SCHEDULING STATUS: **S 3**

PROPRIETARY NAME (and Dosage Form):

Brilinta® (Tablet)

COMPOSITION:

Each tablet contains 90 mg of ticagrelor.

List of excipients:

Tablet Core: Mannitol, dibasic calcium phosphate, magnesium stearate, sodium starch glycolate and hydroxypropyl cellulose.

Tablet Coating: Talc, titanium dioxide, ferric oxide yellow, polyethylene glycol 400 and hypromellose.

Contains sugar.

PHARMACOLOGICAL CLASSIFICATION:

A 8.2 Anticoagulants

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is a selective and reversibly binding adenosine diphosphate (ADP) receptor antagonist acting on the $P2Y_{12}$ ADP-receptor that can prevent ADP-mediated platelet activation and aggregation. Ticagrelor is orally active, and reversibly interacts with the platelet $P2Y_{12}$ ADP-receptor. Ticagrelor does not interact with the ADP binding site itself, but its interaction with platelet $P2Y_{12}$ ADP-receptor prevents signal transduction.

Onset of action:

In patients with stable coronary artery disease on aspirin (acetylsalicylic acid (ASA)), 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 47 %, with the maximum IPA effect of 87,9 %-89,6 % by 2-4 hours

post dose. Ninety percent 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 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.

Summary of clinical studies:

Analyses suggested a possible association between aspirin dose and the primary efficacy results, such that reduced efficacy was observed with ticagrelor and increasing doses of aspirin. Interaction studies have been conducted with ticagrelor and aspirin, and no effects were observed on ticagrelor pharmacokinetics or pharmacodynamics, measured as inhibition of platelet aggregation. Nonetheless, based on the possible association between aspirin dose and clinical efficacy, the range of recommended dose of chronic aspirin to be used concomitantly with ticagrelor is 75-150 mg (see "*Dosage and Directions for Use*" and "*Warnings and Special Precautions*").

The benefits associated with ticagrelor were also independent of the use of other acute and long-term cardiovascular therapies, including heparin, low molecular weight heparin (LMWH), intravenous glycoprotein GpIIb/IIIa (GpIIb/IIIa) inhibitors, lipid-lowering medicines, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and proton pump inhibitors.

Pharmacokinetic properties:

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

Absorption:

Ticagrelor has 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. The C_{max} and AUC of ticagrelor and the active

metabolite increased in an approximately proportional manner with dose over the dose range studied (30-1 260 mg).

The mean absolute bioavailability of ticagrelor was estimated to be 36 %, (range 25,4-64,0 %). Ingestion of a high-fat meal had no effect on ticagrelor C_{max} or the AUC of the active metabolite, but resulted in a 21 % increase in ticagrelor AUC and 22 % decrease in the active metabolite C_{max}. These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food.

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

Metabolism:
CYP3A 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. Ticagrelor and the active metabolite are P-glycoprotein weak inhibitors.

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.

Excretion:
The primary route of ticagrelor elimination is via hepatic metabolism. When radio-labelled 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 mostly via biliary secretion. The mean half life was approximately 6,9 hours (range 4,5-12,8 hours) for ticagrelor and 8,6 hours (range 6,5-12,8 hours) for the active metabolite.

Special populations:

Elderly:

Higher exposures to ticagrelor (approximately 60 % for both C_{max} and AUC) and the active metabolite (approximately 50 % for both C_{max} and AUC) were observed in elderly (≥ 65 years) subjects compared to younger subjects. These differences are not considered clinically significant (see "*Dosage and Directions for Use*").

Paediatric:

Ticagrelor has not been evaluated in a paediatric population (see "*Dosage and Directions for Use*").

Gender:

Higher exposures to ticagrelor (approximately 52 % and 37 % for C_{max} and AUC, respectively) and the active metabolite (approximately 50 % for both C_{max} and AUC) were observed in women compared to men. However there were no differences in the phase 3 clinical studies for efficacy and safety data between men and women.

Renal impairment:

Exposure to ticagrelor and the active metabolite were approximately 20 % lower in patients with severe renal impairment (Cl_{CR} < 30 ml/min) compared to subjects with normal renal function.

The IPA effect of ticagrelor was similar between the 2 groups, however there was more variability observed in individual response in patients with severe renal impairment. No dosing adjustment is needed in patients with renal impairment. No information is available concerning treatment of patients on renal dialysis (see "*Dosage and Directions for Use*").

Hepatic impairment:

C_{max} and AUC for ticagrelor were 12 % and 35 % higher in patients with mild hepatic impairment (Child Pugh A) compared to matching healthy subjects respectively; however the IPA effect of ticagrelor was similar between the 2 groups. No dose adjustment is needed for patients with mild hepatic impairment. Ticagrelor has not been studied in patients with moderate or severe hepatic impairment (see "*Contraindications*", "*Warnings*

and Special Precautions" and "*Dosage and Directions for Use*").

Race:

Patients of Asian descent (573 patients) have a 39 % higher mean bioavailability compared to Caucasian patients (6 198 patients). Patients self-identified as Black (76 patients) 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 (29 patients) was approximately 40 % (20 % after adjusting for body weight) higher compared to that in Caucasians (28 patients). These differences do not require dose adjustment.

INDICATIONS:

BRILINTA 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).

CONTRAINDICATIONS:

Hypersensitivity to ticagrelor (BRILINTA) or any of its excipients in the formulation.
Active pathological bleeding.
Inherited bleeding disorders.
Severe hepatic impairment.
History of intracranial haemorrhage.
Strong CYP3A4 inhibitors (such as ketoconazole, clarithromycin, itraconazole, nefazadone, ritonavir and atazanavir).
CYP3A4 inducers (such as rifampicin, phenytoin, carbemazepine and phenobarbital).

WARNINGS AND SPECIAL PRECAUTIONS:

Bleeding risk:

The use of BRILINTA in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events.

Consideration should be given to the following:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, active or recent gastrointestinal bleeding or moderate hepatic impairment.) The use of BRILINTA is contraindicated in patients with active pathologic bleeding, inherited bleeding disorders and in those with a history of intracranial haemorrhage, and severe hepatic impairment (see "*Contraindications*").

- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics within 24 hours of BRILINTA dosing).

- The safe co-administration of BRILINTA with warfarin has not been established.

No data exist with BRILINTA regarding a haemostatic benefit of platelet transfusions; circulating BRILINTA may inhibit transfused platelets. Since co-administration of BRILINTA with desmopressin did not decrease template bleeding time; desmopressin is unlikely to be effective in managing clinical bleeding events.

CABG-related bleeding: In the 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.

Surgery:

- If a patient requires surgery, medical practitioners should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of BRILINTA treatment should occur.
- In a clinical study, mean Inhibition of Platelet Aggregation (IPA) for BRILINTA at 24, 48, 72 and 120 hours post-dose was 58,4 %, 32,8 %, 19,5 % and 9,7 % respectively.
- **If a patient is to undergo elective surgery and antiplatelet effect is not desired, BRILINTA should be discontinued 5 days prior to surgery.**
- There are no data available in regard to 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.
BRILINTA should be discontinued 5 days prior to surgery or for any procedure in which antiplatelet effect is not desired.

Patients at risk for bradycardic events:
Due to observations of ventricular pauses in a phase II clinical study, 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) were excluded from the main study evaluating the safety and efficacy of BRILINTA. Therefore, due to the limited clinical experience in these patients, caution is advised (see "*Pharmacodynamic properties*").

In a Holter substudy, 6 % of patients on BRILINTA developed ventricular pauses of $\geq$ 3 seconds.

Dyspnoea:
Dyspnoea commonly occurs in patients treated with BRILINTA and may resolve during continued BRILINTA treatment. The mechanism has not yet been elucidated. If a patient develops new, prolonged or worsened dyspnoea during treatment with BRILINTA this should be investigated fully and if not tolerated, treatment with BRILINTA should be stopped (see "*Side Effects*").

Other:
Based on a relationship observed between primary efficacy and maintenance aspirin dose, co-administration of BRILINTA and high maintenance dose of aspirin (300 mg) is not recommended (see "*Pharmacodynamic properties*" and "*Dosage and Directions for Use*").

Co-administration of BRILINTA with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazadone, ritonavir, and atazanavir) should be avoided as co-administration may lead to a substantial increase in exposure to BRILINTA (see *"Contraindications"* and "*Interactions*").

Co-administration of BRILINTA and simvastatin increased mean simvastatin C_{max} by 81 % and AUC by 56 % and increased simvastatin acid C_{max} by 64 % and AUC by 52 %, which may be associated with increased adverse events related to increased simvastatin exposure. The concomitant use of BRILINTA with doses of simvastatin or lovastatin > 40 mg is not recommended.

Concomitant administration of BRILINTA increased digoxin C_{max} by 75 % and AUC by 28 % (see *"Interactions"*).

Discontinuations:
Patients who require discontinuation of BRILINTA are at increased risk for cardiac events. Premature discontinuation of treatment should be avoided. If BRILINTA must be temporarily stopped due to an adverse event(s), it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution (see "*Dosage and Directions for Use*").
No data are available for treatment longer than 12 months.

Effects on ability to drive and use machines:
No studies on the effects of BRILINTA on the ability to drive and use machines have been performed. During treatment for Acute Coronary Syndromes, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

INTERACTIONS:
Effects of other medicines on BRILINTA:

Medicinal products metabolised by CYP3A4:
Ketoconazole *(strong CYP3A4 inhibitors):*
Co-administration of ketoconazole with BRILINTA increased 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, nefazadone, ritonavir and atazanavir) would be expected to have similar effects and should not be given concomitantly with BRILINTA (see *"Contraindications"*).

Diltiazem *(moderate CYP3A4 inhibitors):*

Co-administration of BRILINTA and diltiazem increased the C_{max} of ticagrelor by 69 % and AUC by 174 % and decreased the active metabolite C_{max} by 38 % and AUC was unchanged. There was no effect of BRILINTA on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g. amprenavir, erythromycin, fluconazole and verapamil) may probably be co-administered with BRILINTA.

Rifampicin and other CYP3A4 inducers:

Co-administration of rifampicin with BRILINTA 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 CYP3A4 inducers (e.g.dexamethasone, phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to BRILINTA as well and may result in reduced efficacy of BRILINTA (see "*Contraindications*").

Others:

Clinical pharmacology interaction studies showed that co-administration of BRILINTA with heparin, enoxaparin and aspirin did not have any effect on ticagrelor or the active metabolite plasma levels.

Effects of BRILINTA on other medicines:

Medicinal products metabolised by CYP3A4:

Simvastatin:

Co-administration of BRILINTA 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 2-3 fold.

The concomitant use of BRILINTA with a dose of simvastatin or lovastatin > 40 mg is not recommended.

Atorvastatin**:**

Co-administration of atorvastatin and BRILINTA 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.

Medicinal products metabolised by CYP2C9:

Tolbutamide:

Co-administration of BRILINTA with tolbutamide resulted in no change in the plasma levels of either medicine, which suggest that ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of tolbutamide.

Oral Contraceptives:

Co-administration of BRILINTA and levonorgestrel and ethinyl oestradiol increased ethinyl oestradiol 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 oestradiol are co-administered with BRILINTA.

Digoxin (PgP substrate):

Concomitant administration of BRILINTA increased the digoxin C_{max} by 75 % and AUC by 28 %. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent medicines like digoxin concomitantly with BRILINTA.

PREGNANCY AND LACTATION:

Pregnancy:

Safety in pregnancy has not been established.

Lactation:

The use of BRILINTA during breastfeeding is not recommended.

DOSAGE AND DIRECTIONS FOR USE:

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

BRILINTA can be taken with or without food.

Patients taking BRILINTA should also use aspirin daily unless specifically contraindicated. Following an initial dose of aspirin, BRILINTA should be used with a

maintenance dose of aspirin of 75-150 mg daily (see "*Pharmacodynamic properties*" and "*Warnings and Special Precautions*").

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

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

Treatment is recommended for at least 12 months unless discontinuation of BRILINTA is clinically indicated. In patients with Acute Coronary Syndromes (ACS), premature discontinuation with any antiplatelet therapy, including BRILINTA, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease (see "*Warnings and Special Precautions*").

Special populations:

Paediatric patients:

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

Elderly patients:

No dose adjustment is required.

Patients with renal impairment:

No dose adjustment is necessary for patients with renal impairment (see "*Pharmacokinetic properties").* No information is available concerning treatment of patients on renal dialysis.

Patients with hepatic impairment:

Although the elimination of BRILINTA was statistically significantly delayed in patients with mild hepatic impairment (Child Pugh A), no dose adjustment is necessary in these patients. BRILINTA has not been studied in patients with moderate or severe hepatic

impairment (see "*Pharmacokinetic properties", "Contraindications"* and *"Warnings and Special Precautions").*

SIDE EFFECTS:

Side effects:

Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are defined according to the following conventions: Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1 000, < 1/100), Rare (≥ 1/10 000, < 1/1 000).

The following adverse reactions have been identified following studies with BRILINTA:

Table 1 – Adverse Reactions by System Organ Class (SOC) and by Adverse Event Frequency

System Organ Classification	Very Common	Common	Uncommon	Rare
Metabolism and nutrition disorders	Hyperuricaemia[a]			
Psychiatric disorders			Confusion	
Nervous system disorders		Headache, dizziness	Intracranial haemorrhage[b], paraesthesia	
Eye disorders			Eye haemorrhage (intraocular, conjunctival, retinal)	
Ear and labyrinth disorders		Vertigo		
Respiratory, thoracic and mediastinal disorders	Dyspnoea[b]	Epistaxis	Haemoptysis	
Gastrointestinal Disorders		Abdominal pain, constipation, diarrhoea, gastrointestinal haemorrhage[b], dyspepsia,	Gastritis, retroperitoneal haemorrhage[b]	

System Organ Classification	Very Common	Common	Uncommon	Rare
		nausea, vomiting		
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding[b], rash, pruritus		
Musculoskeletal connective tissue and bone disorders				Haemarthrosis
Renal and urinary disorders		Urinary tract bleeding[b]		
Investigations		Increased blood creatinine[a]		
Injury, poisoning and procedural complications		Post procedural haemorrhage		

[a] Frequencies derived from laboratory observations (uric acid to > ULN of 7 and 6,5 mg/dL for males and females respectively and creatinine increases of > 50 % from baseline) and not crude adverse event report frequency- see laboratory abnormalities section

[b] Represents multiple related adverse events terms

The safety of BRILINTA in patients with acute coronary syndromes (unstable angina, NSTEMI and STEMI) was evaluated in a single large phase 3 study.

Median treatment duration for BRILINTA was 277 days (6 762 patients were treated for greater than 6 months and 3 138 were treated for greater than 12 months).

The most commonly reported adverse events in patients treated with BRILINTA were dyspnoea, headache and epistaxis. During the treatment period, the BRILINTA group had a 7,4 % incidence of discontinuation due to adverse events.

Bleeding:

The following bleeding definitions were used in the phase 3 study:

'Major Fatal/Life-threatening': fatal, or intracranial, or intrapericardial bleed with cardiac tamponade, or hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery, or clinically overt or apparent bleeding associated with a decrease in haemoglobin of more than 5 g/dL, or transfusion of 4 or more units (whole

blood or packed red blood cells [PRBCs]) for bleeding.

'Major Other': Significantly disabling (e.g. intraocular with permanent vision loss) or clinically overt or apparent bleeding associated with a decrease in haemoglobin of 3-5 g/dL, or transfusion of 2-3 units (whole blood or PRBCs) for bleeding.

'Minor': Requires medical intervention to stop or treat bleeding (e.g. epistaxis requiring visit to medical facility for packing).

Minimal bleeds included all other bleeds; these were collected but not adjudicated.

Bleeding events were also mapped to the TIMI (Thrombolysis in Myocardial Infarction) scale. **TIMI Major** is defined as clinically overt bleeding associated with a fall in haemoglobin > 5 g/dL, or intracranial haemorrhage, and **TIMI Minor** is defined as overt bleeding associated with a fall in haemoglobin of 3 g/dL but ≤ 5 g/dL.

Table 2 – Analysis of overall bleeding events

	BRILINTA (%) N = 9 235
Primary Safety Endpoint Total Major	11,6
Secondary Endpoints Fatal/Life-Threatening	5,8
Combined Total Major + Minor bleeding	16,1
Non-CABG Major	4,5
Non-Procedural Major	3,1
Non-Procedural Major + Minor	5,9
TIMI-defined bleeding category TIMI-defined Major	7,9
TIMI-defined Major + Minor	11,4

There were few fatal bleeding events in the phase 3 study, 20 (0,2 %) for BRILINTA.

CABG-related bleeding: In the 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.

Non-CABG related bleeding: When CABG bleeding is removed from the analysis (see Table 3 below), the absolute bleeding rates for all categories are lower.

Table 3 – Non-CABG Related Study-defined Major Bleeding Events and TIMI-defined Bleeding Events

	BRILINTA (%) N = 9 235
Study-defined bleeding category Total Major Bleeding	4,5
Major Fatal/Life-Threatening	2,1
TIMI-defined bleeding category TIMI-defined Major	2,8
TIMI-defined Major + Minor	4,5

Bleeding unrelated to any procedure: As shown in Table 2 study-defined 'Major' and 'Major + Minor' non-procedural bleeding was common with BRILINTA. Discontinuation of treatment due to non-procedural bleeding was 2,9 %.

'Major Fatal/Life-threatening' intracranial non-procedural bleeding events with BRILINTA occurred in 26 patients, of which 11 bleeding events were fatal.

Baseline characteristics including age, gender, weight, race, geographic region, medical history, concurrent conditions and concomitant therapy were assessed to explore any increase in risk of bleeding with BRILINTA. No particular risk group was identified for any subset of bleeding.

Dyspnoea:

Dyspnoea commonly occurs during treatment with BRILINTA although its mechanism

has not been elucidated. Dyspnoea adverse events (AEs) (dyspnoea, dyspnoea at rest, exertional dyspnoea, paroxysmal nocturnal dyspnoea, and nocturnal dyspnoea), when combined, occurred in 13,8 % of patients taking BRILINTA in the phase 3 study. The study did not exclude patients with underlying congestive heart failure (CHF), chronic obstructive pulmonary disorder (COPD), or asthma. Most of the dyspnoea adverse events were mild to moderate in intensity. Dyspnoea serious adverse events occurred in 0,7 % taking BRILINTA. Dyspnoea usually occurred in the initial phase of treatment. Eighty-seven percent of patients taking BRILINTA that had dyspnoea experienced a single episode. Approximately 30 % of all dyspnoea resolved within 7 days. Patients who had dyspnoea tended to be older and more frequently had dyspnoea, CHF, COPD, or asthma at baseline. Clinical data do not suggest that the occurrence of dyspnoea with BRILINTA is due to new or worsening heart or lung disease (see "*Warnings and Special Precautions*").

In patients who underwent pulmonary function testing in the clinical programme, there was no indication of an adverse effect of BRILINTA on pulmonary function.

Laboratory abnormalities:
In the phase 3 clinical study, serum uric acid concentration increased to more than upper limit of normal in 22 % of patients receiving BRILINTA.

Mean serum uric acid concentration increased approximately 15 % with BRILINTA and reduced after treatment was stopped.

In the phase 3 clinical study, serum creatinine concentration increased by > 50 % in 8 % of patients receiving BRILINTA. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Signs of reversibility on discontinuation were observed even in those with the greatest on treatment increases.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
There is no known antidote to reverse the effects of BRILINTA, and BRILINTA is not expected to be dialysable (see "*Warnings and Special Precautions*"). Treatment of overdose should follow local standard medical practice. The expected effect of excessive BRILINTA dosing is increased bleeding risk associated with platelet inhibition. If

bleeding occurs appropriate supportive measures should be taken.

BRILINTA 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 effects which may occur with overdose include dyspnoea and ventricular pauses. In the event of overdose, observe for these potential adverse effects and consider ECG monitoring.

IDENTIFICATION:

Round, biconvex, yellow, film-coated tablets. The tablets are marked with "90" above "T" on one side and plain on the other.

PRESENTATION:

BRILINTA is packed in clear PVC/PVDC aluminium foil blister packs in cartons of 14, 56, 60, 168 or 180 tablets.
Packs of 14, 56 and 168 tablets contain 14 tablets per blister.
Packs of 60 and 180 tablets contain 20 tablets per blister.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.
Do not remove the blisters from the outer carton until required for use.
Keep out of reach of children.

REGISTRATION NUMBER:

44/8.2/1041

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

AstraZeneca Pharmaceuticals (Pty) Limited
Building 2, Northdowns Office Park
17 Georgian Crescent West,
Bryanston
2191

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