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

Xygrel 90

(Ticagrelor Tablets 90 mg)

Composition:

Each film coated tablet contains:

Ticagrelor IP	90 mg
Colours: Ferric Oxide Yellow USP-NF & Titanium Dioxide IP	
Excipients:	Q.S

Drug Description:

Ticagrelor is 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(propylthio)-3H-[1,2,3]-triazolo[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:

Ticagrelor is a crystalline powder with an aqueous solubility of approximately 10 µg/mL at room temperature.

Clinical Pharmacology:

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.

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 t_{max} of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median t_{max} of 2.5 h (range 1.5-5.0). The mean absolute bioavailability of ticagrelor is about 36% (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21% increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and 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 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 C_{max} of ticagrelor 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 was administered immediately prior to dialysis showing that ticagrelor is not dialyzable. Exposure of the active metabolite increased to a lesser extent. The IPA effect of ticagrelor was independent of dialysis in patients with end stage renal disease and similar to healthy adults with normal renal function.

Effects of Other Drugs on Ticagrelor

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. 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. Tmax 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.

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.

Indications and Usage:

For the prevention of thrombiotic 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).

Dosage and Administration:

Dosing: Initiate treatment with 180 mg oral loading dose following an ACS event. Continue treatment with 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.

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).

Dosage Forms and Strengths:

Ticagrelor 90 mg is supplied as a Light yellow, Capsule shaped, film coated tablets with two breaklines on both sides.

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: 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 75100 mg.

Dyspnoea: In clinical trials, about 14% of patients treated with ticagrelor developed dyspnoea. Dyspnoea 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.

In a substudy of PLATO, 199 subjects underwent pulmonary function testing irrespective of whether they reported dyspnoea. 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 dyspnoea that is determined to be related to ticagrelor, no specific treatment is required; continue ticagrelor without interruption if possible. In the case of intolerable dyspnoea 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 haemostasis is achieved.

Bradyarrhythmias: Ticagrelor can cause ventricular pauses. Bradyarrhythmias including AV block have been reported in the post marketing setting. 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 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.

Adverse Reactions:

Bleeding: Ticagrelor causes non CABG related major bleeding (3.9% vs. 3.3% with clopidogrel in PLATO trial).

Dyspnoea: Ticagrelor causes dyspnoea in 13.8% cases vs. 7.8% with clopidogrel.

Other side effects include nausea (4.3%), dizziness (4.5%), bradycardia including ventricular pauses (6%), syncope (1.7%), and increased serum uric acid level in blood (disappear on stopping ticagrelor)

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.

Opioids

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

Simvastatin, Lovastatin

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

Digoxin

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

Use in Specific Populations:

Pregnancy

Available data from case reports with ticagrelor use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Lactation

Breastfeeding is not recommended during treatment with ticagrelor.

Paediatric Use

The safety and effectiveness of ticagrelor in paediatric patients have not been established.

Geriatric Use

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

Hepatic Impairment

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.

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

Overdosage:

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

Platelet transfusion did not reverse the antiplatelet effect of ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding. Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

Storage:

Store protected from moisture, at a temperature not exceeding 25°C.
Keep out of reach of children.

Presenation:

Xygrel 90 is available in blister of 10 Tablets.

Manufactured by:

INTAS

INTAS PHARMACEUTICALS LTD.
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