For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

PRESCRIBING INFORMATION

1. PRODUCT NAME

Combikit of Ticagrelor Tablets IP 90 mg & Aspirin Gastro-Resistant Tablets IP 75 mg

Tiare Kit टियरे किट

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Kit Contains:

(A) 14 Ticagrelor Tablets IP 90 mg
Each film coated tablet contains:
Ticagrelor IP 90 mg
Excipients q.s.
Colours: Ferric Oxide Yellow USP-NF & Titanium Dioxide IP

(B) 7 Aspirin Gastro-Resistant Tablets IP 75 mg
Each enteric coated tablet contains:
Aspirin IP 75 mg
Excipients q.s.
Colour: Sunset Yellow FCF & Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH

Ticagrelor is available as 90 mg film coated tablets
Aspirin is available as 75 mg gastro resistant tablets.

4. CLINICAL PARTICULARS

4.1. Indications
Tiare Kit (contains Ticagrelor tablets 90mg, and Aspirin tablets 75mg) is indicated for the prevention of atherothrombotic events in adult patients with
- acute coronary syndromes (ACS) or
- a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

4.2. Posology and Method of Administration
The recommended dose of the Tiare Kit is one tablet of (A) Ticagrelor 90mg, one tablet of (B) Aspirin 75 mg shall be administered at day time and one tablet of (A) Ticagrelor 90mg shall be administered at night time. (See blister for the dosage directions)

Ticagrelor can be administered with or without food. For patients who are unable to swallow tablets whole, Ticagrelor tablets can be crushed, mixed with water and drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater).

Aspirin tablets 75mg is for oral administration to adults only. Take the tablet with water, do not cut, chew or crush the tablet. Swallow whole.

Ticagrelor:

Dosing
Administer 90mg twice daily during the first year after an ACS event.

Do not administer Ticagrelor with another oral P2Y12 platelet inhibitor.

Use Ticagrelor with a daily maintenance dose of aspirin of 75 mg. A patient who misses a dose of Ticagrelor should take one tablet (their next dose) at its scheduled time.

Missed dose
Lapses in therapy should also be avoided. A patient who misses a dose of Ticagrelor should take only one tablet (their next dose) at its scheduled time.

Aspirin

For the management of cardiovascular or cerebrovascular disease

Patients should seek the advice of a doctor before commencing therapy for the first time. The usual dosage, for long-term use, is 75-150 once daily. In some circumstances a higher dose may be appropriate, especially in the short term, and up to 300mg a day may be used on the advice of a doctor. In general, acetylsalicylic acids should be used with caution in elderly patients who are more prone to adverse events. The usual adult dose is recommended in the absence of severe renal or hepatic insufficiency. Treatment should be reviewed at regular intervals.

Antithrombotic action

150mg at diagnosis and 75mg daily thereafter. Tablets taken at diagnosis should be chewed in order to gain rapid absorption.

Children

Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).

4.3. Contraindications

Ticagrelor:
- History of Intracranial Hemorrhage

Ticagrelor is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population.
- Active Bleeding

Ticagrelor is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.
- Hypersensitivity

Ticagrelor is contraindicated in patients with hypersensitivity (e.g., angioedema) to ticagrelor or any component of the product.
- Severe hepatic impairment
- Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor.

Aspirin:
- Hypersensitivity to salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint and certain patients who may suffer from bronchospasm, rhinitis and urticaria), or to any of the excipients.
- Active or history of peptic ulceration and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages.
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia or concurrent anticoagulant therapy.
- Patients who are suffering from gout.
- Severe hepatic impairment.
- Severe renal impairment.
- Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).
- Doses >100 mg/day during the third trimester of pregnancy (see section 4.6); Methotrexate used at doses >15mg/week.

4.4. Special Warnings and Precautions for Use

Ticagrelor:

General Risk of Bleeding
Drugs that inhibit platelet function including Ticagrelor increase the risk of bleeding.
If possible, manage bleeding without discontinuing Ticagrelor. Stopping Ticagrelor increases the risk of subsequent cardiovascular events.

Concomitant Aspirin Maintenance Dose
After the initial loading dose of aspirin, use Ticagrelor with a maintenance dose of aspirin of 75 100 mg.

Dyspnea
If a patient develops new, prolonged, or worsened dyspnea that is determined to be related to Ticagrelor, no specific treatment is required; continue Ticagrelor without interruption if possible. In the case of intolerable dyspnea requiring discontinuation of Ticagrelor, consider prescribing another antiplatelet agent.

Discontinuation of Ticagrelor
Discontinuation of Ticagrelor will increase the risk of myocardial infarction, stroke, and death. If Ticagrelor must be temporarily discontinued (e.g., to treat bleeding or for significant surgery), restart it as soon as possible. When possible, interrupt therapy with Ticagrelor for five days prior to surgery that has a major risk of bleeding. Resume Ticagrelor as soon as hemostasis is achieved.

Bradyarrhythmias
Ticagrelor can cause ventricular pauses. Bradyarrhythmias including AV block have been reported in the postmarketing setting. Patients with a history of sick sinus syndrome, 2nd or 3rd degree AV block or bradycardia-related syncope not protected by a pacemaker may be at increased risk of developing bradyarrhythmias with ticagrelor.

Severe Hepatic Impairment
Avoid use of Ticagrelor in patients with severe hepatic impairment. Severe hepatic impairment is likely to increase serum concentration of ticagrelor.

Laboratory Test Interferences
False negative functional tests for Heparin Induced Thrombocytopenia (HIT). Ticagrelor has been reported to cause false negative results in platelet functional tests (to include, but may not be limited to, the heparin-induced platelet aggregation (HIPA) assay) for patients with Heparin Induced Thrombocytopenia (HIT). This is related to inhibition of the P2Y12-receptor on platelets in the test by ticagrelor in the affected patient's serum/plasma. Information on concomitant treatment with Ticagrelor is required for interpretation of HIT
functional tests. Based on the mechanism of Ticagrelor interference, Ticagrelor is not expected to impact PF4 antibody testing for HIT.

Creatinine elevations
Creatinine levels may increase during treatment with ticagrelor. 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 ticagrelor, 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 ticagrelor. Caution is advised in patients with history of hyperuricaemia or gouty arthritis. As a precautionary measure, the use of ticagrelor in patients with uric acid nephropathy is discouraged.

Thrombotic Thrombocytopenic Purpura (TTP)
Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely with the use of ticagrelor. 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.

Aspirin:
Aspirin 75 mg tablets are not suitable for use as an anti-inflammatory/ analgesic/ antipyretic.
Caution should be exercised in patients with allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration, since the use of NSAIDs may result in deterioration of renal function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Aspirin may also precipitate bronchospasm or induce attacks of asthma in susceptible subjects or promote other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid (see section 4.8). Aspirin Tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

The elderly may be more susceptible to the toxic effects of salicylates. Continuous prolonged use of aspirin should be avoided in the elderly because of the risk of gastrointestinal bleeding and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly.

Caution should be taken in patients with glucose-6-phosphate dehydrogenase deficiency as haemolytic anaemia may occur.

Aspirin 75 mg tablets is not recommended during menorrhagia where it may increase menstrual bleeding.

Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation and therefore it should be discontinued several days before scheduled surgical procedures. Haematological and haemorrhagic effects can occur, and may be severe. Use with caution before surgery, including tooth extraction. Patients should report any unusual bleeding symptoms to their physician.

Care is advised when stopping antiplatelet therapy after stent insertion either after a fixed period of time or in preparation for a planned surgical procedure, as the balance between stent thrombosis and excessive bleeding has to be carefully assessed.

There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason aspirin should not be given to children aged under 16 years unless specifically indicated (e.g. for Kawasaki's disease).

Aspirin is to be used with caution in cases of hypertension and patients with a stomach ulcer or a history of stomach ulcers or duodenal ulcer or haemorrhagic episodes or undergoing therapy with anticoagulants. Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.

Before commencing long term aspirin therapy for the management of cardiovascular or cerebrovascular disease patients should consult their doctor who can advise on the relative benefits versus the risks for the individual patient.

Concomitant treatment with Aspirin and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage. If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin-reuptake inhibitors and Deferasirox.

The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with Aspirin 75mg tablets taken at over dosage.
Aspirin should be avoided in late pregnancy and generally during breast feeding.

4.5. Drug Interactions

Ticagrelor:

Strong CYP3A Inhibitors
Strong CYP3A inhibitors substantially increase ticagrelor exposure and so increase the risk of dyspnea, bleeding, and other adverse events. Avoid use of strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin).

Strong CYP3A Inducers
Strong CYP3A inducers substantially reduce ticagrelor exposure and so decrease the efficacy of ticagrelor. Avoid use with strong inducers of CYP3A (e.g., rifampin, phenytoin, carbamazepine and phenobarbital).

Aspirin:
Use of ticagrelor with aspirin maintenance doses above 100 mg reduced the effectiveness of ticagrelor.

Opioids
As with other oral P2Y12 inhibitors, co-administration of opioid agonists delay and reduce the absorption of ticagrelor and its active metabolite presumably because of slowed gastric emptying. Consider the use of a parenteral anti-platelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

Simvastatin, Lovastatin
Ticagrelor increases serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg.

Digoxin
Ticagrelor inhibits the P-glycoprotein transporter; monitor digoxin levels with initiation of or change in Ticagrelor therapy.

Cyclosporine (P-gp and CYP3A inhibitor)
Co-administration of cyclosporine (600 mg) with ticagrelor increased ticagrelor Cmax and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite was increased by 32% and Cmax was decreased by 15% in the presence of cyclosporine.
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.

Medicinal products metabolised by CYP2C9
Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either medicinal product, which suggests that ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of medicinal products 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 ticagrelor.

Medicinal products known to induce bradycardia
Caution should be exercised when administering ticagrelor concomitantly with medicinal products known to induce bradycardia.

Other concomitant therapy
ticagrelor was commonly administered with ASA, 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. No evidence of clinically significant adverse interactions with these medicinal products 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 ticagrelor with medicinal products 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 ticagrelor as this may increase the risk of bleeding.

Aspirin:

Contraindicated combinations

Methotrexate (used at doses >15 mg/week):
The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with Aspirin 75 mg tablets is contraindicated.

Not recommended combinations

Uricosuric agents, e.g. probenecid and sulfinpyrazone
Salicylates reverse the effect of probenecid and sulfinpyrazone. The combination should be avoided.

Combinations requiring precautions for use or to be taken into account

Anticoagulants e.g. coumarin, heparin, warfarin and phenindione
Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored.

Anti-platelet agents (e.g clopidogrel and dipyridamole) and selective serotonin re-uptake inhibitors (SSRIs; such as sertraline or paroxetine):
Increased risk of gastrointestinal bleeding

Antidiabetics, e.g. sulphonylureas
Salicylics may increase the hypoglycaemic effect of sulphonylureas.

Digoxin and lithium:
Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations.Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.

Diuretics and antihypertensives
NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. Patients with hypertension should be carefully monitored. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency. Diuretics: Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

Other non-steroidal anti-inflammatory drugs (NSAIDs):
Concurrent administration can increase side effects. Use of two or more NSAIDs increases risk of gastrointestinal haemorrhage.

Ibuprofen:
Ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Ciclosporin, tacrolimus
Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

Systemic Corticosteroids:
The risk of gastrointestinal bleeding and ulceration is increased when acetylsalicylic acid and corticostetoids are co-administered (see section 4.4). Corticosteroids reduce the plasma salicylate concentration and salicylate toxicity may occur following withdrawal of corticosteroids.

Methotrexate (used at doses <15 mg/week)
The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

Carbonic anhydrase inhibitors
Reduced excretion of acetazolamide; salicylate intoxication has occurred in patients on high dose salicylate regimes and carbonic anhydrase inhibitors. Concurrent administration of carbonic anhydrase inhibitors such as acetazolamide and salicylates may result in severe acidosis and increased central nervous system toxicity.

Antacids and adsorbents
The excretion of aspirin is increased in alkaline urine; kaolin possibly reduces absorption. Antacids will reduce the effect of aspirin. Principle incompatibilities are iron salts, carbonates and alkali hydroxides.

Mifepristone
The manufacturer of mifepristone recommends that aspirin should be avoided until eight to twelve days after mifepristone has been discontinued.

Alcohol
Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

Antiemetics
Metoclopramide enhances the effects of aspirin by increasing the rate of absorption.

Anti-epileptics
Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered. Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Leukotriene antagonists
The plasma concentration of zafirlukst is increased.

Antibacterials
The toxicity of sulphonamides may be increased.

Thyroid function tests:
Aspirin may interfere with thyroid function tests.

4.6. Use in Special Populations (such as pregnant women, **lactating women, paediatric patients, geriatric patients etc.)**

Ticagrelor:

Pregnancy
Ticagrelor has no drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.
Ticagrelor given to pregnant rats and pregnant rabbits during organogenesis caused structural abnormalities in the offspring at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. When ticagrelor was given to rats during late gestation and lactation, pup death and effects on pup growth were seen at approximately 10 times the MRHD.

Lactation
There are no data on the presence of ticagrelor or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Ticagrelor and its metabolites were present in rat milk at higher concentrations than in maternal plasma. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Breastfeeding is not recommended during treatment with Ticagrelor *[Reference: BRILINTA USFDA Label. Dated Oct-2019].*

Fertility
Ticagrelor had no effect on male or female fertility in animals

Pediatric Use
The safety and effectiveness of Ticagrelor in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness were observed between elderly and younger patients.

Hepatic Impairment
Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Avoid use of Ticagrelor in patients with severe hepatic impairment. There is limited experience with Ticagrelor in patients with moderate hepatic impairment; consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor. No dosage adjustment is needed in patients with mild hepatic impairment.

Renal Impairment
No dosage adjustment is needed in patients with renal impairment.

Patients with End-Stage Renal Disease on dialysis
In patients with ESRD maintained on intermittent hemodialysis, no clinically significant difference in concentrations of ticagrelor and its metabolite and platelet inhibition are expected compared to those observed in patients with normal renal function. It is not known whether these concentrations will lead to similar reductions in risk of CV death, myocardial infarction or stroke or similar bleeding risk in patients with ESRD on dialysis.

Aspirin:

Pregnancy

Low doses (up to 100 mg/day)
Doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100- 500 mg/day
There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension).
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy.
- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- Inhibition of uterine contractions resulting in delayed or prolonged labour.
- Consequently, acetylsalicylic acid at doses of 100 mg/day and higher is contraindicated during the third trimester of pregnancy.

Lactation
As aspirin is excreted in breast milk, Aspirin should not be taken by patients who are breast-feeding, as there is a risk of Reye's syndrome in the infant. High maternal doses may impair platelet function in the infant.

4.7. Effects on Ability to Drive and Use Machines

Ticagrelor:
Ticagrelor has no or negligible influence on the ability to drive and use machines. During treatment with ticagrelor, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

Aspirin:
Aspirin does not usually affect the ability to drive or operate machinery.

4.8. Undesirable Effects

Ticagrelor:

Adverse reactions are listed by MedDRA System Organ Class (SOC). Within each SOC the adverse reactions are ranked by frequency category. Frequency categories are defined according to the following conventions: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	Very common	Common	Uncommon	Rare
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Tumour bleedings[a]	
Blood and lymphatic system disorders	Blood disorder bleedings[b]			Thrombotic Thrombocytopenic Purpura[c]
Immune system disorders			Hypersensitivity including angioedema[c]	
Metabolism and nutrition disorders	Hyperuricaemia[d]	Gout/Gouty Arthritis		
Psychiatric disorders			Confusion	
Nervous system disorders		Dizziness, Syncope, Headache	Intracranial haemorrhage	
Eye disorders			Eye haemorrhage[e]	
Ear and labyrinth disorders		Vertigo	Ear haemorrhage	
Vascular disorders		Hypotension		
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Respiratory system bleedings[f]		
Gastrointestinal disorders		Gastrointestinal haemorrhage[g], Diarrhoea, Nausea, Dyspepsia, Constipation	Retroperitoneal Haemorrhage	
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding[h], Rash, Pruritus		
Musculoskeletal connective tissue and bone			Muscular bleedings[i]	
Renal and urinary disorders		Urinary tract bleeding[j]		
Reproductive system and breast disorders			Reproductive system bleedings[k]	
Investigations		Blood creatinine increased[d]		
Injury, poisoning and procedural complications		Post procedural haemorrhage, Traumatic bleedings[l]		

[a] e.g. bleeding from bladder cancer, gastric cancer, colon cancer
[b] e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis
[c] Identified in post-marketing experience
[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. epistaxis, haemoptysis
[g] e.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage
[h] e.g. ecchymosis, skin haemorrhage, petechiae
[i] e.g. haemarthrosis, muscle haemorrhage
[j] e.g. haematuria, cystitis haemorrhagic
[k] e.g. vaginal haemorrhage, haematospermia, postmenopausal haemorrhage
[l] e.g. contusion, traumatic haematoma, traumatic haemorrhage

Aspirin:
Side effects are grouped on the basis of System Organ Class. Within each system organ class the frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	*Common*: Increased bleeding tendencies. *Rare*: Thrombocytopenia, granulocytosis, aplastic anaemia. *Not known*: Cases of bleeding with prolonged bleeding time such as epistaxis, haematuria, purpura, ecchymoses, haemoptysis, haematoma, cerebral haemorrhage and gingival bleeding. Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Aspirin decreases platelet adhesiveness and, in large doses, may cause hypoprothrombinaemia. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses). Haemolytic anaemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
Immune system disorders	*Rare*: Hypersensitivity reactions, skin rashes, urticarial, asthma, bronchospasm, angio-oedema, allergic oedema, anaphylactic reactions including shock.
Metabolism and digestive system disorders	*Not known*: Hyperuricemia.
Nervous system disorders	*Rare*: Intracranial haemorrhage. *Not known*: Headache, vertigo.
Ear and labyrinth disorders	*Not known*: Reduced hearing ability; tinnitus.
Vascular disorders	*Rare*: Hemorrhagic vasculitis.
Respiratory, thoracic and mediastinal disorders	*Uncommon*: Rhinitis, dyspnoea. *Rare*: Bronchospasm, asthma attacks.
Reproductive System and mammary disorders	*Rare*: Menorrhagia.
Gastrointestinal disorders	*Common*: Dyspepsia. *Rare*: Severe gastrointestinal haemorrhage, nausea, vomiting, gastritis. *Not known*: Gastric or duodenal ulcers and perforation, diarrhoea.
Hepatobiliary disorders	*Not known*: Hepatic insufficiency.
Skin and subcutaneous tissue disorders	*Uncommon*: Urticaria. *Rare*: Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme.
Renal and urinary tract disorders	*Not known*: Impaired renal function, salt and water retention, urate kidney stones.

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. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

Ticagrelor:

There is currently no known treatment to reverse the effects of Ticagrelor, and ticagrelor is not dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.

Platelet transfusion did not reverse the antiplatelet effect of Ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding.

Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

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

Aspirin:

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Symptoms

Common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation.

Some degree of acid-base disturbance is present in most cases.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults or children over the age of four years. In children aged four years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier.

Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.

Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

Treatment

Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate.

The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L) or lower concentrations associated with severe clinical or metabolic features. Patients under ten years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

5. PHARMACOLOGICAL PROPERTIES

Ticagrelor:

5.1 Mechanism of action

Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

Aspirin:

The antiplatelet effect of aspirin is largely unrelated to its systemic bioavailability and its duration of effect does not correlate with the presence of intact salicylic acid in the circulation. The antiplatelet effect is considered to be largely pre-systemic, associated with acetylation of platelet cyclo-oxygenase in the portal circulation.

Aspirin (acetylsalicylic acid) irreversibly acetylates platelet cyclo-oxygenase thereby inhibiting the biosynthesis of thromboxane, a potent vasoconstrictor and inducer of platelet aggregation. It also inhibits the action of cyclo-oxygenase in the vascular endothelial wall preventing the synthesis of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. However, as the endothelial cell is capable of synthesising new cyclo-oxygenase, whereas the platelet is not, the effect on thromboxane is longer lasting.

5.2 Pharmacodynamic Properties

Ticagrelor:

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6-week study examining both acute and chronic platelet inhibition effects in response to 20 µM ADP as the platelet aggregation agonist.

The onset of IPA was evaluated on Day 1 of the study following loading doses of 180 mg ticagrelor or 600 mg clopidogrel. As shown in Figure 3, IPA was higher in the ticagrelor group at all-time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours.

The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 µM ADP.

As shown in figure, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in figure 4 shows that after 24 hours, IPA in the ticagrelor group (58%) was similar to IPA in clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to IPA in the placebo group. It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel.

Fig 1: Mean inhibition of platelet aggregation (±se) following single oral doses of placebo, 180 mg ticagrelor or 600 mg clopidogrel

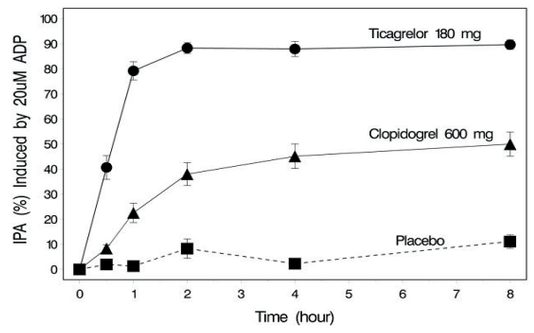
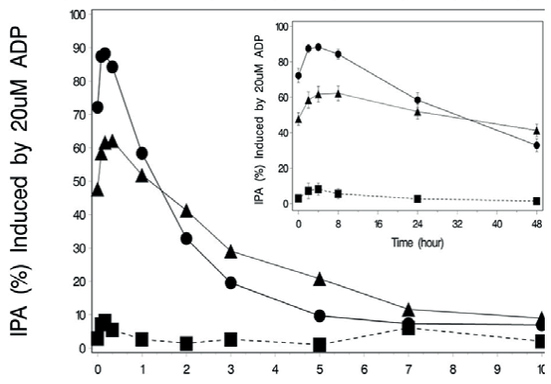


Fig: 2 – Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily Ticagrelor▲ clopidogrel■ placebo



Transitioning from clopidogrel to ticagrelor resulted in an absolute IPA increase of 26.4 and from ticagrelor to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to ticagrelor without interruption of antiplatelet effect *[Reference: BRILINTA USFDA Label. Dated Oct-2019].*

Aspirin:

Due to the low dose enteric-coated formulation of Aspirin 75mg Gastro-Resistant Tablets acetylsalicylic acid is slowly released into the portal circulation and is deacetylated by the liver to inactive salicylate before reaching the systemic circulation. It is postulated that platelets passing through the portal circulation are exposed to acetylsalicylic acid concentrations sufficient to achieve effective thromboxane inhibition, while systemic prostacyclin synthesis remains essentially unaffected.
Ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use

5.3 Pharmacokinetic Properties

Ticagrelor:

Ticagrelor demonstrates dose proportional pharmacokinetics.

Absorption

Ticagrelor can be taken with or without food. Absorption of ticagrelor occurs with a median t_{max} of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median t_{max} of 2.5 h (range 1.5-5.0).

The mean absolute bioavailability of ticagrelor is about 36% (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21% increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and Cmax within 80-125% for ticagrelor and AR-C124910XX) with a median t_{max} of 1.0 hour (range 1.0 – 4.0) for ticagrelor and 2.0 hours (range 1.0 –8.0) for AR-C124910XX.

Distribution

The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (>99%).

Metabolism

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30-40% of the exposure of ticagrelor.

Excretion

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% 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 major metabolite of ticagrelor is most likely to be biliary secretion. The mean t1/2 is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Specific Populations

Elderly

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

Paediatric population

Ticagrelor has not been evaluated in a paediatric population.

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 *[Reference: BRILINTA USFDA Label. Dated Oct-2019].*

Hepatic impairment

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.

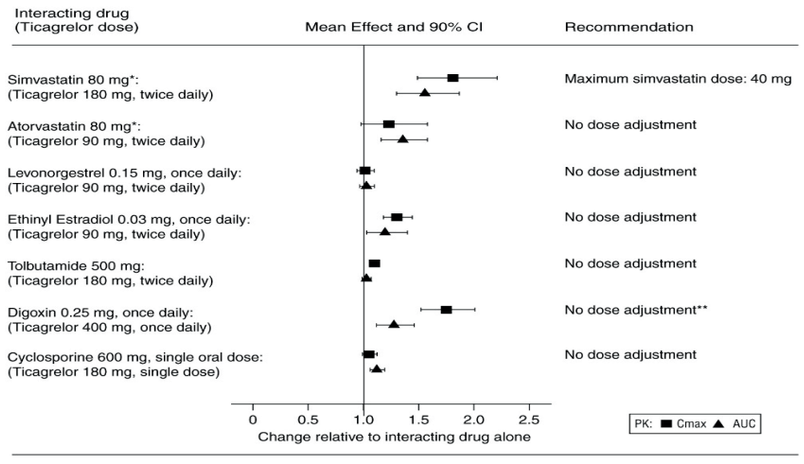
Ethnicity

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 (Cmax and AUC) to ticagrelor in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians. The exposure in patients self-identified as Hispanic or Latino was similar to that in Caucasians.

Effects of Other Drugs on Ticagrelor

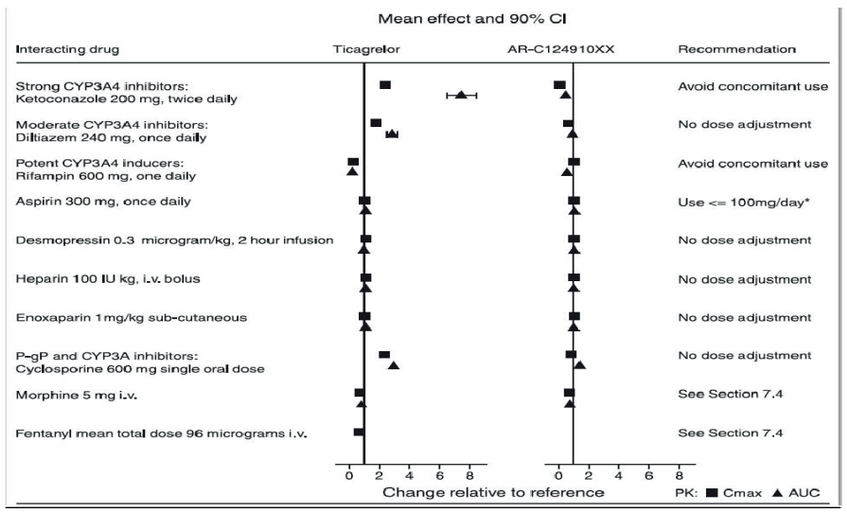
CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. The effects of other drugs on the pharmacokinetics of ticagrelor are presented in Figure 6 as change relative to ticagrelor given alone (test/reference). Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors have lesser effects (e.g., diltiazem). CYP3A inducers (e.g., rifampin) substantially reduce ticagrelor blood levels. P-gp inhibitors (e.g., cyclosporine) increase ticagrelor exposure.

Fig 3: effect of co-administered drugs on the pharmacokinetics of ticagrelor



Effects of Ticagrelor on Other Drugs

Ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the P-gp transporter. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity *[Reference: BRILINTA USFDA Label. Dated Oct-2019].*



*Similar increases in AUC and Cmax were obsereved for all metabolites
**Monitor digoxin levels with initiation of or change in Ticagrelor therapy

Fig 4: impact of ticagrelor on the pharmacokinetics of co-administered drugs

Aspirin:

Aspirin is rapidly absorbed after oral administration of conventional release preparations, with some hydrolysis to salicylate before absorption. Absorption is delayed by the presence of food and is impaired in patients suffering migraine attacks.

Absorption is more rapid in patients with achlorhydria and also following administration of polysorbates and antacids. Plasma concentrations of the drug increase disproportionately to the dose; e.g. a 325 mg dose having a half-life of 2-3 hours and higher doses showing lower plasma concentrations in the presence of an increased half-life due to a disproportionate increase in the volume of distribution.

Aspirin is found in saliva, milk, plasma and synovial fluid at concentrations less than in blood and crosses the placenta. Salicylate/protein binding extensive. Aspirin/protein binding to a small extent. In the blood, rapid hydrolysis to salicylic acid; glucuronic acid/glycine conjugation to form glucuronides and salicyluronic acid. Salicylate reabsorbed by renal tubules in acid urine, and alkaline diuresis will increase the rate of excretion; 85% of dose excreted as free salicylate.

The absolute bioavailability of aspirin from Aspirin 75mg Gastro-Resistant Tablets (compared with intravenous aspirin solution) is approximately 25%.

6. NONCLINICAL PROPERTIES

Ticagrelor:

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29-fold the maximally recommended dose of 90 mg twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

Mutagenesis

Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility

Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC) *[Reference: BRILINTA USFDA Label. Dated Oct-2019].*

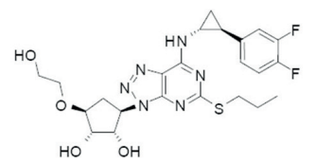
Aspirin:

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Prescribing Information.

7. DESCRIPTION

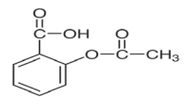
Ticagrelor:

Ticagrelor contains ticagrelor, a cyclopentyltriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor. Chemically it is (1S,2S,3R,5S)-3- [7 [[(1R,2S)-2-(3,4-difluorophenyl) cyclopropyl] amino]-5-propylsulfanyltriazolo [4,5 d] pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1,2-diol. The empirical formula of ticagrelor is $C_{23}H_{28}F_2N_6O_4S$ and its molecular weight is 522.57. The chemical structure of ticagrelor is:



Aspirin:

Aspirin is an orally administered non-steroidal anti-inflammatory agent. Chemically it is 2-acetyloxybenzoic acid. The empirical formula of Aspirin is $C_9H_8O_4$. It's molecular weight is 180.16 g/mol. The chemical structure of Aspirin is:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None

8.2 Packing Information

Each combikit contains 14 tablets of (A) Ticagrelor Tablets IP 90 mg and 7 tablets of (B) Aspirin Gastro-Resistant Tablets IP 75 mg in Strip Pack.

8.3 Storage and Handling Instructions

Store at a temperature not exceeding 30°C, Protect from light & moisture.

9. PATIENT COUNSELING INFORMATION

Ticagrelor:

Advise the patient to read package insert.
Advise patients daily doses of aspirin should not exceed 100 mg and to avoid taking any other medications that contain aspirin.
Advise patients that they:

- Will bleed and bruise more easily.
- Will take longer than usual to stop bleeding.
- Should report any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine.

Advise patients to contact their doctor if they experience unexpected shortness of breath, especially if severe.

Advise patients to inform physicians and dentists that they are taking Ticagrelor before any surgery or dental procedure.

Advise women that breastfeeding is not recommended during treatment with Ticagrelor.

Aspirin:

Advise the patient to read package insert.
Discuss the following with patients prior to initiating treatment with Aspirin and periodically during the course of ongoing treatment.

Bleeding

- Inform patients that they may bruise or bleed more easily or that it may take longer to stop bleeding and to report to their physician any prolonged, unusual or excessive bleeding. Inform patients to notify their physician about blood in their stool or urine and the signs and symptoms of occult bleeding.
- Inform patients about the signs and symptoms of GI side effects and seek medical advice when experiencing any of these signs and symptoms.

Hypersensitivity

- Advise the patient to discontinue Aspirin and seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction occur.

Alcohol Consumption

- Inform patients they should not take Aspirin 2 hours before or 1 hour after consuming alcohol. Counsel patients who drink three or more alcoholic drinks every day about the risk of bleeding involved in chronic, heavy alcohol use while taking Aspirin.

Administration Instructions

- Advise patients to swallow Aspirin capsules whole and not to chew or crush them.
- Remind patients not to discontinue Aspirin without first notifying and discussing with their physician. Advise patients not to use extra medicine to make up a missed dose.
- Advise patients not to take ibuprofen around the same time as Aspirin.

Pregnancy and Lactation

- Advise patients that ASA containing products such as Aspirin cause harm to fetuses especially during the third trimester of pregnancy. Inform patients to notify their physician if they are pregnant, plan to become pregnant, breastfeed or are considering breastfeeding prior or during receiving treatment with Aspirin.

10. DETAILS OF MANUFACTURER

Manufactured by:
Mascot Health Series Pvt. Ltd.
Plot No. 79,80, Sec-6A, IIE, Sidcul,
Haridwar-249403

Marketed by :
MSN LABORATORIES PRIVATE LIMITED,
MSN House, Plot No. C-24, Industrial Estate,
Sanath Nagar, Hyderabad - 500 018, Telangana, India

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg. Lic. No.: 68/UA/2009

12. DATE OF REVISION

JAN 2022

13. Shelf life

Refer the carton for shelf life details.

MFLL0001-00