GRELOR®

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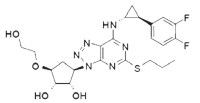
Ticagrelor Tablets 60 mg & 90 mg

DESCRIPTION:

GRELOR contains Ticagrelor, a cyclopentyltriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor.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:



CLINICAL PHARMACOLOGY:

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

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. 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. Mean maximum IPA following the last dose of Ticagrelor was 88% and 62% for Clopidogrel. 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.

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 (GRELOR) without interruption of antiplatelet effect.

Pharmacokinetics:

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

Absorption:

Ticagrelor (GRELOR) 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 (GRELOR) 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.

Specific Populations:

The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of Ticagrelor are modest and do not require dose adjustment.

Patients with End-Stage Renal Disease on Hemodialysis:

In patients with end stage renal disease on hemodialysis AUC and Cmax of Ticagrelor (GRELOR) 90 mg administered on a day without dialysis were 38% and 51% higher respectively, compared to subjects with normal renal function. A similar increase in exposure was observed when Ticagrelor (GRELOR) was administered immediately prior to dialysis showing that Ticagrelor (GRELOR) is not dialyzable. Exposure of the active metabolite increased to a lesser extent. The IPA effect of Ticagrelor (GRELOR) was independent of dialysis in patients with end stage renal disease and similar to healthy adults with normal renal function.

INDICATIONS & USES:

GRELOR is indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). For at least the first 12 months following ACS, it is superior to Clopidogrel. GRELOR also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS.

DOSAGE & ADMINISTRATION:

Dosing:

In the management of ACS, initiate GRELOR 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 GRELOR with another oral $P2Y_{12}$ platelet inhibitor.

Use GRELOR with a daily maintenance dose of aspirin of 75-100 mg. A patient who misses a dose of GRELOR should take one tablet (their next dose) at its scheduled time.

Administration:

For patients who are unable to swallow tablets whole, GRELOR Tablets can be crushed, mixed with water and drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater).

CONTRAINDICATIONS:

History of Intracranial Hemorrhage:

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

Active Bleeding:

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

Hypersensitivity:

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

WARNINGS & PRECAUTIONS:

General Risk of Bleeding:

Drugs that inhibit platelet function including GRELOR increase the risk of bleeding.

If possible, manage bleeding without discontinuing GRELOR. Stopping GRELOR 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 GRELOR 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 GRELOR, no specific treatment is required; continue GRELOR without interruption if possible. In the

case of intolerable dyspnea requiring discontinuation of GRELOR, consider prescribing another antiplatelet agent.

Discontinuation of GRELOR:

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

Bradyarrhythmias:

Ticagrelor can cause ventricular pauses. Bradyarrhythmias including AV block have been reported. Patients with a history of sick sinus syndrome, 2nd or 3rd degree AV block or bradycardia-related syncope not protected by a pacemaker were excluded from PLATO and PEGASUS and may be at increased risk of developing bradyarrhythmias with Ticagrelor.

Severe Hepatic Impairment:

Avoid use of GRELOR 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.

Laboratory Test Interferences:

False negative functional tests for Heparin Induced Thrombocytopenia (HIT): Ticagrelor has been reported to cause false negative results in platelet functional tests (to include, but may not be limited to, the heparin-induced platelet aggregation (HIPA) assay) for patients with Heparin Induced Thrombocytopenia (HIT). This is related to inhibition of the $P2Y_{12}$-receptor on the healthy donor platelets in the test by Ticagrelor in the affected patient's serum/plasma. Information on concomitant treatment with Ticagrelor is required for interpretation of HIT functional tests. Based on the mechanism of GRELOR interference, GRELOR is not expected to impact PF4 antibody testing for HIT.

ADVERSE REACTIONS:

The following important adverse reactions are described:

- Bleeding
- Dyspnea
- Bradycardia
- Rash
- Hypersensitivity (Angioedema)

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

Opioids:

As with other oral $P2Y_{12}$ inhibitors, co-administration of opioid agonists delay and reduce the absorption of Ticagrelor and its active metabolite presumably because of slowed gastric emptying. Consider the use of a parenteral anti-platelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

Simvastatin, Lovastatin:

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

Digoxin:

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

OVERDOSE:

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

Platelet transfusion did not reverse the antiplatelet effect of GRELOR 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.

DOSAGE FORMS & STRENGTHS:

GRELOR tablets are available as:

- 60 mg FCT (Film Coated Tablets)
  Packaging: 14 Tablets X 4 Blisters X 3 Dose Packs
- 90 mg FCT (Film Coated Tablets)
  Packaging: 14 Tablets X 4 Blisters X 3 Dose Packs

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