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

Ticastro-AS

(COMBIKIT OF TICAGRELOR TABLETS 90 mg AND ASPIRIN GASTRO-RESISTANT TABLETS IP 75 mg)

COMPOSITION:
Each Kit Contains:
A) 14 Ticagrelor Tablets IP 90 mg
Each film coated tablet contains:
Ticagrelor IP 90 mg
Colours: Ferric Oxide Yellow USP-NF & Titanium Dioxide IP
Excipients: Q.S.
B) 7 Aspirin Gastro-resistant Tablets IP 75 mg
Each enteric coated tablet contains:
Aspirin IP 75 mg
Colours: Lake of Sunset Yellow FCF & Titanium Dioxide IP
Excipients: Q.S.

1 DOSAGE FORM AND STRENGTH: TABLETS
- Ticagrelor Tablets 90 mg
- Aspirin Gastro-resistant Tablets IP 75 mg

2 CLINICAL PARTICULARS
2.1 Therapeutic indications
For the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with acute coronary syndromes (ACS) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG) where both ticagrelor and aspirin are required.
2.2 Posology and method of administration
After an ACS event, administer one tablet of ticagrelor 90 mg twice daily and one tablet of aspirin 75mg once daily.
It is for oral use only. Do not crush, cut or chew tablets. Swallow whole.
Ticagrelor can be administered with or without food. Aspirin tablets should preferably be taken after meals, with plenty of liquid.
Do not administer ticagrelor with another oral P2Y12 platelet inhibitor.
2.3 Contraindications
- Hypersensitivity to the ticagrelor or acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics or antipyretics or 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 pathological bleeding.
- 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 inexposure to ticagrelor.
- Active, or history of peptic ulceration and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular or intracranial haemorrhages.
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopeniaor 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; Methotrexate used at doses >15mg/week.

2.4 SpecialWarnings and PrecautionsFor Use
Ticagrelor
Bleeding risk
The use of ticagrelor in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. If clinically indicated, ticagrelor should be used with caution in the following patient groups:
- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding). The use of ticagrelor is contraindicated in patients with active pathological bleeding, in those with a history of intracranial haemorrhage, and in patients with severe hepatic impairment.
- 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 ticagrelor dosing.

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. Since co-administration of ticagrelor with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.
Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may increase haemostasis. Ticagrelor may be resumed after the cause of bleeding has been identified and controlled.
Surgery
Patients should be advised to inform physicians and dentists that they are taking ticagrelor before any surgery is scheduled and before any new medicinal product is taken.
In clinical trial with patients undergoing coronary artery bypass grafting (CABG), ticagrelor had more bleeding than clopidogrel when stopped within 1 day prior to surgery but a similar rate of major bleeds compared to clopidogrel after stopping therapy 2 or more days before surgery. If a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be discontinued 5 days prior to surgery.
Patients with prior ischaemic stroke
ACS patients with prior ischaemic stroke can be treated with ticagrelor for up to 12 months.In clinical trial, patients with history of MI with prior ischaemic stroke were not included. Therefore, in the absence of data, treatment beyond one year is not recommended in these patients.
Hepatic impairment
Use of ticagrelor is contraindicated in patients with severe hepatic impairment. There is limited experience with ticagrelor in patients with moderate hepatic impairment, therefore, caution is advised in these patients.
Patients at risk for bradycardic events
Holter ECG monitoring has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel. Patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) have been excluded from the main studies evaluating the safety and efficacy of ticagrelor. Therefore, due to the limited clinicalexperience, ticagrelor should be used with caution in these patients.
In addition, caution should be exercised when administering ticagrelor concomitantly with medicinal products known toinduce bradycardia. However, no evidence of clinically significant adverse reactions was observed in the clinical trialafter concomitant administration with one or more medicinal products known to induce bradycardia (e.g. 96% betablockers, 33% calcium channel blockers diltiazem and verapamil and 4% digoxin).
During the Holter substudy in clinical trial, more patients had ventricular pauses ≥3 seconds with ticagrelor than withclopidogrel during the acute phase of their ACS. The increase in Holter-detected ventricular pauses with ticagrelor washigher in patients with chronic heart failure (CHF) than in the overall study population during the acute phase of ACS, butnot at one month with ticagrelor or compared to clopidogrel. There were no adverse clinical consequences associatedwith this imbalance (including syncope or pacemaker insertion) in this patient population.
Dyspnoea
Dyspnoea was reported in patients treated with ticagrelor. Dyspnoea is usually mild to moderate in intensity and oftenresolves without need for treatment discontinuation. Patients with asthma/chronic obstructive pulmonary disease(COPD) may have an increased absolute risk of experiencing dyspnoea with ticagrelor. Ticagrelor should be used withcaution in patients with history of asthma and/or COPD. The mechanism has not been elucidated.If a patient reportsnew, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with ticagrelorshould be stopped.
Creatinine elevations
Creatinine levels may increase during treatment with ticagrelor. The mechanism has not been elucidated. Renal functionshould be checked according to routine medical practice. In patients with ACS, it is recommended that renal function isalso 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 receptorblocker (ARB).
Uric acid increase
Hyperuricaemia may occur during treatment with ticagrelor. Caution is advised in patients with historyof hyperuricaemia or gouty arthritis. As a precautionary measure, the use of ticagrelor in patients with uric acidnephropathy is discouraged.
Thrombotic Thrombocytopenic Purpura (TTP)
Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely with the use of ticagrelor. It is characterized by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renaldysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.
Interference with platelet function tests to diagnose heparin induced thrombocytopenia (HIT)
In the heparin induced platelet activation (HIPA) test used to diagnose HIT, anti-platelet factor 4/heparin antibodies inpatient serum activate platelets of healthy donors in the presence of heparin.
False negative results in a platelet function test (to include, but may not be limited to the HIPA test) for HIT have beenreported in patients administered ticagrelor. This is related to inhibition of the P2Y12-receptor on the healthy donorplatelets in the test by ticagrelor in the patient's sera/plasma. Information on concomitant treatment with ticagrelor isrequired for interpretation of HIT platelet function tests.
In patients who have developed HIT, the benefit-risk of continued treatment with ticagrelor should be assessed, taking both the prothrombotic state of HIT and the increased risk of bleeding with concomitant anticoagulant and ticagrelor treatment into consideration.
Other
Based on a relationship observed in clinical trial between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of ticagrelor and high maintenance dose ASA (>300 mg) is not recommended.
Premature discontinuation
Premature discontinuation with any antiplatelet therapy could result in an increased risk of cardiovascular (CV) death, MI or stroke due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided.
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. 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.
Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks.
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.
2.5 Drug Interactions
Ticagrelor
Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CYP3A4. Ticagrelor is also a P-glycoprotein (P-gp)substrate and a weak P-gp inhibitor and may increase the exposure of P-gp substrates.
Effects of medicinal and other products on ticagrelor
CYP3A4 inhibitors
- Strong CYP3A4 inhibitors – Co-administration of ketoconazole with ticagrelor increased the ticagrelor C_{max} and AUCequal 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, nefazodone, ritonavir, and atazanavir) would be expected to have similar effects and therefore concomitant use of strong CYP3A4 inhibitors with ticagrelor is contraindicated.
- Moderate CYP3A4 inhibitors – Co-administration of diltiazem with ticagrelor increased the ticagrelor C_{max} by 69% andAUC to 2.7-fold and decreased the active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, erythromycin and fluconazole) would be expected to have a similar effect and can as well be co-administered with ticagrelor.
- A 2-fold increase of ticagrelor exposure was observed after daily consumption of largequantities of grapefruit juice(3x200 ml). This magnitude of increased exposure is not expected to be clinically relevant to most patients.

CYP3A inducers
Co-administration of rifampicin with ticagrelor decreased ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of the active metabolite was unchanged and the AUC was decreased by 46%, respectively. Other CYP3A inducers(e.g. phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to ticagrelor as well.
Co-administration of ticagrelor with potent CYP3A inducers may decrease exposure and efficacy of ticagrelor, therefore,their concomitant use with ticagrelor is discouraged.
Cyclosporine (P-gp and CYP3A inhibitor)
Co-administration of cyclosporine (600 mg) with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite was increased by 32% and C_{max} was decreased by 15% in thepresence of cyclosporineand moderate CYP3A4 inhibitors (e.g. verapamil, quinidine) that also may increase ticagrelor exposure. If theassociation cannot be avoided, their concomitant use should be made with caution.
Others
Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin and ASAor desmopressin did not have any effect on the pharmacokinetics of ticagrelor or the active metabolite or on ADPinducedplatelet aggregation compared with ticagrelor alone. If clinically indicated, medicinal products that alterhaemostasis should be used with caution in combination with ticagrelor.
A delayed and decreased exposure to oral P2Y12 inhibitors, including ticagrelor and its active metabolite, has beenobserved in patients with ACS treated with morphine (35% reduction in ticagrelor exposure). This interaction may berelated to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but dataindicate the potential for reduced ticagrelor efficacy in patients co-administered ticagrelor and morphine. In patients withACS, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12inhibitor may be considered.
Effects of ticagrelor on other medicinal products
Medicinal products metabolised by CYP3A4
- *Simvastatin* – Co-administration of ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56%and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2- to 3-fold. Coadministrationof ticagrelor with doses of simvastatin exceeding 40 mg daily could cause adverse reactions ofsimvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasmalevels. Ticagrelor may have similar effect on lovastatin. The concomitant use of ticagrelor with doses of simvastatin orlovastatin greater than 40 mg is not recommended.
- *Atorvastatin* - Co-administration of atorvastatin and ticagrelor increased atorvastatin acid C_{max} by 23% and AUC by36%. Similar increases in AUC and C_{max} were observed for allatorvastatin acid metabolites. These increases are notconsidered clinically significant.
- A similar effect on other statins metabolised by CYP3A4 cannot be excluded. Patients inPLATO receiving ticagrelortook a variety of statins, with no concern of an association with statin safety among the 93% of the PLATO cohort takingthese medicinal products.

Ticagrelor is a mild CYP3A4 inhibitor. Co-administration of ticagrelor and CYP3A4 substrates with narrow therapeuticindices (i.e. cisapride or ergot alkaloids) is not recommended, asticagrelor may increase the exposure to these medicinal products.
P-gp substrates (including digoxin, cyclosporine)
Concomitant administration of ticagrelor increased the digoxin C_{max} by 75% and AUC by 28%. The mean trough digoxinlevels were increased about 30% with ticagrelor co-administration with some individual maximum increases to 2 fold. Inthe presence of digoxin, the C_{max} and AUC of ticagrelor and its active metabolite were not affected. Therefore,appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependentmedicinal products like digoxin concomitantly with ticagrelor.
There was no effect of ticagrelor on cyclosporine blood levels. Effect of ticagrelor on other P-gp substrates has not beenstudied.
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 ofmedicinal products like warfarin and tolbutamide.
Oral contraceptives
Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased ethinyl estradiol exposureapproximately 20% but did not alter the pharmacokinetics of levonorgestrel. No clinically relevant effect on oralcontraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with ticagrelor.
Medicinal products known to induce bradycardia
Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised whenadministering ticagrelor concomitantly with medicinal products known to induce bradycardia. However,no evidence of clinically significant adverse reactions was observed in the PLATO trial after concomitant administrationwith one or more medicinal products known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channelblockers diltiazem and verapamil and 4% digoxin).
Other concomitant therapy
In clinical studies, 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 conditionsfor long-term and also heparin, low molecular weight heparin and intravenous GpIIb/IIIa inhibitors for short durations. No evidence ofclinically significant adverse interactions with these medicinal products was observed. Co-administration of ticagrelor with heparin, enoxaparin or desmopressin had no effect on activated partialthromboplastin time (aPTT), activated coagulation time (ACT) or factor Xa assays. However, due to potentialpharmacodynamic interactions, caution should be exercised with the concomitant administration of ticagrelor withmedicinal products known to alter haemostasis.
Due to reports of cutaneous bleeding abnormalities with SSRIs (e.g. paroxetine, sertraline and citalopram), caution isadvised 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:
Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply 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.
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 coadministered. 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 zafirlukast is increased.
Antibacterials:
The toxicity of sulphonamides may be increased.
Thyroid function tests:
Aspirin may interfere with thyroid function tests.
2.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.)
Ticagrelor
Women of childbearing potential/Contraception in males and females
Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during ticagrelor therapy.
Pregnancy
There are no or limited amount of data from the use of ticagrelor in pregnant women. Studies in animals have shown reproductive toxicity. Ticagrelor is not recommended during pregnancy.
Breast-feeding
Available pharmacodynamic/toxicological data in animals have shown excretion of ticagrelor and its active metabolites in milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ticagrelor therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Fertility
Ticagrelor had no effect on male or female fertility in animals.
Aspirin
Pregnancy
Low doses (up to 100 mg/day):
Clinical studies indicate that 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. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.
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.
Breastfeeding
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.
2.7 Effects on ability to drive and use machines
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 does not usually affect the ability to drive or operate machinery.
2.8 Undesirable effects
Ticagrelor
The most commonly reported adverse reactions in patients treated with ticagrelor in clinical trials were bleeding and dyspnoea.
The most commonly reported (very common [≥1/10] and common [≥1/100 to <1/10]) and and/or clinically relevant treatment-related adverse drug reactions (ADRs) were blood disorder bleedings, hyperuricemia, gout/gouty

	Checked by				Approved by
Department	PMQC	R.A.	Packing Dev.	Q.A.	Head Q.A.
Signature					
Date					

Product Name : Ticastro-AS
Size : 125 x 580 (mm) Front Side
No. of Col. : 1
Date : 02/07/22

File name : 92 1850 0 9405950-Ticastro-AS KIT-PIL
Col. Shade No. : Pantone Black

arthritis, dizziness, syncope, headache, vertigo, hypotension, dyspnoea, respiratory system bleedings, gastrointestinal haemorrhage, diarrhoea, nausea, dyspepsia, constipation, subcutaneous or dermal bleeding, rash, pruritus, urinary tract bleeding, blood creatinine increased, post procedural haemorrhage, traumatic bleedings.
very common.
Other reported adverse reactions(uncommon [≥1/1,000 to <1/100] and not known frequency) are as following:tumour bleedings, hypersensitivity including angioedema, confusion, intracranial haemorrhage, eye haemorrhage, ear haemorrhage, retroperitoneal haemorrhage, muscular bleeding, reproductive system bleeding, thrombotic thrombocytopenic purpura.

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 andgingival bleeding. Symptoms may persist for a period of 4–8 days after acetylsalicylic aciddiscontinuation. As a result there may be an increased risk of bleeding duringsurgical procedures. Aspirin decreases platelet adhesiveness and, in large doses, may causehypoprothrombinaemia. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which maylead 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, angiooedema,allergic oedema, anaphylactic reactions including shock.
Metabolism and digestive systemdisorders	*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.

2.9 Overdose

Ticagrelor

Ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse reactions which may occur with overdose include dyspnoea and ventricular pauses.
In the event of an overdose, the above potential adverse reactions could occur and ECG monitoring should be considered.
There is currently no known antidote to reverse the effects of ticagrelor, and ticagrelor is not dialyzable. Treatment of overdose should follow local standard medical practice. The expected effect of excessive ticagrelor dosing is prolonged duration of bleeding risk associated with platelet inhibition. Platelet transfusion is unlikely to be of clinical benefit in patients with bleeding. If bleeding occurs other appropriate supportive measures should be taken.

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.

3 PHARMACOLOGICAL PROPERTIES

3.1 Mechanism of action

Ticagrelor

Ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which 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. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of CV events such as death, MI or stroke.
Ticagrelor also increases local endogenous adenosine levels by inhibiting the equilibrative nucleoside transporter-1 (ENT-1).
Ticagrelor has been documented to augment the following adenosine-induced effects in healthy subjects and in patients with ACS: vasodilation (measured by coronary blood flow increases in healthy volunteers and ACS patients; headache inhibition of platelet function (in human whole blood in vitro) and dyspnoea. However, a link between the observed increases in adenosine and clinical outcomes (e.g. morbidity-mortality) has not been clearly elucidated.

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 presystemic, associated with acetylation of platelet cyclooxygenase in the portal circulation.
Aspirin (acetylsalicylic acid) irreversibly acetylates platelet cyclooxygenase thereby inhibiting the biosynthesis of thromboxane, a potent vasoconstrictor and inducer of platelet aggregation. It also inhibits the action of cyclooxygenase 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 synthesizing new cyclooxygenase, whereas the platelet is not, the effect on thromboxane is longer lasting.

3.2 Pharmacodynamic Property

Ticagrelor

Onset of action

In patients with stable coronary artery disease (CAD) on 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 41%, with the maximum IPA effect of 89% by 2-4 hours post dose, and maintained between 2-8 hours.90% of patients had final extent IPA >70% by 2 hours post dose.

Offset of action

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

Switching data

Switching from clopidogrel 75 mg to ticagrelor 90 mg twice daily results in an absolute IPA increase of 26.4% and switching from ticagrelor to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to ticagrelor without any interruption of antiplatelet effect.

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.
Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply 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.

3.3 Pharmacokinetic properties

Ticagrelor

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

Absorption

Absorption of ticagrelor is rapid with a median tmax of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median tmax of approximately 2.5 hours. Following an oral ticagrelor 90 mg single dose under fasted conditions in healthy subjects, C_{max} is 529 ng/ml and AUC is 3451 ng*h/ml. The metabolite parent ratios are 0.28 for C_{max} and 0.42 for AUC. The pharmacokinetics of ticagrelor and ARC124910XX in patients with a history of MI were generally similar to that in the ACS population. Based on a population pharmacokinetic analysis of the PEGASUS study the median ticagrelor C_{max} was 391 ng/ml and AUC was 3801 ng*h/ml at steady state for ticagrelor 60 mg. For ticagrelor 90 mg C_{max} was 627 ng/ml and AUC was 6255 ng*h/ml at steady-state.
The mean absolute bioavailability of ticagrelor was estimated to be 36%. Ingestion of a high-fat meal resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max} but had no effect on ticagrelor C_{max} or the AUC of the active metabolite. These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food. Ticagrelor as well as the active metabolite are P-gp substrates.
Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, has a comparable bioavailability to whole tablets with regards to AUC and C_{max} for ticagrelor and the active metabolite. Initial exposure (0.5 and 1 hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

Distribution

The steady state volume of distribution of ticagrelor is 87.5 l. Ticagrelor and the active metabolite is extensively bound to human plasma protein (>99.0%).

Biotransformation

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition.
The major metabolite of ticagrelor is AR-C124910XX, which is also active as assessed by in vitro binding to the platelet P2Y12 ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for ticagrelor.

Elimination

The primary route of ticagrelor elimination is via hepatic metabolism. When radiolabelled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the active metabolite is most likely via biliary secretion. The mean t1/2 was approximately 7 hours for ticagrelor and 8.5 hours for the active metabolite.

Special populations

Elderly

Higher exposures to ticagrelor (approximately 25% for both C_{max} and AUC) and the active metabolite were observed in elderly (≥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.

Hepatic impairment

C_{max} and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively, however, the IPA effect of ticagrelor was similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. Ticagrelor has not been studied in patients with severe hepatic impairment and there is no pharmacokinetic information in patients with moderate hepatic impairment. In patients that had moderate or severe elevation in one or more liver function tests at baseline, ticagrelor plasma concentrations were on average similar or slightly higher as compared to those without baseline elevations. No dose adjustment is recommended in patients with moderate hepatic impairment.

Ethnicity

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

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%.

4 NONCLINICAL PROPERTIES

Ticagrelor

Preclinical data for ticagrelor and its major metabolite have not demonstrated unacceptable risk for adverse effects for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxic potential.
Gastrointestinal irritation was observed in several animal species at clinical relevant exposure levels.
In female rats, ticagrelor at high dose showed an increased incidence of uterine tumours (adenocarcinomas) and anincreased incidence of hepatic adenomas. The mechanism for uterine tumours is likely hormonal imbalance which can lead to tumours in rats. The mechanism for the hepatic adenomas is likely due to a rodent-specific enzyme induction in the liver. Thus, the carcinogenicity findings are considered unlikely to be relevant for humans.
In rats, minor developmental anomalies were seen at a maternal toxic dose (safety margin of 5.1). In rabbits, a slight delay in hepatic maturity and skeletal development was seen in foetuses from dams at high dose without showing maternal toxicity (safety margin of 4.5).
Studies in rats and rabbits have shown reproductive toxicity, with slightly reduced maternal body weight gain and reduced neonatal viability and birth weight, with delayed growth. Ticagrelor produced irregular cycles (mostly extended cycles) in female rats, but did not affect overall fertility in male and female rats. Pharmacokinetic studies performed with radiolabelled ticagrelor have shown that the parent compound and its metabolites are excreted in the milk of rats.

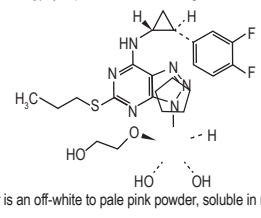
Aspirin

The acute toxicity of acetylsalicylic acid in animals has been studied and reviewed in detail by Boyd. The signs of poisoning in rats from doses in the lethal range are due to varying degrees of gastroenteritis, hepatitis, nephritis, pulmonary edema, encephalopathy, shock and minor toxic effects on other organs and tissues. Death is due to convulsions or cardiovascular shock. The major difference between species appears to be the ability to vomit toxic doses seen in man, cats and dogs, but not in mice, rats and rabbits. Otherwise, the pathological reaction to toxic doses of acetylsalicylic acid is similar in all species in which such studies have been reported. The acute oral LD50 values have been reported as being over 1.0 g/kg in man, cat and dog, 0.92 g/kg in female and 1.48 g/kg in male albino rats, 1.19 g/kg in guinea pig, 1.1 g/kg in mouse and 1.8 g/kg in rabbit.
Chronic toxicity studies were reported in mice and rats. When acetylsalicylic acid was administered at 2 to 20 times the maximum tolerated clinical dose to mice for up to one year, a dose-related deleterious effect was observed on mean survival time, number of young born and number of young raised to weaning age. No evidence of carcinogenic effect was found.
The chronic oral LD50 in male albino rats has been reported as 0.24 g/kg/day when given for 100 days. At these daily doses acetylsalicylic acid produced no anorexia and no loss of body weight.
It did produce polydipsia, aciduria, diuresis, drowsiness, hyperreflexia, piloerection, rapid and deep respiration, tachycardia, and during the second month, soft stools, epistaxis, sialorrhea, dacryorrhea and death in hypothermic coma. Autopsy disclosed the presence of a hypertrophied stomach, renal congestion, mild hepatitis and pneumonitis. While teratogenic effects were noted in animals at near lethal doses, there is no evidence to indicate that acetylsalicylic acid is teratogenic in man.

5 DESCRIPTION

Ticagrelor

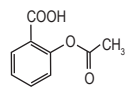
Ticagrelor, a cyclopentyltriazolopyrimidine, inhibit platelet activation and aggregation mediated by the P2Y12 ADP-receptor.Its molecular formula is $C_{23}H_{28}F_2N_6O_4S$ and a molecular weight is 522.6. The chemical name for Ticagrelor is, 2S, 3R, 5S)-3-[7-[[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl] amino]-5(propylthio)-3H-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1,2-diol.Ticagrelor has the following structural formula:



Ticagrelor is an off-white to pale pink powder, soluble in methanol.

Aspirin

Aspirin is acetyl salicylic acid. Its molecular formula is $C_9H_8O_4$ and a molecular weight is 180.2. The chemical name for aspirin is2-acetoxybenzoic acid.Aspirin is colourless crystals or a white crystalline powder; odourless or almost odourless. It is freely soluble in ethanol (95%), soluble in chloroform and in ether; slightly soluble in water. It has the following structural formula:



6 PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities: Not applicable
6.2 Shelf-life: 2 years
6.3 Packaging information: 21's Aluminium Strip (14+7)
6.4 Storage and handing instructions:
Store protected from moisture, at a temperature not exceeding 25°C. Keep out of reach of children.

7 PATIENT COUNSELLING INFORMATION

Ticagrelor

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.

Aspirin

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 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 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.

STORAGE:
Store protected from moisture, at a temperature not exceeding 25°C.

PRESENTATION:
Ticastro-AS is available in a combikit of 14 Ticagrelor Tablets 90 mg & 7 Aspirin Tablets 75 mg.

Manufactured by:

INTAS PHARMACEUTICALS LTD.
Samardung Road, Kabrey Block,
Namthang Elaka, South Sikkim-737 132. INDIA

92 1850 0 9405950

	Checked by				Approved by
Department	PMQC	R.A.	Packing Dev.	Q.A.	Head Q.A.
Signature					
Date					

Product Name : Ticastro-AS
Size : 125 x 580 (mm) Back Side
No. of Col. : 1
Date : 02/07/22

File name : 92 1850 0 9405950-Ticastro-AS KIT-PIL
Col. Shade No. : Pantone Black