PROFESSIONAL INFORMATION

AXOLTA RANGE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AXOLTA 10 mg, film coated tablets.

AXOLTA 15 mg, film coated tablets.

AXOLTA 20 mg, film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AXOLTA 10 mg: each film coated tablet contains rivaroxaban 10 mg.

Contains sugar (lactose monohydrate 53,57 mg per tablet).

AXOLTA 15 mg: each film coated tablet contains rivaroxaban 15 mg.

Contains sugar (lactose monohydrate 80,36 mg per tablet).

AXOLTA 20 mg: each film coated tablet contains rivaroxaban 20 mg.

Contains sugar (lactose monohydrate 107,14 mg per tablet).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablets

AXOLTA 10 mg are light pink coloured, round shaped, biconvex, filmcoated tablets debossed with "LU" on one side and "R76" on the other side.

AXOLTA 15 mg are reddish brown coloured, round shaped, biconvex, filmcoated tablets debossed with "LU" on one side and "R77" on the other side.

AXOLTA 20 mg are white coloured, round shaped, biconvex, filmcoated tablets debossed with "LU" on one side and "R78" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AXOLTA 10 mg is indicated for:

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

AXOLTA 15 mg and 20 mg is 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

AXOLTA 10 mg:

Posology

Prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs:

The recommended dose is one AXOLTA 10 mg tablet once daily for the prevention of venous thromboembolism (VTE) in major orthopaedic surgery.

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

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.

Missed dose:

If a dose is missed the patient should take AXOLTA 10 mg immediately and continue on the following day with the once daily intake as before.

Special populations

Patients with hepatic impairment:

Prevention of VTE: AXOLTA 10 mg 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 of the 10 mg 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. No clinical data are available for patients with severe hepatic impairment.

Patients with renal impairment:

Prevention of VTE: No dose adjustment is required if AXOLTA 10 mg is administered in patients with mild (creatinine clearance 80 - 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 mL/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population.
Therefore AXOLTA 10 mg must be used with caution in these patients (see section 4.4).

AXOLTA 15 mg and AXOLTA 20 mg :

Posology

There is no need for monitoring of coagulation parameters during treatment with AXOLTA 15 mg and AXOLTA 20 mg.

Prevention of stroke and systemic embolism (SPAF):

The recommended dose is one AXOLTA 20 mg tablet once daily.
For patients with moderate renal impairment (creatinine clearance < 50 - 30 mL/min) the

recommended dose is one AXOLTA 15 mg tablet once daily.

Duration of treatment:

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

Missed dose:

If a dose is missed the patient should take AXOLTA 15 mg or AXOLTA 20 mg immediately and continue with the once daily intake as recommended on the following day.

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

Maximum daily dose:

The recommended maximum daily dose is one AXOLTA 20 mg tablet.

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 AXOLTA 15 mg tablet twice daily for the first three weeks followed by one AXOLTA 20 mg 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 AXOLTA 15 mg twice daily treatment phase the patient should take AXOLTA 15 mg immediately to ensure intake of 30 mg per day. In this case two AXOLTA 15 mg tablets may be taken at once. The patient should continue with the regular one AXOLTA 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the AXOLTA 20 mg once daily treatment phase the patient should take

AXOLTA 20 mg immediately to ensure intake of 20 mg per day. The patient should continue with the regular one AXOLTA 20 mg 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

Patients with hepatic impairment:

SPAF: AXOLTA 15 mg and AXOLTA 20 mg is contraindicated in patients with hepatic disease with or without coagulopathy (see section 4.3).

DVT and PE treatment: AXOLTA 15 mg and AXOLTA 20 mg is 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 sections 4.3 and 5.2).

Patients with renal impairment:

SPAF: No dose adjustment is required if AXOLTA 20 mg is administered in patients with mild (creatinine clearance ≤ 80 - 50 mL/min) renal impairment. For patients with moderate (creatinine clearance < 50 - 30 mL/min) renal impairment the recommended dose is one AXOLTA 15 mg once daily.

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

Use of AXOLTA 15 mg or AXOLTA 20 mg is not recommended in patients with creatinine clearance <

15 mL/min (see sections 4.4 and 5.2).

DVT, PE and post-surgery treatment*:* No dose adjustment is required if AXOLTA is administered in patients with mild (creatinine clearance ≤ 80 to 50 mL/min) or moderate (creatinine clearance < 50 - 30 mL/min) renal impairment (see section 5.2).

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

Use of AXOLTA 15 mg or AXOLTA 20 mg is not recommended in patients with creatinine clearance < 15 mL/min (see sections 4.4 and 5.2).

SPAF – converting from warfarin to **AXOLTA 15 mg or AXOLTA 20 mg:**

Warfarin treatment should be stopped and AXOLTA 15 mg or AXOLTA 20 mg therapy should be initiated when the international normalised ratio (INR) is ≤ 3,0.

When converting patients from warfarin to AXOLTA 15 mg or AXOLTA 20 mg, INR values will be falsely elevated after the intake of AXOLTA 15 mg or AXOLTA 20 mg. The INR is not valid to measure the anticoagulant activity of AXOLTA 15 mg or AXOLTA 20 mg, and therefore should not be used (see section 4.4).

DVT and PE treatment **– converting from warfarin to AXOLTA 15 mg:**

Warfarin treatment should be stopped and AXOLTA 15 mg or 20 mg therapy should be initiated when the INR is ≤ 2,5.

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

SPAF - converting from AXOLTA **15 mg** ***or AXOLTA*** **20 mg** ***to warfarin:***

There is a potential for inadequate anticoagulation during the transition from AXOLTA 15 mg or

AXOLTA 20 mg to warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that AXOLTA 15 mg and AXOLTA 20 mg can contribute to an elevated INR.

In patients converting from AXOLTA 15 mg or AXOLTA 20 mg 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 AXOLTA 15 mg or AXOLTA 20 mg and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of AXOLTA 15 mg or AXOLTA 20 mg). Once AXOLTA 15 mg or AXOLTA 20 mg is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

***DVT and PE treatment* - converting from AXOLTA 15 mg or 20 mg to warfarin:**

There is a potential for inadequate anticoagulation during the transition from AXOLTA 15 mg to warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that AXOLTA can contribute to an elevated INR.

In patients converting from AXOLTA 15 mg or 20 mg to warfarin, the 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 AXOLTA 15 mg or AXOLTA 20 mg and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of AXOLTA 15 mg or AXOLTA 20 mg). Once AXOLTA 15 mg or AXOLTA 20 mg is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

SPAF - converting from parenteral anticoagulants to AXOLTA 15 mg or AXOLTA 20 mg:

For patients currently receiving a parenteral anticoagulant, start AXOLTA 15 mg or AXOLTA 20 mg, 0 - 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).

***DVT and PE treatment* - converting from parenteral anticoagulants to AXOLTA 15 mg:**

For patients currently receiving a parenteral anticoagulant, start AXOLTA 15 mg, 0 - 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).

SPAF - converting from AXOLTA 15 mg or AXOLTA 20 mg to parenteral anticoagulants:

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

***DVT and PE treatment* - converting from AXOLTA 15 mg or 20 mg to parenteral anticoagulants:**

Discontinue AXOLTA and give the first dose of parenteral anticoagulant at the time that the next AXOLTA dose would have been taken.

Body weight:

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

Ethnic differences:

No dose adjustment is required based on ethnic differences.

Elderly (above 65 years) and gender:

No dose adjustment is required for these patient populations.

Paediatric population

Children and adolescents (from birth to 18 years):

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

Method of administration

The film coated tablets are for oral use.

AXOLTA 15 mg and 20 mg should be taken with food.

AXOLTA 10 mg can be taken with or without food.

4.3 Contraindications

- hypersensitivity to rivaroxaban or to any of the ingredients of AXOLTA
- clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding)
- known existing inherited bleeding disorders
- hepatic disease with or without coagulopathy leading to a clinically relevant bleeding risk
- pregnancy and lactation.

4.4 Special warnings and precautions for use

Patients with prosthetic valves:

Safety and efficacy of AXOLTA 15 mg and AXOLTA 20 mg have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that AXOLTA 20 mg (AXOLTA 15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population.

Bleeding risk:

AXOLTA should be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- active ulcerative gastrointestinal disease
- recent gastrointestinal ulcerations
- 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.

Haemorrhagic risk:

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

In clinical studies 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 vitamin K antagonist (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 above, 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).

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

Although treatment with AXOLTA does not require routine monitoring of exposure, AXOLTA levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of AXOLTA exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see sections 5.1 and 5.2).

Surgery and interventions:

If an invasive procedure or surgical intervention is required, AXOLTA 15 mg and AXOLTA 20 mg should be stopped at least 24 hours before the intervention, if possible and based on clinical judgement of the healthcare professional.

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

AXOLTA 15 mg and AXOLTA 20 mg should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (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 risk for development of an epidural or spinal haematoma, which may result in long-term 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 healthcare provider should consider the potential benefit versus the risk before neuraxial intervention in patients who are anticoagulated or considered to be anticoagulated for thromboprophylaxis.

At least 18 hours should elapse after the last administration of AXOLTA 15 mg and AXOLTA 20 mg before removal of an epidural catheter.

Following removal of the catheter, at least 6 hours should elapse before the next AXOLTA 15 mg and AXOLTA 20 mg dose is administered.

If a traumatic puncture occurs, the administration of AXOLTA 15 mg and AXOLTA 20 mg should be delayed for 24 hours.

DVT and PE treatment – renal impairment:

AXOLTA 15 mg or AXOLTA 20 mg is to be used with caution in patients with moderate renal impairment (creatinine clearance < 50 - 30 mL/min) receiving co-medications leading to increased AXOLTA plasma concentrations (see section 4.5).

SPAF, DVT and PE treatment – severe 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 the underlying disease these patients are at an increased risk of both bleeding and thrombosis. Therefore, AXOLTA (all strengths) should be used with caution in patients with severe renal impairment.

AXOLTA should also be used with caution in patients with creatinine clearance 15 - 29 mL/min. Use is not recommended in patients with creatinine clearance < 15 mL/min (see sections 4.2 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.

Interaction with other medicines:

AXOLTA 15 mg and AXOLTA 20 mg is 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 medicines are strong inhibitors of both CYP 3A4 and P-glyvoprotein (P-gp). Therefore, these medicines 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).

Care should be taken if patients are treated concomitantly with medicines affecting haemostasis such as nonsteroidal anti-inflammatory medicines (NSAIDs), platelet aggregation inhibitors, or other antithrombotics (see section 4.5).

For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

Women of childbearing potential:

AXOLTA should be used in women of childbearing potential only with effective contraception (see section 4.6).

QTc prolongation:

No QTc prolonging effect was observed with AXOLTA.

Patients with antiphospholipid syndrome:

Direct acting oral anticoagulants (DOACs) including AXOLTA 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.

Hip fracture surgery:

AXOLTA has not been studied in interventional clinical studies in patients undergoing hip fracture surgery to evaluate efficacy and safety.

Patients with non-valvular atrial fibrillation who undergo percutaneous coronary intervention (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:

AXOLTA 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 AXOLTA have not been established in these clinical situations.

Dosing recommendations before and after invasive procedures and surgical intervention other than elective hip or knee replacement surgery:

If an invasive procedure or surgical intervention is required, AXOLTA should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the healthcare provider.

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

AXOLTA should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating doctor (see section 5.2).

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 drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, have been reported in association with the use of AXOLTA (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. AXOLTA 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.

Excipients:

AXOLTA contains lactose. Patients with the rare hereditary conditions of galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not take AXOLTA.

AXOLTA contains less than 1 mmol sodium (0,023 g) per tablet, that is to say essentially ‘sodium free’.

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 medicine, 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 other major CYP isoforms.

CYP induction:

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

Effects on AXOLTA

CYP3A4 and P-gp inhibitors:

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

Ketoconzaole:

Co-administration of AXOLTA with the 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.

Ritonavir:

Co-administration of AXOLTA 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. Data on

the co-administration of AXOLTA with the HIV protease inhibitor ritonavir (100 mg twice daily) is not available.

The use of AXOLTA is therefore not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (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 concentrations to a lesser extent.

Clarithromycin:

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 considered as not clinically relevant.

Erythromycin:

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 considered as clinically not relevant 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:

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 considered as clinically not relevant, in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Dronedarone:

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

PHARMACODYNAMIC INTERACTIONS

Anticoagulants:

After combined administration of enoxaparin (40 mg single dose) with AXOLTA 10 mg (single dose), an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests – partial thromboplastin time (PTT), activated partial thromboplastin time (aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban (see section 4.5).

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 after concomitant administration of AXOLTA 15 mg 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 AXOLTA was co-administered with 500 mg acetylsalicylic acid, however, care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicines typically increase the bleeding risk (see section 4.4).

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

Selective serotonin re-uptake inhibitors (SSRIs) and selective noradrenaline re-uptake inhibitors (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.

Warfarin:

Converting patients from warfarin (INR 2,0 - 3,0) to AXOLTA 20 mg or from AXOLTA(20 mg to warfarin (INR 2,0 - 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 (ETP) were additive.

If it is desired to test the pharmacodynamic effects of AXOLTA 15 mg or AXOLTA 20 mg during the conversion period, anti-Factor Xa activity, prothrombinase-induced clotting time (PiCT), and Heptest® can be used 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 AXOLTA 15 or 20 mg (see section 4.2).

If it is desired to test the pharmacodynamic effects of warfarin during the 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 AXOLTA.

CYP3A4 inducers:

Co-administration of AXOLTA 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 5.1).

The concomitant use of AXOLTA with other strong CYP 3A4 inducers (e.g. phenytoin, carbamazepine. phenobarbitone or St. John's Wort) may also lead to a decreased rivaroxaban plasma concentration. Strong CYP 3A4 inducers should be co-administered with caution.

Other concomitant therapies:

There were no mutual pharmacokinetic interactions between AXOLTA 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 AXOLTA.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

AXOLTA should be used in women of childbearing potential only with effective contraception.

Pregnancy

Safety and efficacy of AXOLTA 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, AXOLTA is contraindicated in pregnancy (see section 4.3).

Breastfeeding

Safety and efficacy of AXOLTA has not been established in nursing mothers. In rats, rivaroxaban is secreted into breast milk. Therefore AXOLTA may only be administered after breastfeeding is discontinued (see section 4.3).

Fertility

There is no data on fertility with AXOLTA.

4.7 Effects on ability to drive and use machines

Adverse reactions like syncope and dizziness have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects

a). Summary of the safety profile

The safety of AXOLTA has been evaluated in studies including patients exposed to rivaroxaban 10 mg undergoing major orthopaedic surgery of the lower limbs (total hip replacement or total knee replacement), in 3997 hospitalised medically ill patients treated up to 39 days, and in three phase III VTE treatment trials with patients exposed either to rivaroxaban 15 mg twice daily for 3 weeks followed by rivaroxaban 20 mg once daily, or to rivaroxaban 20 mg once dally treated up to 21 months.

Furthermore, safety of rivaroxaban (as in AXOLTA), has also been evaluated in patients with non-valvular atrial fibrillation from two phase III trials with at least one dose of either rivaroxaban 15 mg or 20 mg.

Due to the pharmacological mode of action, AXOLTA 15 mg and AXOLTA 20 mg may be associated with an increased risk of occult or overt bleeding from any tissue and organ which may result in post

haemorrhagic anaemia. The risk of bleedings may be increased in certain patient groups e.g. patients with uncontrolled severe arterial hypertension, impaired renal and hepatic function and/or on concomitant medication affecting haemostasis (see section 4.2).

The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9).

Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases, as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

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

In other clinical studies with rivaroxaban 10 mg, single cases of adrenal haemorrhage and conjunctival haemorrhage, and fatal gastrointestinal ulcer haemorrhage were reported, jaundice and hypersensitivity were rare and haemoptysis was uncommon.

b). Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Frequent Less frequent	Anaemia (incl. respective laboratory parameters) Thrombocytosis (incl. platelet counts increased) [A], thrombocytopenia
Immune system disorders	Less frequent	Allergic reaction, allergic dermatitis, angioedema and allergic oedema, anaphylactic reactions including anaphylactic shock

Nervous system disorders	Frequent Less frequent	Dizziness, headache Cerebral and intracranial haemorrhage, syncope
Eye disorders	Frequent	Eye haemorrhage (incl. conjunctival haemorrhage)
Cardiac disorders	Less frequent	Tachycardia
Vascular disorders	Frequent	Hypotension, haematoma, postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage)
Respiratory, thoracic and mediastinal disorders	Frequent	Epistaxis, haemoptysis
Gastrointestinal disorders	Frequent Less frequent	Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation [A], diarrhoea, vomitinq [A] Dry mouth

Hepato-biliary disorders	Less frequent Frequency unknown	Abnormal hepatic function, cholestasis, hepatitis (incl. hepatocellular injury) Jaundice
Skin and subcutaneous tissue disorders	Frequent Less frequent	Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage Urticaria, contusion, Stevens-Johnson syndrome/ toxic epidermal necrolysis, DRESS syndrome
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent Frequency unknown	Pain in extremity [A] Haemarthrosis, muscle haemorrhage Compartment syndrome secondary to a bleeding
Renal and urinary disorders	Frequent Frequency unknown	Urogenital tract haemorrhage (incl. haematuria and menorrhagia [B]), renal impairment (incl. blood creatinine increased, blood urea increased) [A] Renal failure/acute, renal failure secondary to a bleeding sufficient to cause hypoperfusion

General disorders and administrative site conditions	Frequent Less frequent	Fever [A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia) Feeling unwell (incl. malaise), localised oedema [A]
Investigations	Frequent Less frequent	Increase in transaminases Increase in bilirubin, increase in blood alkaline phosphatase [A], increase in LDH [A], increase in lipase [A], increase in amylase [A], increase in GGT[A], increase-in conjugated bilirubin (with or without concomitant increase of ALT)
Injury and poisoning	Frequent Less frequent	Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage) Wound secretion [A], Vascular pseudoaneurysm [C]
[A] observed after major orthopedic surgery of the lower limbs [B] observed in VTE treatment as very common in women < 55 years [C] observed as uncommon in prevention therapy in acute coronary syndrome (ACS) (following percutaneous intervention)		

c). *Description of selected adverse reactions*

Due to the pharmacological mode of action, the use of AXOLTA may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic

anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9, Management of bleeding). In the clinical studies conducted, 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. The risk of bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see section 4.4, Haemorrhagic risk). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases, as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on the SAHPRA website.
An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 OVERDOSE

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. 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.
A specific antidote antagonizing the pharmacodynamic effect of AXOLTA is not available.

Management of overdose:

The use of activated charcoal to reduce absorption in case of AXOLTA overdose may be considered.

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 AXOLTA, the next administration should be delayed, or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 - 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, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (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 AXOLTA.

Protamine sulphate and Vitamin K are not expected to affect the anticoagulant activity of AXOLTA.

There is no experience with antifibrinolytic medicines (tranexamic acid, aminocaproic acid) in individuals receiving AXOLTA. There is neither scientific rationale for benefit nor experience with the systemic haemostatics desmopressin and aprotinin in individuals receiving AXOLTA.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors

ATC code: B01AF01

Pharmacological classification: A.8.2 Anticoagulants

Mechanism of action

Rivaroxaban is a 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 activity 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 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 - 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.

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 - 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.

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.
Anti-factor Xa activity is also influenced by rivaroxaban; however, no standard for calibration is available.
There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests.

Clinical efficacy and safety

The rivaroxaban clinical program was designed to demonstrate the efficacy of rivaroxaban for the prevention of venous thromboembolic events (VTE), i.e. proximal and distal deep vein thrombosis (DVT)
and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs. Over 9500 patients (7050 in total hip replacement surgery and 2531 in total knee replacement surgery) were studied in controlled randomised double-blind phase III clinical studies.

5.2 Pharmacokinetic properties

Absorption and bioavailability:

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake.

Administration of rivaroxaban tablets with food (high-calorie / high-fat meal) showed no significant food effects. Rivaroxaban 10 mg dose can be taken with or without food (see section 4.2).

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 % were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg should be taken with food (see section 4.2).

Under fed conditions rivaroxaban 15 mg and 20 mg tablets demonstrated dose-proportionality.

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

Distribution:

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

Biotransformation 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 other 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.
Elimination of rivaroxaban and metabolites occurs via both renal and faecal routes.

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 - 9 hours in young individuals, and with terminal half-lives of 11 - 13 hours in the elderly.

Linearity/non-linearity:

Rivaroxaban pharmacokinetics is linear with no relevant undue accumulation beyond steady-state

after multiple doses.

Pharmacokinetics in special patient groups

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).

Inter-ethnic differences:

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding pharmacokinetics and pharmacodynamics (see section 4.2).

Hepatic impairment:

The effect of hepatic impairment on rivaroxaban pharmacokinetics 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 critical aspect of liver impairment is the reduced synthesis of normal coagulation factors in the liver. Since this aspect is captured by only one of the five 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 (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 pharmacodynamic 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 medicine clearance which indicates significant liver disease. Unbound AUC was increased 2,6-fold. 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, V, II, I which are synthesised in the liver. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD (pharmacokinetic-pharmacodynamic) 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 - 50 mL/min), moderate (creatinine clearance < 50 - 30 mL/min) or severe (creatinine clearance < 30 - 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 - 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.

Paediatric population

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Croscarmellose sodium

Hypromellose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium lauryl sulphate

Film coating – Opadry Pink (10 mg)/Brown (15 mg)/White (20 mg):

Hypromellose

Iron oxide red (10 mg and 15 mg)

Macrogol

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, protect from light and moisture.

Keep blisters in carton until required for use.

6.5 Nature and contents of container

Axolta tablets are available in clear PVC/PVDC blister packs, with printed aluminium foil backing, packed in a printed outer carton containing 30 tablets (10 and 20 mg) or 45 tablets (15 mg).

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

AXOLTA 10 mg: A55/8.2/0140

AXOLTA 15 mg: A55/8.2/0141

AXOLTA 20 mg: A55/8.2/0142

9. DATE OF FIRST AUTHORISATION

04 April 2023