

PROPOSED PACKAGE INSERT FOR TICAGRELOR

For the use of a registered medical practitioner or a hospital or a laboratory only

R_x **Ticagrelor Tablets IP 90 mg**

AMERICAN
Ticasprin 90
टिकासप्रिन Tablets

COMPOSITION

Each film coated tablet contains:

Ticagrelor IP.....90 mg

Excipients.....q.s.

Colours : Yellow Oxide of Iron & Titanium Dioxide IP

DOSEAGE FORM:-

Tablets

INDICATION:-

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 those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

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. After one year administer 60 mg twice daily. Do not administer Ticagrelor with another oral P2Y12 platelet inhibitor. Use Ticagrelor with a daily maintenance dose of aspirin of 75-100 mg.

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 SPECIAL 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. In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. 20 mg/kg/day is approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on an mg/m2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. At the mid-dose of 100 mg/kg/day, delayed development of liver and skeleton was seen. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred. In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m2 basis).

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

In PLATO and PEGASUS, about half of patients in each study were ≥65 years of age and about 15% were ≥75 years of age. No overall differences in safety or effectiveness were observed between elderly and younger patients.

Hepatic Impairment

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

Renal Impairment

No dosage adjustment is needed in patients with renal impairment. Patients 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 ICH in this population.

Active Bleeding

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

Hypersensitivity

Ticagrelor is contraindicated in patients with hypersensitivity (e.g., angioedema) to ticagrelor or any component of the product.

WARNINGS AND PRECAUTIONS

General Risk of Bleeding

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

Concomitant Aspirin Maintenance Dose

In PLATO the use of ticagrelor with maintenance doses of aspirin above 100 mg decreased the effectiveness of ticagrelor. Therefore, after the initial loading dose of aspirin, use ticagrelor with a maintenance dose of aspirin of 75-100 mg.

Dyspnea

In clinical trials, about 14% of patients treated with ticagrelor developed dyspnea. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment, but led to study drug discontinuation in 0.9% of ticagrelor and 0.1% of clopidogrel patients in PLATO and 4.3% of ticagrelor 60 mg and 0.7% on aspirin alone patients in PEGASUS. In a substudy of PLATO, 199 subjects underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment. If a patient develops new, prolonged, or worsened dyspnea that is determined to be related to ticagrelor, no specific treatment is required; continue ticagrelor without interruption if possible. In the case of intolerable dyspnea requiring discontinuation

of ticagrelor, consider prescribing another antiplatelet agent.

Discontinuation of Ticagrelor

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

Severe Hepatic Impairment

Avoid use of ticagrelor in patients with severe hepatic impairment. Severe hepatic impairment is likely to increase serum concentration of ticagrelor. There are no studies of ticagrelor patients with severe hepatic impairment.

DRUG INTERACTIONS

Strong CYP3A Inhibitors

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

Strong CYP3A Inducers

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

Aspirin

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

Simvastatin, Lovastatin

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

Digoxin

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

UNDESIRABLE EFFECTS

The following adverse reactions are also discussed elsewhere in the labeling:

- Bleeding
- Dyspnea

OVERDOSE

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

PHARMACODYNAMICS AND PHARMACOKINETIC PROPERTIES

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 3, IPA was higher in the ticagrelor group at all-time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours. The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 μM ADP. As shown in Figure 4, 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.

Pharmacokinetics

Ticagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy volunteers.

Absorption

Ticagrelor can be taken with or without food. Absorption of ticagrelor occurs with a median tmax 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 tmax of 2.5 h (range 1.5-5.0). The mean absolute bioavailability of ticagrelor is about 36% (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor Cmax, but resulted in a 21% increase in AUC. The Cmax of its major metabolite was decreased by 22% with no change in AUC. Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and Cmax within 80-125% for ticagrelor and AR-C124910XX) with a median tmax of 1.0 hour (range 1.0 –4.0) for ticagrelor and 2.0 hours (range 1.0–8.0) for AR-C124910XX.

Distribution

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

Metabolism

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

Excretion

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean t1/2 is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

INCOMPATIBILITIES

No incompatibilities have been found with ticagrelor.

SHELF-LIFE

Refer to pack

PACKAGING INFORMATION

14 tablets packed in an Alu-Alu Blister.

STORAGE AND HANDLING INSTRUCTIONS

Store in a cool, dark & dry place below 30°C.

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