderate P-gp inhibitor, led to a 1,5-fold increase in mean rivaroxaban AUC and a 1,4-fold increase in C_{max}. This increase, which is close to the magnitude of the normal variability of AUC and C_{max}, is likely not clinically relevant in most patients, but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times daily), which inhibits CYP 3A4 and P-gp moderately, led to a 1,3-fold increase in mean rivaroxaban AUC and C_{max}. This increase is within the magnitude of the normal variability of AUC and C_{max} and is likely not clinically relevant in most patients but can be potentially significant in high-risk patients.
In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1,8-fold increase in mean rivaroxaban AUC and 1,6-fold increase in C_{max} when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2,0-fold increase in mean rivaroxaban

AUC and 1,6-fold increase in C_{max} when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered a moderate CYP 3A4 inhibitor, led to a 1,4-fold increase in mean rivaroxaban AUC and a 1,3-fold increase in mean C_{max}. This increase is within the magnitude of the normal variability of AUC and C_{max} and is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

CYP3A4 inducers:

Co-administration of ROTHROM film-coated tablets with the strong CYP 3A4 and P-gp inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects (see section 5.2).

The concomitant use of ROTHROM film-coated tablets with other strong CYP 3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort *(Hypericum perforatum)*) may also led to a decreased rivaroxaban plasma concentration.

Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

Pharmacodynamic interactions:

Anticoagulants:

After combined administration of enoxaparin (40 mg single dose) with ROTHROM 10 film-coated tablets (10 mg single dose), an additive effect on anti-factor Xa activity can be observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban. Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors:

No clinically relevant prolongation of bleeding time was observed of rivaroxaban and 500 mg naproxen. Nevertheless, there may be individuals with more pronounced pharmacodynamic response (see section 4.4).

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding times was observed in a subset of patients which was not correlated to platelet aggregation, P-selection or GPIIb/IIIa receptor levels (see section 4.4).

Caution is needed if ROTHROM film-coated tablets is given with medicine that affects bleeding, such as NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors (see section 4.4).

Warfarin:

Converting patients from the vitamin K antagonist warfarin (INR 2,0 to 3,0) to ROTHROM 20 film-coated tablets or from ROTHROM 20 film-coated tablets to warfarin (INR 2,0 to 3,0) increased prothrombin time/INR (Neoplastin®) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of ROTHROM 15 film-coated tablets or ROTHROM 20 film-coated tablets during the conversion period, anti-Factor Xa activity, prothrombinase-induced clotting time (PiCT), and HepTest® can be use as these tests were not affected by warfarin.

From day 4 after stopping warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of ROTHROM 15 film-coated tablets or ROTHROM 20 film-coated tablets (see section 4.2).

If it is desired to test the pharmacodynamic effects of warfarin during conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and ROTHROM film-coated tablets.

SSRIs/SNRIs:

As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

Interactions shown not to exist:

There were no mutual pharmacokinetic or pharmacodynamic interactions between ROTHROM film-coated tablets and midazolam (substrate of CYP 3A4), digoxin (substrate of P-glycoprotein) or atorvastatin (substrate of CYP 3A4 and P-gp).

Co-administration of the proton pump inhibitor omeprazole, the H_2 receptor antagonist ranitidine, the antacid aluminium hydroxide/magnesium hydroxide, naproxen, clopidogrel or enoxaparin did not affect rivaroxaban bioavailability and pharmacokinetics.

Interactions with laboratory parameters:

Clotting parameter tests (PT, aPTT, HepTest®) are affected as expected by the mode of action of ROTHROM film-coated tablets (see section 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy:

The use of ROTHROM is contraindicated in pregnancy (see section 4.3).

Safety and efficacy of ROTHROM film-coated tablets have not been established in pregnant women.

In rats and rabbits, rivaroxaban showed pronounced maternal toxicity with placental changes related to its pharmacological mode of action (e.g. haemorrhagic complications) leading to reproductive toxicity. No primary teratogenic potential was identified.

Due to the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, ROTHROM film-coated tablets is contraindicated in pregnancy (see section 4.3).

Women of child-bearing potential:

ROTHROM film-coated tablets should be used in women of childbearing potential only with effective contraception (see section 4.4).

Lactation:

The use of ROTHROM is contraindicated in breastfeeding (see section 4.3).

Safety and efficacy of ROTHROM film-coated tablets have not been established in nursing mothers.

In rats, rivaroxaban is secreted into breast milk. Therefore, ROTHROM film-coated tablets may only be administered after breastfeeding is discontinued (see section 4.3).

Fertility:

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats, no effects were seen.

4.7. Effects on ability to drive and use machines

Syncope and dizziness have been reported with ROTHROM and may affect the ability to drive and use machines (see section 4.8).

Patients experiencing these adverse reactions should not drive or use machine when taking ROTHROM film-coated tablets.

4.8. Undesirable effects

Blood and lymphatic system disorders:

Frequent: Bleeding (see section 4.4), anaemia (including respective laboratory parameters), post-procedural haemorrhage (including post-operative anaemia and wound haemorrhage), contusion.

Less frequent: Thrombocythaemia (including increased platelet count), vascular pseudoaneurysm, thrombocytopenia.

Immune system disorders:

Less frequent: Allergic reaction, hypersensitivity, anaphylactic reactions including anaphylactic shock, angioedema, allergic oedema.

Endocrine disorders:

Frequency not known: Adrenal haemorrhage.

Nervous system disorders:

Frequent: Dizziness, headache.

Less frequent: Cerebral and intracranial haemorrhage, syncope (including loss of consciousness).

Eye disorders:

Frequent: Eye haemorrhage (including conjunctival haemorrhage).

Cardiac disorders:

Less frequent: Tachycardia.

Vascular disorders:

Frequent: Hypotension, haematoma.

Respiratory, thoracic and mediastinal disorders:

Frequent: Epistaxis, haemoptysis.

Gastrointestinal disorders:

Frequent: Gingival bleeding, gastrointestinal tract haemorrhage (including rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting.

Less frequent: Dry mouth, haematemesis.

Frequency not known: Fatal gastrointestinal ulcer haemorrhage.

Hepato-biliary disorders:

Frequent: Increase in transaminases.

Less frequent: Abnormal hepatic function, jaundice, hepatic impairment, increased bilirubin, increased blood alkaline phosphatase, increased GGT, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis (incl. hepatocellular injury).

Skin and subcutaneous tissue disorders:

Frequent: Pruritus (including cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage.

Less frequent: Allergic dermatitis, wound secretion, urticaria (including cases of generalised urticaria), Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis, DRESS syndrome.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Pain in extremity.

Less frequent: Haemarthrosis, muscle haemorrhage.

Frequency not known: Compartment syndrome secondary to a bleeding.

Renal and urinary disorders:

Frequent: Urogenital tract haemorrhage (including haematuria), renal impairment (including increased blood creatinine and blood urea).

Frequency not known: Renal failure / acute renal failure secondary to a bleeding sufficient to cause hypoperfusion.

Reproductive system and breast disorders:

Frequent: Menorrhagia.

General disorders and administrative site conditions:

Frequent: Fever, peripheral oedema, decreased general strength and energy (including fatigue and asthenia).

Less frequent: Feeling unwell (including malaise), localised oedema.

Investigations:

Frequent: Increase in transaminases (including increased ALT and AST), increased GGT.

Less frequent: Increase in bilirubin, blood alkaline phosphatase, LDH, lipase, amylase and conjugated bilirubin (with or without concomitant increase in ALT).

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.

Suspected adverse reactions can also be reported directly to the Holder of the Certificate of Registration (HCR) via Patientsafety.sacg@novartis.com.

4.9 Overdose

Overdose may lead to haemorrhagic complications.

Rare cases of overdose up to 1,960 mg have been reported. In case of overdose, the patient should be observed carefully for bleeding complications or other adverse reactions (see section "Management of

bleeding"). Due to limited absorption, a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg or above.

Treatment:

A specific reversal medicine (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available.

The use of activated charcoal to reduce absorption in case of overdose may be considered. Administration of activated charcoal up to 8 hours after overdose may reduce the absorption of rivaroxaban.

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Management of bleeding:

Should a bleeding complication arise in a patient receiving ROTHROM film-coated tablets, the next administration should be delayed, or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours. Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, either the administration of a specific factor Xa inhibitor reversal medicine (andexanet alfa), which antagonises the pharmacodynamic effect of rivaroxaban, or specific procoagulant reversal products should be considered, such as prothrombin complex concentration (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving ROTHROM film-coated tablets. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings.

Protamine sulphate and Vitamin K are not expected to affect the anticoagulant activity of ROTHROM film-coated tablets.

There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving ROTHROM film-coated tablets. There is neither scientific rationale for benefit nor experience with the systemic haemostatic's desmopressin and aprotinin in individuals receiving ROTHROM film-coated tablets.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A 8.2 Anticoagulants

Mechanism of action:

Rivaroxaban is highly selective direct factor Xa inhibitor with oral bioavailability. Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. FXa directly converts prothrombin to thrombin through the prothrombinase complex and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound FXa increases 300 000-fold compared to that of free FXa and causes an explosive burst of thrombin generation.

Selective inhibitors of FXa can terminate the amplified burst of thrombin generation. Consequently, several specific and global clotting tests are affected by rivaroxaban. Dose dependent inhibition of factor Xa activity was observed in humans.

Pharmacodynamic effects:

Dose dependent inhibition of factor Xa was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r-value equals 0,98) if Neoplastin® is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT (Neoplastin®) 2 to 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 seconds to 25 seconds (baseline values before surgery 12 seconds to 15 seconds).

In patients receiving rivaroxaban for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE, the 5/95 percentiles for PT (Neoplastin®) 2 to 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 17 seconds to 32 seconds for 15 mg twice daily or 15 seconds to 30 seconds for 20 mg once daily, respectively. At trough (8 to 16 hours after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 seconds to 24 seconds and for 20 mg once daily (18 to 30 hours after tablet intake) from 13 seconds to 20 seconds.

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin®) 1 to 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 14 seconds to 40 seconds in patients treated with 20 mg once daily and from 10 seconds to 50 seconds in patients with moderate renal impairment treated with 15 mg once daily. At trough (16 to 36 hours after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 seconds to 26 seconds and in patients with moderate renal impairment treated with 15 mg once daily from 12 seconds to 26 seconds.

The activated partial thromboplastin time (aPTT) and HepTest® are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban.
There is no need for monitoring of coagulation parameters during treatment with rivaroxaban. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests.

5.2. Pharmacokinetic properties

Absorption and bioavailability:

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake. The absolute bioavailability of rivaroxaban is approximately 100 % for the 10 mg dose.

The oral bioavailability for the 20 mg tablet dose is 66 %, under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39 % may occur when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 10 mg dose can be taken with or without food; however the 15 mg and 20 mg dose should be taken with food (see section 4.2).

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %.

Distribution:

Plasma protein binding in human is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with V_{ss} being approximately 50 L.

Metabolism and elimination:

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP 3A4, CYP 2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma with no major or active circulating metabolites being present. With a systemic clearance of about 10 L/h, rivaroxaban can be classified as a low-clearance substance. Elimination of rivaroxaban from plasma occurred with terminal half-lives of 5 to 9 hours in young individuals and with terminal half-lives of 11 to 13 hours in the elderly.

Special populations:

Elderly patients:

Elderly patients exhibited higher plasma concentrations than younger patients with mean AUC values being approximately 1,5-fold higher, mainly due to reduced (apparent) total and renal clearance (see section 4.2).

Different weight categories:

Extremes in body weight (< 50 kg versus > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %) (see section 4.2).

Children and adolescents:

Safety and efficacy have not been established for children and adolescents below 18 years (see section 4.2).

Hepatic impairment:

The effect of hepatic impairment on rivaroxaban has been studied in subjects categorised according to the Child Pugh classification, a standard procedure in clinical development. In patients for whom anticoagulation is intended, the clinical aspects of liver impairment is the reduced synthesis of normal coagulation factors in the liver. Since this aspect is captured by only one of the clinical/biochemical measurements composing the Child Pugh classification system the bleeding risk in patients may not clearly correlate with this classification scheme.

Rivaroxaban is contraindicated in patients with hepatic disease with or without coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B & C (see section 4.3).

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1,2-fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. No relevant difference in pharmacokinetic properties was observed between these groups.

In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2,3-fold compared to healthy volunteers, due to significantly impaired drug clearance which indicates significant liver disease. Unbound AUC was increased 2,6-fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment.
There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2,6 as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2,1. The global clotting test PT assesses the extrinsic pathway that comprises of the coagulation factors VII, X, II, I which are synthesised in the liver. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

No data are available for Child Pugh C patients (see sections 4.2 and 4.3).

Renal impairment:

There was an increase in rivaroxaban exposure being inversely correlated to the decrease in renal function, as assessed via creatinine clearance measurements.

In individuals with mild (creatinine clearance ≤ 80 to 50 ml/min), moderate (creatinine clearance < 50 to 30 ml/min) or severe (creatinine clearance < 30 to 15 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were 1,4; 1,5 and 1,6-fold increased respectively as compared to healthy volunteers (see sections 4.2 and 4.4).

Corresponding increases in pharmacodynamic effects were more pronounced (see sections 4.2 and 4.4).

In individuals with mild, moderate or severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1,5; 1,9 and 2,0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1,3; 2,2 and 2,4 respectively.

There are no data in patients with creatinine clearance < 15 ml/min.
Use is not recommended in patients with creatinine clearance < 15 ml/min.
Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance < 30 to 15 ml/min) (see sections 4.2 and 4.4).
Due to the underlying disease, patients with severe renal impairment are at an increased risk of both bleeding and thrombosis.

Concomitant administration of strong CYP 3A4 inducers:
In a phase I trial, co-administration of rivaroxaban with the strong CYP 3A4 and P-gp inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects (see section 4.5).

In a phase IIb trial, the PK/PD of an adapted rivaroxaban dosing regimen (30 mg twice daily in the first 3 weeks of treatment, followed by 20 mg twice daily) has been studied in 19 patients treated for DVT or PE and who concomitantly were medicated with a strong CYP 3A4 and P-gp inducer (rifampicin or phenytoin). The adapted dosing regimen in these patients led to a similar exposure and pharmacodynamics when compared to patients treated for DVT (15 mg twice daily in the first 3 weeks of treatment, followed by 20 mg once daily) without the concomitant administration of a strong CYP 3A4 inducer.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Each ROTHROM 10 film-coated tablet contains cellulose microcrystalline, croscarmellose sodium, hypromellose, lactose monohydrate (Granulac® 200), magnesium stearate, silica colloidal anhydrous,

sodium laurilsulfate and opadry® orange 04F530012 (consisting of hypromellose, iron oxide red, macrogol, sunset yellow FCF, talc and titanium dioxide).

Each ROTHROM 15 film-coated tablet contains cellulose microcrystalline, croscarmellose sodium, hypromellose, lactose monohydrate (Granulac® 200), magnesium stearate, silica colloidal anhydrous, sodium laurilsulfate and opadry® orange 04F530006 (consisting of hypromellose, iron oxide red, macrogol, sunset yellow FCF and titanium dioxide).

Each ROTHROM 20 film-coated tablet contains cellulose microcrystalline, croscarmellose sodium, hypromellose, lactose monohydrate (Granulac® 200), magnesium stearate, silica colloidal anhydrous, sodium laurilsulfate and opadry® orange 04F530010 (consisting of hypromellose, iron oxide black, iron oxide red, iron oxide yellow, macrogol, sunset yellow FCF and titanium dioxide).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25 °C.

6.5. Nature and contents of container

ROTHROM film-coated tablets are available in PVC/PVdC-Alu blister strips and in plastic (HDPE) containers with twist off caps with 2 g desiccant.

ROTHROM film-coated tablets are available in pack sizes of 10, 30 or 42 film-coated tablets.

The blister packs are packed into an outer cardboard carton.

Not all packs may be marketed.

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBER

ROTHROM 10: 52/8.2/0857

ROTHROM 15: 52/8.2/0858

ROTHROM 20: 52/8.2/0859

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 March 2022.

10. DATE OF REVISION OF THE TEXT

03 September 2022.

[1]Company Reg. No.: 1990/001979/07