Summary of Product Characteristics
BRILINTA 90 mg
(Ticagrelor 90 mg film-coated tablets)

1. Name of the medicinal product

Brilinta 90 mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 90 mg of ticagrelor.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

Round, biconvex, yellow film-coated tablet, marked with ‘90’ above ‘T’ on one side and plain on the reverse.

4. Clinical particulars

4.1 Therapeutic indications

Brilinta, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (unstable angina, non-ST-elevation myocardial infarction [NSTEMI] or ST-elevation myocardial infarction [STEMI]), including patients managed medically and those managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

4.2 Posology and method of administration

Posology

Treatment should be started with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily. Patients taking Brilinta should also take ASA daily, unless specifically contraindicated, at a maintenance dose of 75–150 mg. Treatment for up to 12 months is recommended unless discontinuation is clinically indicated. A missed dose should be managed by taking only the next dose at its scheduled time; a double dose should not be taken to make up for a missed dose.

Special populations

No dose adjustment is necessary in the elderly or in patients with renal impairment. Ticagrelor has not been studied in patients on dialysis. Ticagrelor is contraindicated in patients with severe hepatic impairment and should be used with caution in moderate hepatic impairment.

Paediatric population

The safety and efficacy of ticagrelor in children below 18 years of age have not been established.

Method of administration

For oral use, with or without food. For patients unable to swallow the tablet whole, it may be crushed to a fine powder, mixed in water and drunk immediately.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active pathological bleeding.
- History of intracranial haemorrhage.
- Severe hepatic impairment.
- Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, atazanavir), as this may lead to a substantial increase in ticagrelor exposure.

4.4 Special warnings and precautions for use

Bleeding risk

The use of ticagrelor in patients at known increased risk of bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. Ticagrelor should be used with caution in patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, or active or recent gastrointestinal bleeding), and in patients receiving medicines that may increase the risk of bleeding. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, ticagrelor should be discontinued 5 days before surgery.

Dyspnoea

Dyspnoea has been reported in patients treated with ticagrelor. It is usually mild to moderate and often resolves without the need to discontinue treatment. Patients with asthma or chronic obstructive pulmonary disease may have an increased absolute risk; ticagrelor should be used with caution in these patients.

Cardiac and other precautions

Ticagrelor may cause ventricular pauses and bradyarrhythmias; caution is advised in patients at increased risk of bradycardic events (e.g. sick sinus syndrome without a pacemaker, second- or third-degree AV block, or bradycardia-related syncope). Increases in serum creatinine and uric acid may occur; renal function and, in patients with a history of hyperuricaemia or gouty arthritis, uric acid should be monitored. Ticagrelor should be discontinued in patients with hepatic events suggestive of drug-induced liver injury.

4.5 Interaction with other medicinal products and other forms of interaction

Ticagrelor is a substrate and a weak inhibitor of CYP3A4 and of the P-glycoprotein transporter. Co-administration with strong CYP3A4 inhibitors is contraindicated, and with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine) is discouraged, as it may reduce ticagrelor efficacy. Ticagrelor may increase the exposure of CYP3A4 substrates with a narrow therapeutic index (e.g. simvastatin, lovastatin — doses above 40 mg should be avoided) and of P-gp substrates such as digoxin (monitoring recommended). Maintenance doses of ASA above 150 mg should be avoided. Caution is advised with other antiplatelet or anticoagulant medicines and with medicines known to cause bradycardia.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of ticagrelor in pregnant women. Ticagrelor is not recommended during pregnancy. Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during treatment.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of ticagrelor and its active metabolites in milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

Fertility

Ticagrelor had no effect on male or female fertility in animal studies.

4.7 Effects on ability to drive and use machines

Ticagrelor has no or negligible influence on the ability to drive and use machines. Dizziness and confusion have been reported; patients who experience these symptoms should be cautious while driving or using machines.

4.8 Undesirable effects

The most commonly reported adverse reactions are bleeding events and dyspnoea. The adverse reactions are listed below by System Organ Class and frequency, defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reaction
Neoplasms benign, malignant and unspecified	Uncommon	Tumour bleedings
Blood and lymphatic system disorders	Very common	Blood disorder bleedings
	Not known	Haemolytic uraemic syndrome
Immune system disorders	Uncommon	Hypersensitivity including angioedema
Metabolism and nutrition disorders	Common	Hyperuricaemia
	Uncommon	Gout / gouty arthritis
Psychiatric disorders	Uncommon	Confusion
Nervous system disorders	Common	Dizziness, syncope, headache
	Uncommon	Intracranial haemorrhage, paraesthesia
Eye disorders	Uncommon	Eye haemorrhage (conjunctival, retinal, intraocular)
Ear and labyrinth disorders	Common	Vertigo
	Uncommon	Ear haemorrhage
Vascular disorders	Common	Hypotension
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea
	Common	Respiratory-system bleedings (epistaxis, haemoptysis)
Gastrointestinal disorders	Common	Gastrointestinal haemorrhage, diarrhoea, nausea, dyspepsia, constipation
	Uncommon	Retroperitoneal haemorrhage
Skin and subcutaneous tissue disorders	Common	Subcutaneous or dermal bleeding, rash, pruritus
Musculoskeletal and connective tissue disorders	Uncommon	Muscle haemorrhage
Renal and urinary disorders	Common	Urinary-tract bleeding
	Not known	Renal failure
Reproductive system and breast disorders	Uncommon	Reproductive-system bleeding
Investigations	Common	Blood creatinine increased
Injury, poisoning and procedural complications	Common	Post-procedural haemorrhage, traumatic bleedings

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the National Regulatory Authority.

4.9 Overdose

Ticagrelor overdose may lead to bleeding and to gastrointestinal adverse reactions or ventricular pauses. There is currently no known antidote to reverse the effects of ticagrelor, and ticagrelor is not expected to be dialysable. Treatment of overdose should follow local standard medical practice; the expected effect of excessive ticagrelor dosing is prolonged duration of the bleeding-risk associated with platelet inhibition. Platelet transfusion is unlikely to be of clinical benefit in patients with bleeding. Bleeding should be managed with appropriate supportive measures.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excluding heparin. ATC code: B01AC24.

Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines and is an oral, direct-acting, selective and reversibly binding P2Y12 receptor antagonist that prevents ADP-mediated P2Y12-dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but, when bound to the P2Y12 receptor, prevents ADP-induced signal transduction. Because platelet activation and aggregation contribute to the pathogenesis of atherothrombotic events, ticagrelor reduces the incidence of such events in patients with acute coronary syndromes.

5.2 Pharmacokinetic properties

Ticagrelor is rapidly absorbed, with a median time to peak concentration of about 1.5 hours, and has a mean absolute bioavailability of about 36%. It forms an active metabolite (AR-C124910XX) which is also pharmacologically active. Ticagrelor and its active metabolite are extensively bound to plasma proteins (>99%). Ticagrelor is metabolised principally by CYP3A4, and is eliminated mainly via hepatic metabolism; the mean elimination half-life is approximately 7 hours for ticagrelor and 8.5 hours for the active metabolite.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single- and repeated-dose toxicity, and genotoxicity. Gastrointestinal effects were observed in animals at clinically relevant exposures. Ticagrelor was not carcinogenic in the mouse and produced tumours of uncertain human relevance in the rat only at high exposures.

6. Pharmaceutical particulars

6.1 List of excipients

The full quantitative list of excipients should be confirmed from the applicant's finished-product formulation (3.2.P.1); for the tablet core this typically includes mannitol, dibasic calcium phosphate dihydrate, sodium starch glycolate, hydroxypropylcellulose and magnesium stearate, and for the film coat hypromellose, titanium dioxide, macrogol, talc and iron oxide yellow. Any excipient of known effect present must additionally be declared in section 2 and warned in section 4.4.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

To be confirmed from the applicant's stability data.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Keep out of the reach and sight of children.

6.5 Nature and contents of container

Push-through blister of clear (transparent) unplasticised polyvinyl chloride (PVC) film-coated with polyvinylidene chloride (PVDC), sealed to a hard aluminium foil lidding, presented in a carton together with the package insert.

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

AstraZeneca UK Limited.

Manufacturer

AstraZeneca AB, Sweden.

8. Marketing Authorisation Number

H2013/CTD472/339/R1

9. Date of first authorisation / renewal of the authorisation

10. Date of revision of the text