Professional Information for TICANARY 90

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TICANARY 90 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 90 mg ticagrelor.

Excipients with known effect:

Contains sugar alcohol: 126 mg mannitol per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Yellow coloured, round, biconvex, film-coated tablets, debossed with "90 & M" on one side and plain on other side, free from physical defects.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TICANARY 90 is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with acute coronary syndromes (ACS) (unstable angina, non-ST elevation myocardial infarction [NSTEMI] or ST elevation myocardial infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

4.2 Posology and method of administration

Posology

TICANARY 90 treatment should be initiated with a single 180 mg loading dose (2 tablets of 90 mg) and then continued at 90 mg twice daily.

Patients taking TICANARY 90 should also use aspirin daily unless specifically contraindicated. Following an initial dose of aspirin, TICANARY 90 should be used with a maintenance dose of aspirin of 75 – 150 mg daily (see sections 4.4 and 5.1).

Medical practitioners who desire to switch patients from clopidogrel to TICANARY 90 should administer the first 90 mg dose of TICANARY 90 24 hours following the last dose of clopidogrel. There is no data on switching patients from other ADP receptor inhibitors to TICANARY 90.

Treatment is recommended for at least 12 months unless discontinuation of TICANARY 90 is clinically indicated. In patients with acute coronary syndromes (ACS), premature discontinuation with any antiplatelet therapy, including TICANARY 90, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease (see section 4.4).

Special populations

Elderly patients

No dose adjustment is required.

Patients with renal impairment

No dose adjustment is necessary for patients with renal impairment (see section 5.2). No information is available concerning treatment of patients on renal dialysis.

Patients with hepatic impairment

Although the elimination of TICANARY 90 was statistically significantly delayed in patients with mild

hepatic impairment (Child Pugh A), no dose adjustment is necessary in these patients. TICANARY 90 has not been studied in patients with moderate or severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Paediatric patients

Safety and efficacy in children below the age of 18 have not been established.

Method of administration

Oral use.

TICANARY 90 can be taken with or without food.

Lapses in therapy should be avoided. A patient who misses a dose of TICANARY 90 should take one 90 mg tablet (their next dose) at its scheduled time.

4.3 Contraindications

- Hypersensitivity to ticagrelor or to any of the excipients of TICANARY 90 listed in section 6.1.
- Active pathological bleeding.
- History of intracranial haemorrhage (see section 4.8).
- Severe hepatic impairment (see sections 4.2, 4.4 and 5.2).
- Strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, nefazodone, ritonavir and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor (see section 4.5).
- Inherited bleeding disorders.
- CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine and phenobarbital).

4.4 Special warnings and precautions for use

Bleeding risk

The use of TICANARY 90 in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events (see sections 4.8 and 5.1). If clinically

indicated, TICANARY 90 should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding). The use of TICANARY 90 is contraindicated in patients with active pathological bleeding, in those with a history of intracranial haemorrhage, and in patients with severe hepatic impairment (see section 4.3).
- Patients with concomitant administration of medicines that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics) within 24 hours of TICANARY 90 dosing.
- The safe co-administration of TICANARY 90 with warfarin has not been established.

Platelet transfusion did not reverse the antiplatelet effect of ticagrelor, as contained in TICANARY 90, in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding. Since co-administration of ticagrelor with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events (see section 4.5).

CABG-related bleeding: In a phase 3 study, 12 % underwent coronary artery bypass graft (CABG) surgery. Major fatal/Life-threatening bleeding occurred in approximately 42 % of patients and fatal CABG bleeding has occurred in 6 patients.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may increase haemostasis. TICANARY 90 may be resumed after the cause of bleeding has been identified and controlled.

Surgery

If a patient requires surgery, healthcare professionals should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of TICANARY 90 treatment should occur. In a clinical study, mean inhibition of platelet aggregation (IPA) for ticagrelor at 24-, 48-, 72- and 120-hours post-dose was 58,4 %, 32,8 %, 19,5 % and 9,7 %

respectively.

Patients should be advised to inform healthcare professionals and dentists that they are taking TICANARY 90 before any surgery is scheduled and before any new medicine is taken.

If a patient is to undergo elective surgery and antiplatelet effect is not desired, TICANARY 90 should be discontinued 5 days prior to surgery (see section 5.1).

There are no data available regarding major regional block techniques and neuraxial blocks. Caution is advised in patients with increased risk of bleeding such as those undergoing spinal anaesthesia, epidural anaesthesia and lumbar puncture.
Neurological monitoring for neuroaxial haematoma is recommended consistent with standard of care, during peri-operative and post-operative care.

Patients with prior ischemic stroke

ACS patients with prior ischaemic stroke can be treated with TICANARY 90 for up to 12 months. Treatment beyond one year is not recommended in these patients.

Hepatic impairment

Use of TICANARY 90 is contraindicated in patients with severe hepatic impairment (see sections 4.2 and 4.3). There is limited experience with TICANARY 90 in patients with moderate hepatic impairment, therefore, caution is advised in these patients (see sections 4.2 and 5.2).

Patients at risk for bradycardic events

Holter ECG monitoring has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel. Patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) have been excluded from the main studies

evaluating the safety and efficacy of ticagrelor. Therefore, due to the limited clinical experience, TICANARY 90 should be used with caution in these patients (see section 5.1).

In addition, caution should be exercised when administering TICANARY 90 concomitantly with medicines known to induce bradycardia.

Dyspnoea

Dyspnoea was reported in patients treated with TICANARY 90. Dyspnoea is usually mild to moderate in intensity and often resolves without need for treatment discontinuation. Patients with asthma/chronic obstructive pulmonary disease (COPD) may have an increased absolute risk of experiencing dyspnoea with TICANARY 90. TICANARY 90 should be used with caution in patients with history of asthma and/or COPD. The mechanism has not been elucidated. If a patient reports new, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with TICANARY 90 should be stopped.

Creatine elevations

Creatinine levels may increase during treatment with TICANARY 90. The mechanism has not been elucidated. Renal function should be checked according to routine medical practice. In patients with ACS, it is recommended that renal function is also checked one month after initiating the treatment with TICANARY 90, paying special attention to patients ≥ 75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an angiotensin receptor blocker (ARB).

Uric acid increase

Hyperuricaemia may occur during treatment with TICANARY 90. Caution is advised in patients with history of hyperuricaemia or gouty arthritis. As a precautionary measure, the use of TICANARY 90 in patients with uric acid nephropathy is discouraged.

Thrombotic thrombocytopenic purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP) has been reported with the use of ticagrelor, as contained in TICANARY 90. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

Interference with platelet function tests to diagnose heparin induced thrombocytopenia (HIT)

In the heparin induced platelet activation (HIPA) test used to diagnose HIT, anti-platelet factor 4/heparin antibodies in patient serum activate platelets of healthy donors in the presence of heparin.

False negative results in a platelet function test (to include but may not be limited to the HIPA test) for HIT have been reported in patients administered ticagrelor. This is related to inhibition of the $P2Y_{12}$-receptor on the healthy donor platelets in the test by ticagrelor in the patient's sera/plasma. Information on concomitant treatment with TICANARY 90 is required for interpretation of HIT platelet function tests.

In patients who have developed HIT, the benefit-risk of continued treatment with TICANARY 90 should be assessed, taking both the prothrombotic state of HIT and the increased risk of bleeding with concomitant anticoagulant and TICANARY 90 treatment into consideration.

Other

Co-administration of TICANARY 90 and high maintenance dose aspirin (> 300 mg) is not recommended (see section 5.1).

Premature discontinuation

Premature discontinuation with any antiplatelet therapy, including TICANARY 90, could result in an increased risk of cardiovascular (CV) death, MI or stroke due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided.

4.5 Interaction with other medicines and other forms of interaction

Ticagrelor, as contained in TICANARY 90, is primarily a CYP3A4 substrate and a mild inhibitor of CYP3A4. Ticagrelor is also a P-glycoprotein (P-gp) substrate and a weak P-gp inhibitor and may increase the exposure of P-gp substrates.

Effects of medicines and other products on TICANARY 90

CYP3A4 inhibitors

- Strong CYP3A4 inhibitors – Co-administration of ketoconazole with ticagrelor increased the ticagrelor C_{max} and AUC equal to 2,4-fold and 7,3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89 % and 56 %, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, itraconazole, nefazodone, ritonavir, and atazanavir) would be expected to have similar effects and therefore concomitant use of strong CYP3A4 inhibitors with TICANARY 90 is contraindicated (see section 4.3).
- Moderate CYP3A4 inhibitors – Co-administration of diltiazem with ticagrelor increased the ticagrelor C_{max} by 69 % and AUC to 2,7-fold and decreased the active metabolite C_{max} by 38 % and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, erythromycin, fluconazole and verapamil) would be expected to have a similar effect and can as well be co-administered with TICANARY 90.
- A 2-fold increase of ticagrelor exposure was observed after daily consumption of large quantities of grapefruit juice (3 x 200 mL). This magnitude of increased exposure is not expected to be clinically relevant to most patients.

CYP3A inducers

Co-administration of rifampicin with ticagrelor decreased ticagrelor C_{max} and AUC by 73 % and 86 %, respectively. The C_{max} of the active metabolite was unchanged and the AUC was decreased by 46 %, respectively. Other CYP3A inducers (e.g. dexamethasone, phenytoin, carbamazepine and

phenobarbital) would be expected to decrease the exposure to ticagrelor as well.
Co-administration of TICANARY 90 with potent CYP3A inducers may decrease exposure and efficacy of TICANARY 90 (see section 4.3).

Ciclosporin (P-gp and CYP3A inhibitor)

Co-administration of ciclosporin (600 mg) with ticagrelor increased ticagrelor C_{max} and AUC equal to 2,3-fold and 2,8-fold, respectively. The AUC of the active metabolite was increased by 32 % and C_{max} was decreased by 15 % in the presence of ciclosporin.

No data are available on concomitant use of ticagrelor with other active substances that also are potent P-gp inhibitors and moderate CYP3A4 inhibitors (e.g. verapamil, quinidine) that also may increase ticagrelor exposure. If the association cannot be avoided, their concomitant use should be made with caution.

Others

Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin and aspirin or desmopressin did not have any effect on the pharmacokinetics of ticagrelor or the active metabolite or on ADP-induced platelet aggregation compared with ticagrelor alone. If clinically indicated, medicines that alter haemostasis should be used with caution in combination with TICANARY 90.

A delayed and decreased exposure to oral $P2Y_{12}$ inhibitors, including ticagrelor and its active metabolite, has been observed in patients with ACS treated with morphine (35 % reduction in ticagrelor exposure). This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced TICANARY 90 efficacy in patients co-administered TICANARY 90 and morphine. In patients with ACS, in whom morphine cannot be withheld and fast $P2Y_{12}$ inhibition is deemed crucial, the use of a parenteral $P2Y_{12}$ inhibitor may be considered.

Effect of TICANARY 90 on other medicines

Medicines metabolised by CYP3A4

- *Simvastatin* – Co-administration of ticagrelor with simvastatin increased simvastatin C_{max} by 81 % and AUC by 56 % and increased simvastatin acid C_{max} by 64 % and AUC by 52 % with some individual increases equal to 2- to 3-fold. Co-administration of TICANARY 90 with doses of simvastatin exceeding 40 mg daily could cause adverse reactions of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. TICANARY 90 may have similar effect on lovastatin. The concomitant use of TICANARY 90 with doses of simvastatin or lovastatin greater than 40 mg is not recommended.
- *Atorvastatin* - Co-administration of atorvastatin and ticagrelor increased atorvastatin acid C_{max} by 23 % and AUC by 36 %. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.
- A similar effect on other statins metabolised by CYP3A4 cannot be excluded.

Ticagrelor is a mild CYP3A4 inhibitor. Co-administration of TICANARY 90 and CYP3A4 substrates with narrow therapeutic indices (i.e. cisapride or ergot alkaloids) is not recommended, as TICANARY 90 may increase the exposure to these medicines.

P-gp substrates (including digoxin, ciclosporin)

Concomitant administration of ticagrelor increased the digoxin C_{max} by 75 % and AUC by 28 %. The mean trough digoxin levels were increased about 30 % with ticagrelor co-administration with some individual maximum increases to 2-fold. In the presence of digoxin, the C_{max} and AUC of ticagrelor and its active metabolite were not affected. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent medicines like digoxin concomitantly with TICANARY 90.

There is no effect of TICANARY 90 on ciclosporin blood levels. Effect of TICANARY 90 on other P-gp

substrates has not been studied.

Medicines metabolised by CYP2C9

Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either medicines, which suggests that ticagrelor, as contained in TICANARY 90, is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of medicines like warfarin and tolbutamide.

Oral contraceptives

Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased ethinyl estradiol exposure approximately 20 % but did not alter the pharmacokinetics of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with TICANARY 90.

Medicines known to induce bradycardia

Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering TICANARY 90 concomitantly with medicines known to induce bradycardia (see section 4.4).

Other concomitant therapy

In clinical studies, ticagrelor was commonly administered with aspirin, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers as needed for concomitant conditions for long-term and also heparin, low molecular weight heparin and intravenous GpIIb/IIIa inhibitors for short durations (see section 5.1). No evidence of clinically significant adverse interactions with these medicines was observed.

Co-administration of ticagrelor with heparin, enoxaparin or desmopressin had no effect on activated partial thromboplastin time (aPTT), activated coagulation time (ACT) or factor Xa assays. However, due to potential pharmacodynamic interactions, caution should be exercised with the concomitant

administration of TICANARY 90 with medicines known to alter haemostasis.

Due to reports of cutaneous bleeding abnormalities with SSRIs (e.g. paroxetine, sertraline and citalopram), caution is advised when administering SSRIs with TICANARY 90 as this may increase the risk of bleeding.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during TICANARY 90 therapy.

Pregnancy

There are no or limited amount of data from the use of TICANARY 90 in pregnant women. Studies in animals have shown reproductive toxicity. TICANARY 90 is not recommended during pregnancy.

Breastfeeding

Available pharmacodynamic/toxicological data in animals have shown excretion of ticagrelor and its active metabolites in milk. A risk to newborns and infants cannot be excluded.
The use of TICANARY 90 during breastfeeding is not recommended.

Fertility

TICANARY 90 had no effect on male or female fertility in animals.

4.7 Effects on ability to drive and use machines

TICANARY 90 can cause side effects, such as dizziness and confusion and can affect the ability to drive a vehicle and use machines. Caution is advised when driving a vehicle or operating machinery until the effects of TICANARY 90 are known.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients treated with TICANARY 90 were bleeding and dyspnoea.

Table 1: Adverse reactions by frequency and system organ class (SOC)

System organ class	Frequent	Less frequent	Frequency unknown
Neoplasms benign and malignant (including cysts and polyps)		Tumour bleedings[a]	
Blood and the lymphatic system disorders	Blood disorder bleedings[b]		Thrombotic thrombocytopenic purpura[j]
Immune system disorders		Hypersensitivity including angioedema[j]	
Metabolism and nutrition disorders	Hyperuricaemiad, gout/gouty arthritis		
Psychiatric disorders		Confusion	
Nervous system disorders	Dizziness, syncope, headache	Intracranial haemorrhage, paraesthesia	
Eye disorders		Eye haemorrhage[e]	
Ear and labyrinth disorders	Vertigo	Ear haemorrhage	
Vascular disorders	Hypotension		
Respiratory, thoracic	Dyspnoea, epistaxis,		

and mediastinal disorders	haemoptysis		
Gastrointestinal disorders	Abdominal pain, gastrointestinal haemorrhage[g], diarrhoea, nausea, vomiting, dyspepsia, constipation	Retroperitoneal haemorrhage	
Skin and subcutaneous tissue disorders	Subcutaneous or dermal bleeding[h], rash, pruritus		
Musculoskeletal and connective tissue disorders		Haemarthrosis, muscular bleedings	
Renal and urinary disorders	Urinary tract bleeding[f]		
Reproductive system and breast disorders		Reproductive system bleedings[i]	
Investigations	Increased blood creatinine[d]		
Injury, poisoning and procedural complications	Post procedural haemorrhage, traumatic bleedings[c]		

[a] e.g. bleeding from bladder cancer, gastric cancer, colon cancer

[b] e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis

[c] e.g. contusion, traumatic haematoma, traumatic haemorrhage

[d] Frequencies derived from lab observations (Uric acid increases to > upper limit of normal from

baseline below or within reference range. Creatinine increases of > 50 % from baseline.) and not crude adverse event report frequency.

[e] e.g. conjunctival, retinal, intraocular bleeding

[f] e.g. haematuria, cystitis haemorrhagic

[g] e.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage

[h] e.g. ecchymosis, skin haemorrhage, petechiae

[i] e.g. vaginal haemorrhage, haematospermia, postmenopausal haemorrhage

[j] Identified in post-marketing experience

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

TICANARY 90 is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse reactions which may occur with overdose include dyspnoea and ventricular pauses (see section 4.8).

In the event of an overdose, the above potential adverse reactions could occur and ECG monitoring should be considered.

There is currently no known antidote to reverse the effects of TICANARY 90, and TICANARY 90 is not dialysable (see section 5.2).

Treatment of overdose should follow local standard medical practice. The expected effect of excessive TICANARY 90 dosing is prolonged duration of bleeding risk associated with platelet

inhibition. Platelet transfusion is unlikely to be of clinical benefit in patients with bleeding (see section 4.4). If bleeding occurs other appropriate supportive measures should be taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 8.2 Anticoagulants.

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin.

ATC code: B01AC24.

Mechanism of action

TICANARY 90 contains ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents ADP- mediated $P2Y_{12}$ dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the $P2Y_{12}$ receptor prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of CV events such as death, MI or stroke.

Pharmacodynamic effects

Onset of action

In patients with stable coronary artery disease (CAD) on aspirin, ticagrelor demonstrates a rapid onset of pharmacological effect as demonstrated by a mean inhibition of platelet aggregation (IPA) for ticagrelor at 0,5 hours after 180 mg loading dose of about 41 %, with the maximum IPA effect of 89 % by 2 – 4 hours post dose, and maintained between 2 – 8 hours. 90 % of patients had final extent IPA > 70 % by 2 hours post dose. The high IPA effect of ticagrelor between 87 – 89 % was maintained between 2 – 8 hours.

Offset of action

If a CABG procedure is planned, ticagrelor bleeding risk is increased compared to clopidogrel when discontinued within less than 96 hours prior to procedure.

Offset of effect

After the ticagrelor and the active metabolite concentrations decline to a level less than that required for receptor saturation, IPA gradually decreases with declining plasma concentrations. Since ticagrelor binds reversibly, the recovery of platelet function does not depend on replacement of platelets.

Switching data

Switching from clopidogrel 75 mg to ticagrelor 90 mg twice daily results in an absolute IPA increase of 26,4 % and switching from ticagrelor to clopidogrel results in an absolute IPA decrease of 24,5 %. Patients can be switched from clopidogrel to ticagrelor without any interruption of antiplatelet effect (see section 4.2).

5.2 Pharmacokinetic properties

Ticagrelor demonstrates linear pharmacokinetics and exposure to ticagrelor and the active metabolite (AR-C124910XX) are approximately dose proportional up to 1260 mg.

Absorption

Absorption of ticagrelor is rapid with a median t_{max} of approximately 1,5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median t_{max} of approximately 2,5 hours. Following an oral ticagrelor 90 mg single dose under fasted conditions in healthy subjects, C_{max} is 529 ng/mL and AUC is 3451 ng*h/mL. The metabolite parent ratios are 0,28 for C_{max} and 0,42 for AUC. The pharmacokinetics of ticagrelor and ARC124910XX in patients with a history of MI were generally similar to that in the ACS population. Based on a population pharmacokinetic analysis of the PEGASUS study the median ticagrelor C_{max} was 391 ng/mL and AUC was 3801 ng*h/mL at steady state for ticagrelor 60 mg. For ticagrelor 90 mg C_{max} was 627 ng/mL and

AUC was 6255 ng*h/mL at steady state.

The mean absolute bioavailability of ticagrelor was estimated to be 36 %. Ingestion of a high-fat meal resulted in a 21 % increase in ticagrelor AUC and 22 % decrease in the active metabolite C_{max} but had no effect on ticagrelor C_{max} or the AUC of the active metabolite. These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food. Ticagrelor as well as the active metabolite are P-gp substrates.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, has a comparable bioavailability to whole tablets with regards to AUC and C_{max} for ticagrelor and the active metabolite. Initial exposure (0,5 and 1 hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

Distribution

The steady state volume of distribution of ticagrelor is 87,5 L. Ticagrelor and the active metabolite is extensively bound to human plasma protein (> 99,7 %).

Biotransformation

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition. The major metabolite of ticagrelor is AR-C124910XX, which is also active as assessed by *in vitro* binding to the platelet $P2Y_{12}$ ADP-receptor. The systemic exposure to the active metabolite is approximately 30 – 40 % of that obtained for ticagrelor.

Elimination

The primary route of ticagrelor elimination is via hepatic metabolism. When radiolabelled ticagrelor is administered, the mean recovery of radioactivity is approximately 84 % (57,8 % in faeces, 26,5 % in

urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1 % of the dose. The primary route of elimination for the active metabolite is most likely via biliary secretion. The mean $t_{1/2}$ was approximately 7 hours for ticagrelor and 8,5 hours for the active metabolite.

Special populations

Elderly

Higher exposures to ticagrelor (approximately 25 % for both C_{max} and AUC) and the active metabolite were observed in elderly (≥ 75 years) ACS patients compared to younger patients by the population pharmacokinetic analysis. These differences are not considered clinically significant (see section 4.2).

Gender

Higher exposures to ticagrelor and the active metabolite were observed in women compared to men. These differences are not considered clinically significant.

Renal impairment

Exposure to ticagrelor was approximately 20 % lower and exposure to the active metabolite was approximately 17 % higher in patients with severe renal impairment (creatinine clearance < 30 mL/min) compared to subjects with normal renal function. In patients with end stage renal disease on haemodialysis AUC and C_{max} of ticagrelor 90 mg administered on a day without dialysis were 38 % and 51 % higher compared to subjects with normal renal function. A similar increase in exposure was observed when ticagrelor was administered immediately prior to dialysis (49 % and 61 %, respectively) showing that ticagrelor is not dialysable. Exposure of the active metabolite increased to a lesser extent (AUC 13 – 14 % and C_{max} 17 – 36 %). The inhibition of platelet aggregation (IPA) effect of ticagrelor was independent of dialysis in patients with end stage renal disease and similar to subjects with normal renal function (see section 4.2).

Hepatic impairment

C_{max} and AUC for ticagrelor were 12 % and 23 % higher in patients with mild hepatic impairment

compared to matched healthy subjects, respectively, however, the IPA effect of ticagrelor was similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. Ticagrelor has not been studied in patients with severe hepatic impairment and there is no pharmacokinetic information in patients with moderate hepatic impairment. In patients that had moderate or severe elevation in one or more liver function tests at baseline, ticagrelor plasma concentrations were on average similar or slightly higher as compared to those without baseline elevations. No dose adjustment is recommended in patients with moderate hepatic impairment (see sections 4.2 and 4.4).

Ethnicity

Patients of Asian descent have a 39 % higher mean bioavailability compared to Caucasian patients. Patients self-identified as black had an 18 % lower bioavailability of ticagrelor compared to Caucasian patients, in clinical pharmacology studies, the exposure (C_{max} and AUC) to ticagrelor in Japanese subjects was approximately 40 % (20 % after adjusting for body mass) higher compared to that in Caucasians. The exposure in patients self-identified as Hispanic or Latino was similar to that in Caucasians.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Calcium hydrogen phosphate dihydrate

Hydroxypropyl cellulose

Magnesium stearate

Mannitol [E421].

Film-coating:

Opadry yellow (containing hypromellose [E464], iron oxide yellow [E172], polyethylene glycol [E1521], talc [E553b] and titanium dioxide [E171]).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister strips containing 14 tablets, packed into an outer container.

Pack size: 56 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville

7551

8. REGISTRATION NUMBER

56/8.2/1156

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 August 2023

10. DATE OF REVISION OF THE TEXT