SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

XARELTO 10 Film-coated tablets

COMPOSITION:

Each film-coated tablet contains rivaroxaban 10 mg. Contains lactose.

Other excipients

Cellulose microcrystalline, Croscarmellose sodium, Hydroxypropylmethylcellulose 2910, Lactose monohydrate, Magnesium stearate, Sodium laurylsulphate, Titanium dioxide E171, Polyethylene glycol, Ferric oxide red E172.

PHARMACOLOGICAL CLASSIFICATION:

A. 8.2 Anticoagulants.

PHARMACOLOGICAL ACTION:

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

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, 2 - 4 hours after tablet intake (i.e. at the time of maximum effect), ranged from 13 to 25 seconds.

The activated partial thomboplastin time (aPTT) and HepTest® are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamics 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.

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.

Pharmacokinetics

Absorption and Bioavailability

The absolute bioavailability of rivaroxaban is approximately 100 % for the 10 mg dose. 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 Dosage and Direction for Use).

Rivaroxaban pharmacokinetics is linear with no relevant undue accumulation beyond steady-state after multiple doses.

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

Distribution

Plasma protein binding in humans 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

Rivaroxaban is eliminated by metabolic degradation (approximately 2/3 of the administered dose) as well as by direct renal excretion of unchanged compound (approximately 1/3). 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.

Elimination of rivaroxaban and metabolites occurs via both renal and faecal routes.

Approximately 66 % of a rivaroxaban dose is eliminated via the kidneys, with 30 - 40 % excreted as unchanged drug in the urine via both glomerular filtration and active renal secretion. 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 low-clearance drug. 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

Gender/Elderly (above 65 years)

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 Dosage and Directions for Use).

There were no clinically relevant differences in pharmacokinetics between male and female patients (see Dosage and Directions for Use).

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 Dosage and Directions for use).

Children (up to 18 years of age)

No data is available for this patient population (see Dosage and Directions for Use).

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 Dosage and Directions for Use).

Hepatic impairment

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 drug clearance which indicates significant liver disease. 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 (coagulation Factors VII, X, V, II, I), of which Factors II, VII, and X are synthesised in the liver. The elevated PT at baseline and a significantly altered sensitivity in anticoagulant activity towards rivaroxaban plasma exposure (increase in slope for PT / rivaroxaban plasma concentration relationship by more than 2-fold) in cirrhotic patients classified as Child Pugh B indicate the decreased ability of the liver to synthesise coagulation factors. The PK/PD changes in these patients are markers for the severity of the underlying hepatic disease which is expected to lead to a subsequent increased bleeding risk in this patient group. Therefore rivaroxaban is contra-indicated in patients with significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk (see Contra-Indications).

No data are available for Child Pugh C patients (see Dosage and Directions for Use and Contra-Indications).

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 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 Warnings and Dosage and Directions for Use).

Corresponding increases in pharmacodynamic effects were more pronounced (see Warnings and Dosage and Directions for Use).

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.

Due to the underlying disease patients with severe renal impairment are at an increased risk of both bleeding and thrombosis. Rivaroxaban is to be used with caution in patients with severe renal impairment (see Warnings and Dosage and Directions for Use).

INDICATIONS:

Xarelto 10 film-coated tablets are indicated for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.

CONTRA-INDICATIONS:

Xarelto 10 is contra-indicated in patients with:

- Hypersensitivity to rivaroxaban or any excipient of the tablet.
- Clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding).
- Significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk.
- Pregnancy and lactation (see Pregnancy and Lactation).

WARNINGS:

Xarelto 10 like other antithrombotics 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
- Shortly after brain, spinal or ophthalmological surgery

In patients with severe renal impairment (creatinine clearance < 30 mL/min) rivaroxaban plasma levels may be significantly elevated 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 due to limited clinical data Xarelto 10 should be used with caution in patients with severe renal impairment.

Xarelto 10 must be used with caution in patients receiving concomitant systemic treatment with azole-antimycotics (e.g. ketoconazole) or HIV protease inhibitors (e.g. ritonavir). These drugs are strong inhibitors of both CYP 3A4 and P-gp. Therefore, these drugs may increase rivaroxaban plasma concentrations to a clinically relevant degree (see Interactions).

After treatment is initiated patients should be carefully monitored for signs of bleeding complications. This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

Care should be taken if patients are treated concomitantly with drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors, or other antithrombotics (see Interactions).

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

Xarelto 10 should be used in women of childbearing potential only with effective contraception.

No QTc prolonging effect was observed with Xarelto 10.

Since Xarelto 10 contains lactose, patients with rare hereditary problems of lactose or galactose intolerance (e.g., the Lapp lactase deficiency or glucose-galactose malabsorption) should not take Xarelto 10.

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 even increased by use of indwelling epidural catheters or the concomitant use of drugs affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture.

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 physician should consider the potential benefit versus the risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

An epidural catheter should not be withdrawn earlier than 18 hours after the last administration of Xarelto 10.

Xarelto 10 should be administered at earliest 6 hours after the removal of the catheter.

If traumatic puncture occurs the administration of Xarelto 10 should be delayed for 24 hours.

INTERACTIONS:

<u>Pharmacokinetic interactions</u>

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 Pharmacokinetics).

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 Xarelto 10

The concomitant use of Xarelto 10 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 Xarelto 10 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.

Co-administration of Xarelto 10 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.

Therefore Xarelto 10 must be used with caution in patients receiving concomitant systemic treatment with azole-antimycotics or HIV-protease inhibitors (see Warnings).

Erythromycin (500 mg three times daily), which inhibits CYP 3A4 and P-gp moderately, led to a 1,3-fold increase in mean rivaroxaban steady state 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.

Drugs strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP 3A4 or P-gp, potentially increase rivaroxaban plasma concentrations. The expected increase is considered as clinically not relevant.

Co-administration of Xarelto 10 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.

The concomitant use of Xarelto 10 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.

Pharmacodynamic interactions

After combined administration of enoxaparin (40 mg single dose) with Xarelto 10 (10 mg single dose), an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban (see Warnings).

No clinically relevant prolongation of bleeding time was observed after concomitant administration of Xarelto 10 and 500 mg naproxen. Nevertheless there may be individuals with more pronounced pharmacodynamic response (see Warnings).

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction 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 Warnings).

Interactions shown not to exist

There were no mutual pharmacokinetic interactions between Xarelto 10 and midazolam (substrate of CYP 3A4), digoxin (substrate of P-glycoprotein) or atorvastatin (substrate of CYP 3A4 and P-gp).

Co-administration of the H_2 receptor antagonist ranitidine and the antacid aluminum hydroxide /

magnesium hydroxide did not affect rivaroxaban bioavailability and pharmacokinetics.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when Xarelto 10 was co-administered with 500 mg acetylsalicylic acid.

Interactions with laboratory parameters

Clotting parameter tests (PT, aPTT, HepTest®) are affected as expected by the mode of action of Xarelto 10.

PREGNANCY AND LACTATION:

Pregnancy

No human data on the use of Xarelto 10 in pregnant women are available.

In rats and rabbits Xarelto 10 showed pronounced maternal toxicity with placental changes related to its pharmacological mode of action (e.g., haemorrhagic complications). No primary teratogenic potential was identified. Animal data show that rivaroxaban crosses the placental barrier. Therefore use of Xarelto 10 is contra-indicated throughout pregnancy.

Xarelto 10 should be used in women of childbearing potential only with effective contraception.

Lactation

No human data on use of Xarelto 10 in nursing mothers are available. In rats rivaroxaban is secreted into breast milk. Therefore Xarelto 10 may only be administered after breastfeeding is discontinued.

EFFECT ON ABILITY TO DRIVE OR USE MACHINES:

No effect of Xarelto 10 on the ability to drive or operate machinery has been reported.

DOSAGE AND DIRECTIONS FOR USE:

Recommended dose and frequency of administration

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

Xarelto 10 may be taken with or without food.

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

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

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 patient populations

Elderly (above 65 years), Gender and Body Weight:

No dose adjustment is required for these patient populations.

Children (up to 18 years of age)

The safety and efficacy of Xarelto 10 has not been established in children. No clinical data is available for children.

Patients with impaired liver function

Xarelto 10 is contra-indicated in patients with significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk. (see Contra-Indications).

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. No clinical data are available for patients with severe hepatic impairment.

Patients with impaired renal function

No dose adjustment is required if Xarelto 10 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 Xarelto 10 must be used with caution in these patients (see Warnings and Special Precautions).

Ethnic differences

No dose adjustment is required based on ethnic differences.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects

The safety of Xarelto 10 has been evaluated in three phase III studies including 4571 patients undergoing major orthopaedic surgery of the lower limbs (total hip replacement or total knee replacement) treated up to 39 days. The adverse reactions are presented within each frequency grouping and system organ classes; the adverse reactions should be interpreted within the surgical setting.

Frequencies are defined as:

Common: = 1 % to < 10 % (> 1/100 to < 1/10)

Uncommon: = 0,1 % to < 1 % (> 1/1000 to < 1/100)

Rare: = 0,01 % to < 0,1 % (> 1/10 000 to < 1/1 000)

Very rare: < 0,01 % (< 1/10 000)

Due to the pharmacological mode of action, Xarelto 10 may be associated with an increased risk of occult or overt bleeding which may result in post haemorrhagic anaemia. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding. Haemorrhagic complications may present as weakness, asthenia, paleness, dizziness, headache or unexplained swelling. Therefore, the possibility of a haemorrhage should be considered in evaluating the condition in any anticoagulated patient.

Adverse reactions as reported in the three phase III studies are listed below in Table 1, by system organ class (in MedDRA) and frequency.

Table 1: All treatment-emergent adverse drug reactions reported in patients in three phase III studies.

Common **= 1 % to < 10 %**	**Uncommon** **= 0,1 % to < 1 %**	**Rare** **= 0,01 % to < 0,1 %**
BLOOD AND THE LYMPHATIC SYSTEM DISORDERS		
Anaemia (incl. respective lab parameters)	Thrombocythemia (incl. platelet count increased)	
CARDIAC DISORDERS		
	Tachycardia	
GASTROINTESTINAL DISORDERS		
Nausea	Constipation Diarrhoea Abdominal and Gastrointestinal pain (incl. upper abdominal pain, stomach discomfort) Dyspepsia (incl. epigastric discomfort) Dry mouth Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Localised oedema Feeling unwell (incl. fatigue, asthenia) Fever	

Table 1: All treatment-emergent adverse drug reactions reported in patients in three phase III studies.		
Common = 1 % to < 10 %	**Uncommon = 0,1 % to < 1 %**	**Rare = 0,01 % to < 0,1 %**
	Oedema, peripheral	
HEPATOBILIARY DISORDERS		
		Hepatic function abnormal
IMMUNE SYSTEM DISORDERS		
		Dermatitis, allergic
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Wound secretion	
INVESTIGATIONS		
Increased GGT Increase in transaminases (incl. ALT increase, AST increase)	Increased Lipase Increased Amylase Blood bilirubin increased Increased LDH Increased alkaline phosphatase	Bilirubin conjugated increased (with or without concomitant increase of ALT)
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS		
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Dizziness Headache Syncope (incl. loss of consciousness)	
RENAL AND URINARY DISORDERS		
	Renal impairment (incl. blood creatinine increased, blood urea increased)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Pruritus (incl. rare cases of generalised pruritus) Rash Urticaria (incl. rare cases of generalised urticaria)	

Table 1: All treatment-emergent adverse drug reactions reported in patients in three phase III studies.		
Common = 1 % to < 10 %	**Uncommon = 0,1 % to < 1 %**	**Rare = 0,01 % to < 0,1 %**
	Contusion	
VASCULAR DISORDERS		
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage)	Hypotension (incl. blood pressure decreased, procedural hypotension) Haemorrhage (incl. haematoma and rare cases of muscle haemorrhage) Gastrointestinal Tract haemorrhage (incl. gingival bleeding, rectal haemorrhage, haematemesis) Haematuria (incl. blood urine present) Genital tract haemorrhage (incl. menorrhagia) Nose bleed	

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

Special Precautions

See Warnings.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdose following administration of Xarelto 10 may lead to haemorrhagic complications due to its pharmacodynamic properties.

The use of activated charcoal to reduce absorption in case of Xarelto 10 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 Xarelto 10 is not expected to be dialysable.

Should bleeding occur, management of the haemorrhage may include the following steps:

- Delay of next Xarelto 10 administration or discontinuation of treatment as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours.
- Appropriate symptomatic treatment, e.g. mechanical compression (e.g., for severe epistaxis), surgical interventions, fluid replacement and haemodynamic support, blood product or component transfusion should be considered.

If bleeding cannot be controlled by the above measures, consider administration of one of the following procoagulants:

- Activated prothrombin complex concentrate (APCC)
- Prothrombin complex concentrate (PCC)
- Recombinant Factor VIIa (rF VIIa).

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of Xarelto 10. There is no scientific rationale for benefit or experience with systemic haemostatics (e.g. desmopressin, aprotinin, tranexamic acid, aminocaproic acid) in individuals receiving Xarelto 10.

IDENTIFICATION:

Light red, round, biconvex, film-coated tablets, 6 mm in diameter, debossed with “Triangle 10” on the top side and the BAYER-cross on the bottom side of the tablet.

PRESENTATION:

Xarelto 10 film-coated tablets are packed in colourless, transparent PP (polypropylene)/aluminium blister strips or colourless, transparent PVC/PVDC/aluminium blister strips containing 5 or 10 tablets per blister. Pack sizes: 5 tablets (1 x 5’s blister), 10 tablets (1 x 10’s blister), 30 tablets (3 x 10’s blister) or 100 tablets (10 x 10’s blister).

STORAGE INSTRUCTIONS:

Store below 30 °C. Keep blister strips in the original carton until use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

42/8.2/1046

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Bayer (Pty) Ltd

Reg. No.: 1968/011192/07

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