For use in india only

To be sold by retail on the prescription of Cardiologist/Internal Medicine Speciality only

Rx

Ticagrelor tablets IP 60 mg and 90 mg

Tiare

टियरे ६०
टियरे ९०

Composition:
Each film coated tablet contains:
Ticagrelor IP.....60 mg
Colours: Titanium Dioxide IP
Ferric Oxide Yellow - USP-NF
Ferric Oxide Red - USP-NF

Each film coated tablet contains:
Ticagrelor IP.....90 mg
Colours: Titanium Dioxide IP
Ferric Oxide Yellow - USP-NF
Ferric Oxide Red - USP-NF

Warning: (a) Bleeding risk, and (b) Aspirin dose and Ticagrelor effectiveness

(a) BLEEDING RISK
- **Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal bleeding.**
- **Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage.**
- **Do not start ticagrelor in patients undergoing urgent coronary artery bypass graft surgery (CABG).**
- **If possible, manage bleeding without discontinuing ticagrelor. Stopping ticagrelor increases the risk of subsequent cardiovascular events.**

(b) ASPIRIN DOSE AND TICAGRELOR EFFECTIVENESS
- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided**

DESCRIPTION
Ticagrelor contains ticagrelor, a cyclopentyltriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the P2Y12 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:

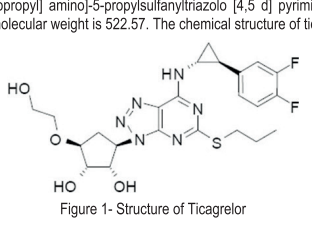


Figure 1- Structure of Ticagrelor

DOSAGE FORMS AND STRENGTHS
Ticagrelor is available as a film coated tablets 60 mg and film coated tablets 90 mg for oral administration.

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

Ticagrelor is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing a thrombotic event.

DOSE AND METHOD OF ADMINISTRATION

Dosing

In the management of ACS, initiate ticagrelor treatment with a 180 mg loading dose. Administer 90 mg 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 75-100 mg. A patient who misses a dose of ticagrelor should take one tablet (their next dose) at its scheduled time. Ticagrelor 90 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event. Treatment may be started without interruption as continuation therapy after the initial one-year treatment with ticagrelor 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in ACS patients with a high risk of an atherothrombotic event.

Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment.

If a switch is needed, the first dose of ticagrelor should be administered 24 hours following the last dose of the other antiplatelet medication.

Administration
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).

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy category: C
There are no adequate and well-controlled studies of ticagrelor use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. Ticagrelor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers
It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ticagrelor, a decision should be made whether to discontinue nursing or to discontinue ticagrelor.

Pediatric use
The safety and effectiveness of ticagrelor in pediatric patients have not been established.

Geriatric use
No 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 receiving dialysis have not been studied.

CONTRAINDICATIONS

History of intracranial hemorrhage
Ticagrelor is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent 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
Ticagrelor is contraindicated in patients with severe hepatic impairment.

Strong CYP3A4 inhibitors
Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated as co-administration may lead to a substantial increase in exposure to ticagrelor.

WARNINGS AND PRECAUTIONS

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 coadministration 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.

Patients with prior ischaemic stroke
ACS patients with prior ischaemic stroke can be treated with ticagrelor for up to 12 months.

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
Due to the limited clinical experience, ticagrelor should be used with caution in 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).
In addition, caution should be exercised when administering ticagrelor concomitantly with medicinal products known to induce bradycardia.

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

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.

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

DRUG INTERACTIONS
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 – 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).
- Moderate CYP3A4 inhibitors – 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 large quantities of grapefruit juice (3x200 ml). This magnitude of increased exposure is not expected to be clinically relevant to most patients.

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).

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 AUC and C_{max} 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.

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

A delayed and decreased exposure to oral $P2Y_{12}$ inhibitors, including ticagrelor and its active metabolite, has been observed in patients with ACS treated with morphine (35% reduction in ticagrelor exposure). This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced ticagrelor efficacy in patients co-administered ticagrelor and morphine. In patients with ACS, in whom morphine cannot be withheld and fast $P2Y_{12}$ inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

Effects of ticagrelor on other medicinal products

Medicinal products metabolised by CYP3A4
- Simvastatin and 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.
- Atorvastatin - Co-administration of atorvastatin and ticagrelor increased atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.
- A similar effect on other statins metabolised by CYP3A4 cannot be excluded.

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

P-gp substrates (including digoxin, cyclosporine)
Concomitant administration of ticagrelor increases the serum concentrations of the digoxin. In the presence of digoxin, the C_{max} and AUC of ticagrelor and its active metabolite were not affected. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent medicinal 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 been studied.

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
Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering ticagrelor concomitantly with medicinal products known to induce bradycardia.

Other concomitant therapy
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.

UNDESIRABLE EFFECTS
The following adverse reactions have been identified following studies or have been reported in post-marketing experience with ticagrelor.
Adverse reactions are listed by MedDRA and 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).

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

SOC	Very common	Common	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Tumour bleedings
Blood and lymphatic system disorders	Blood disorder bleedings		
Immune system disorders			Hypersensitivity including angioedema
Metabolism and nutrition disorders	Hyperuricaemia	Gout/Gouty Arthritis	
Psychiatric disorders			Confusion
Nervous system disorders		Dizziness, Syncope, Headache	Intracranial haemorrhage
Eye disorders			Eye haemorrhage
Ear and labyrinth disorders		Vertigo	Ear haemorrhage
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Respiratory system bleedings	
Gastrointestinal disorders		Gastrointestinal haemorrhage, Diarrhoea, Nausea, Dyspepsia, Constipation	Retroperitoneal haemorrhage
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding, Rash, Pruritus	
Musculoskeletal connective tissue and bone			Muscular bleedings
Renal and urinary disorders		Urinary tract bleeding	
Reproductive system and breast disorders			Reproductive system bleedings
Investigations		Blood creatinine increased	
Injury, poisoning and procedural complications		Post procedural haemorrhage, Traumatic bleedings	

OVERDOSAGE
There is currently no known treatment to reverse the effects of ticagrelor, and ticagrelor is not expected to be 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, and diarrhea) or ventricular pauses. Monitor the ECG.

PHARMACODYNAMICS AND PHARMACOKINETICS

Mechanism of action
Ticagrelor and its major metabolite reversibly interact with the platelet P2Y12 ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

Pharmacodynamics
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 2, 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 60 mg twice daily or clopidogrel 75 mg daily, again in response to 20 µm ADP.
As shown in figure 3, 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.

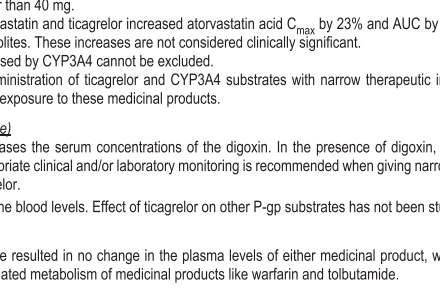


Figure 2 – Mean inhibition of platelet aggregation (±se) following single oral doses of placebo, 180 mg ticagrelor or 600 mg clopidogrel

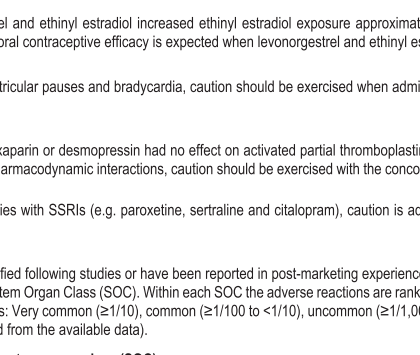


Figure 3 – Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily
Ticagrelor▲ clopidogrel■ placebo

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.

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% (range30% 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.

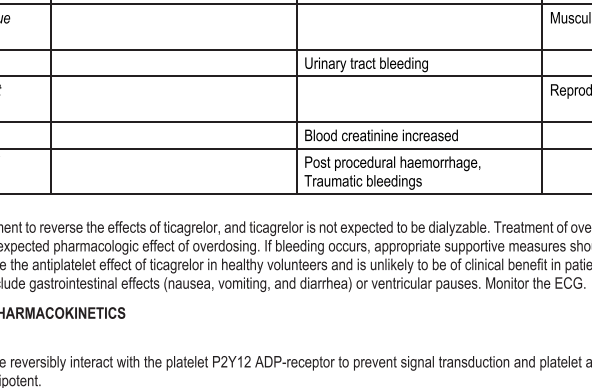
Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and C_{max} within 80 125% for ticagrelor and AR-C124910XX) with a median t_{max} of 1.0 hour (range 1.0-4.0) for ticagrelor and 2.0 hours (range 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 $t_{1/2}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Specific populations
The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in figure4. Effects are modest and do not require dose adjustment.



*Tiare has not been studied in patients with moderate or hepatic impairment.

Figure 4 – Impact of intrinsic factors on the pharmacokinetics of ticagrelor

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 5 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.

Co-administration of 5 mg intravenous morphine with 180 mg loading dose of ticagrelor decreased observed mean ticagrelor exposure by up to 25% in healthy adults and up to 36% in ACS patients undergoing PCI. T_{max} was delayed by 1-2 hours. Exposure of the active metabolite decreased to a similar extent. Morphine co-administration did not delay or decrease platelet inhibition in healthy adults. Mean platelet aggregation was higher up to 3 hours post loading dose in ACS patients co-administered with morphine. Co-administration of intravenous fentanyl with 180 mg loading dose of ticagrelor in ACS patients undergoing PCI resulted in similar effects on ticagrelor exposure and platelet inhibition.

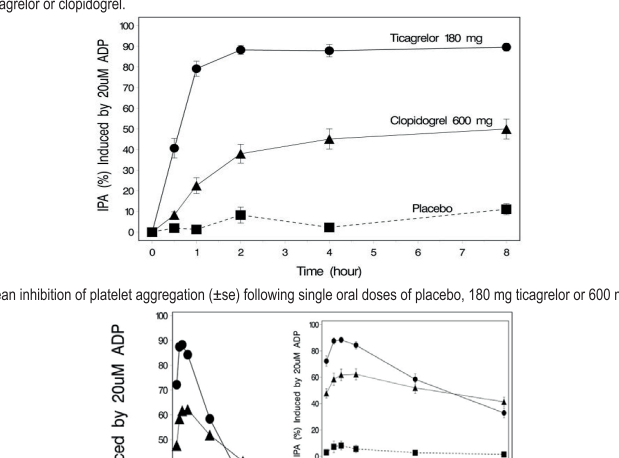
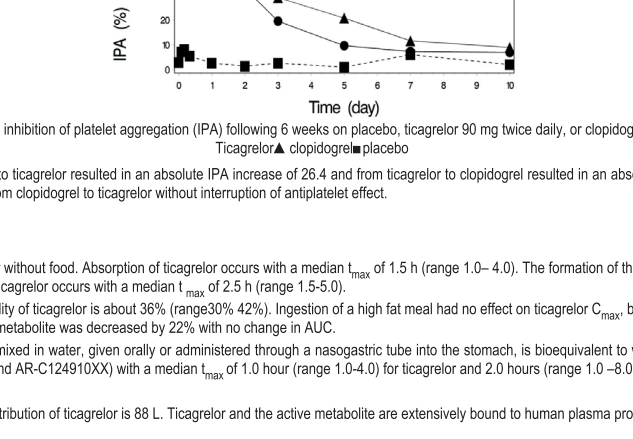


Figure 5 – effect of co-administered drugs on the pharmacokinetics of ticagrelor

Effects of ticagrelor on other drugs
In vitro metabolism studies demonstrate that 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. For specific in vivo effects on the Pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgesterol, tolbutamide, digoxin and cyclosporine, seefigure6.



*Similar increases in AUC and C_{max} were obsereved for all metabolites
**Monitor digoxin levels with initiation of or change in Tiare therapy.

Figure 6 – impact of ticagrelor on the pharmacokinetics of co-administered drugs

INCOMPATIBILITIES
Not applicable.

PACKING INFORMATION
Bottle of 60's
HDPE Container of 1000's
Blister of PVC/PVdC pack of 10's and 14's
Stimulated bulk pack 200's count

STORAGE AND HANDLING INFORMATION
Do not store above 30°C
Keep out of reach for children

Manufactured by:
MSN Laboratories Private Limited,
Formulation Division,
Unit II, Sy.No. 1277 & 1319 to 1324,
Nandigama (Village and Mandal),
Rangareddy District, Pin Code: 509228,
Telangana, India.

D03743-01

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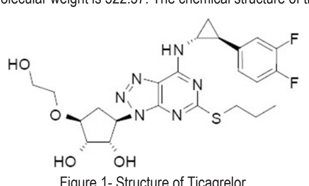

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Ticagrelor is available as a film coated tablets 60 mg and film coated tablets 90 mg for oral administration.

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

Ticagrelor is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing a thrombotic event.

DOSE AND METHOD OF ADMINISTRATION

Dosing

In the management of ACS, initiate ticagrelor treatment with a 180 mg loading dose. Administer 90 mg 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 75-100 mg. A patient who misses a dose of ticagrelor should take one tablet (their next dose) at its scheduled time. Ticagrelor 90 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event. Treatment may be started without interruption as continuation therapy after the initial one-year treatment with ticagrelor 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in ACS patients with a high risk of an atherothrombotic event.

Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment.

If a switch is needed, the first dose of ticagrelor should be administered 24 hours following the last dose of the other antiplatelet medication.

Administration
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).

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy category: C
There are no adequate and well-controlled studies of ticagrelor use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. Ticagrelor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers
It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ticagrelor, a decision should be made whether to discontinue nursing or to discontinue ticagrelor.

Pediatric use
The safety and effectiveness of ticagrelor in pediatric patients have not been established.

Geriatric use
No 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 receiving dialysis have not been studied.

CONTRAINDICATIONS

History of intracranial hemorrhage
Ticagrelor is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent 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
Ticagrelor is contraindicated in patients with severe hepatic impairment.

Strong CYP3A4 inhibitors
Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated as co-administration may lead to a substantial increase in exposure to ticagrelor.

WARNINGS AND PRECAUTIONS

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 coadministration 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.

Patients with prior ischaemic stroke
ACS patients with prior ischaemic stroke can be treated with ticagrelor for up to 12 months.

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
Due to the limited clinical experience, ticagrelor should be used with caution in 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).
In addition, caution should be exercised when administering ticagrelor concomitantly with medicinal products known to induce bradycardia.

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

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.

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

DRUG INTERACTIONS
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 – 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).
- Moderate CYP3A4 inhibitors – 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 large quantities of grapefruit juice (3x200 ml). This magnitude of increased exposure is not expected to be clinically relevant to most patients.

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).

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 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.

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

A delayed and decreased exposure to oral $P2Y_{12}$ inhibitors, including ticagrelor and its active metabolite, has been observed in patients with ACS treated with morphine (35% reduction in ticagrelor exposure). This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced ticagrelor efficacy in patients co-administered ticagrelor and morphine. In patients with ACS, in whom morphine cannot be withheld and fast $P2Y_{12}$ inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

Effects of ticagrelor on other medicinal products

Medicinal products metabolised by CYP3A4
- Simvastatin and 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.
- Atorvastatin - Co-administration of atorvastatin and ticagrelor increased atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.
- A similar effect on other statins metabolised by CYP3A4 cannot be excluded.

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

P-gp substrates (including digoxin, cyclosporine)
Concomitant administration of ticagrelor increases the serum concentrations of the digoxin. In the presence of digoxin, the C_{max} and AUC of ticagrelor and its active metabolite were not affected. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent medicinal 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 been studied.

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
Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering ticagrelor concomitantly with medicinal products known to induce bradycardia.

Other concomitant therapy
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.

UNDESIRABLE EFFECTS
The following adverse reactions have been identified following studies or have been reported in post-marketing experience with ticagrelor.
Adverse reactions are listed by MedDRA and 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).

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

SOC	Very common	Common	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Tumour bleedings
Blood and lymphatic system disorders	Blood disorder bleedings		
Immune system disorders			Hypersensitivity including angioedema
Metabolism and nutrition disorders	Hyperuricaemia	Gout/Gouty Arthritis	
Psychiatric disorders			Confusion
Nervous system disorders		Dizziness, Syncope, Headache	Intracranial haemorrhage
Eye disorders			Eye haemorrhage
Ear and labyrinth disorders		Vertigo	Ear haemorrhage
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Respiratory system bleedings	
Gastrointestinal disorders		Gastrointestinal haemorrhage, Diarrhoea, Nausea, Dyspepsia, Constipation	Retroperitoneal haemorrhage
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding, Rash, Pruritus	
Musculoskeletal connective tissue and bone			Muscular bleedings
Renal and urinary disorders		Urinary tract bleeding	
Reproductive system and breast disorders			Reproductive system bleedings
Investigations		Blood creatinine increased	
Injury, poisoning and procedural complications		Post procedural haemorrhage, Traumatic bleedings	

OVERDOSAGE
There is currently no known treatment to reverse the effects of ticagrelor, and ticagrelor is not expected to be 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, and diarrhea) or ventricular pauses. Monitor the ECG.

PHARMACODYNAMICS AND PHARMACOKINETICS

Mechanism of action
Ticagrelor and its major metabolite reversibly interact with the platelet P2Y12 ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

Pharmacodynamics
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 2, 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 60 mg twice daily or clopidogrel 75 mg daily, again in response to 20 µm ADP.
As shown in figure 3, 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.

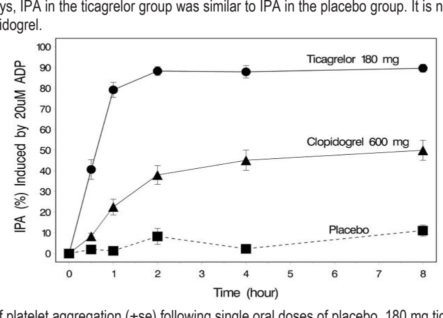


Figure 2 – Mean inhibition of platelet aggregation (±se) following single oral doses of placebo, 180 mg ticagrelor or 600 mg clopidogrel

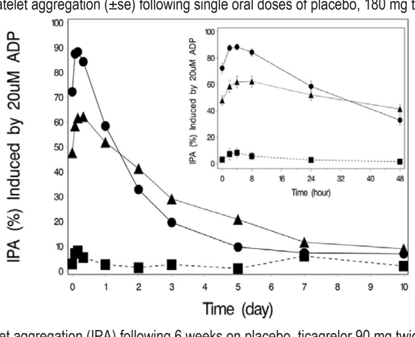


Figure 3 – Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily
Ticagrelor▲ clopidogrel■ placebo

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.

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% (range30% 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.

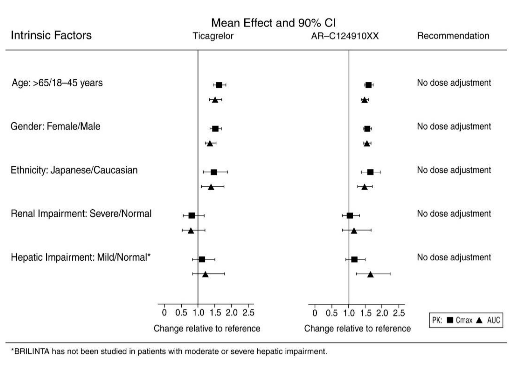
Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and C_{max} within 80 125% for ticagrelor and AR-C124910XX) with a median t_{max} of 1.0 hour (range 1.0-4.0) for ticagrelor and 2.0 hours (range 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 $t_{1/2}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Specific populations
The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in figure4. Effects are modest and do not require dose adjustment.



*Tiare has not been studied in patients with moderate or hepatic impairment.

Figure 4 – Impact of intrinsic factors on the pharmacokinetics of ticagrelor

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 5 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.

Co-administration of 5 mg intravenous morphine with 180 mg loading dose of ticagrelor decreased observed mean ticagrelor exposure by up to 25% in healthy adults and up to 36% in ACS patients undergoing PCI. T_{max} was delayed by 1-2 hours. Exposure of the active metabolite decreased to a similar extent. Morphine co-administration did not delay or decrease platelet inhibition in healthy adults. Mean platelet aggregation was higher up to 3 hours post loading dose in ACS patients co-administered with morphine. Co-administration of intravenous fentanyl with 180 mg loading dose of ticagrelor in ACS patients undergoing PCI resulted in similar effects on ticagrelor exposure and platelet inhibition.

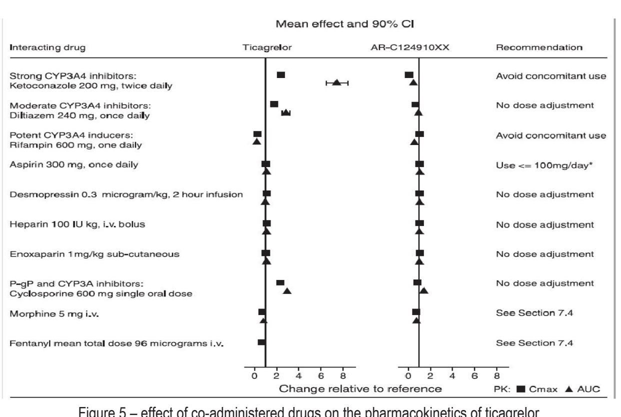
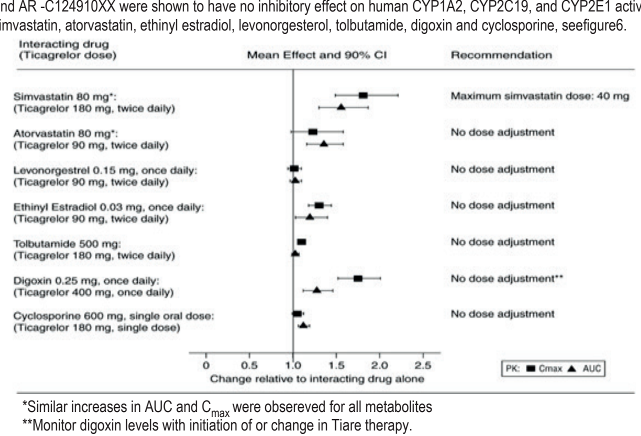


Figure 5 – effect of co-administered drugs on the pharmacokinetics of ticagrelor

Effects of ticagrelor on other drugs
In vitro metabolism studies demonstrate that 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. For specific in vivo effects on the Pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgesterol, tolbutamide, digoxin and cyclosporine, seefigure6.



*Similar increases in AUC and C_{max} were obsereved for all metabolites
**Monitor digoxin levels with initiation of or change in Tiare therapy.

Figure 6 – impact of ticagrelor on the pharmacokinetics of co-administered drugs

INCOMPATIBILITIES
Not applicable.

PACKING INFORMATION
Blister of PVC/PVdC pack of 10's and 14's

Storage : Store protected from light and moisture, at a temperature not exceeding 30°C.

Keep out of reach for children

Manufactured by:
MSN Laboratories Private Limited,
(Formulations Division), Plot No. 42,
Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325,
Telangana, India.

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