ANPLAG® (TICAGRELOR)

اینپلیگ

COMPOSITION
Anplag 60mg Tablets:
Each film coated tablet contain:
Ticagrelor….60mg

Anplag 90mg Tablets:
Each film coated tablet contain:
Ticagrelor….90mg
(As per innovator's specs.)

WARNING: (A) BLEEDING RISK, (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). When possible discontinue Ticagrelor at least 5 days prior to surgery. Suspect bleeding in any patient who is hypotensive and recently has gone under any surgical procedure. 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 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-(3,4difluorophenyl)cyclopropyl]amino}-5(propylthio)-3H-[1,2,3]-triazolo[4,5-d] pyrimidin-3yl]5(2-hydroxyethoxy)cyclopentane-1,2-diol. The empirical formula of ticagrelor is $C_{23}H_{28}F_2N_6O_4S$.

CLINICAL PHARMACOLOGY

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

Pharmacodynamics properties*
Transitioning from clopidogrel to Ticagrelor results in an absolute inhibition of platelet aggregation (IPA) increase of 26.4% and from Ticagrelor to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to Ticagrelor without interruption of antiplatelet effect.

Pharmacokinetics
Ticagrelor demonstrates dose proportional pharmacokinetics.

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 has no effect on ticagrelor Cmax, but results in a 21% increase in AUC. The Cmax of its major metabolite is decreased by 22% with no change in AUC.

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.

Elimination
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 are 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.

Pharmacokinetics in special populations
Elderly
Higher exposures to ticagrelor (approximately 25% for both Cmax and AUC) and the active metabolite are observed in elderly (≥75years) ACS patients compared to younger patients. These differences are not considered clinically significant.

Pediatric population
Ticagrelor has not been evaluated in pediatrics.

Gender
Higher exposures to ticagrelor and the active metabolite are observed in women compared to men. These differences are not considered clinically significant.

Renal impairment
Exposure to ticagrelor is approximately 20% lower and exposure to the active metabolite is approximately 17% higher in patients with severe renal impairment (creatinine clearance <30 ml/min) compared to patients with normal renal function.
Hepatic impairment
Cmax and AUC for ticagrelor are 12% and 23% higher in patients with mild hepatic impairment compared to healthy patients, respectively, however, the IPA effect of ticagrelor is similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. No data is available for Ticagrelor in patients with severe hepatic impairment and there is no pharmacokinetic information in patients with moderate hepatic impairment. In patients that have moderate or severe elevation in one or more liver function tests at baseline, ticagrelor plasma concentrations are on average similar or slightly higher as compared to those without baseline elevations. No dose adjustment is recommended in patients with moderate hepatic impairment.

INDICATIONS
Ticagrelor is indicated to reduce the rate of
• Cardiovascular death
• Myocardial infarction
• Stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI)
• Also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS

DOSAGE AND ADMINISTRATION

Adult dosage
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. A patient who misses a dose of Ticagrelor should take one tablet (their next dose) at its scheduled time.

Administration requirements
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).

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.

Severe Hepatic Impairment
Ticagrelor is contraindicated in patients with severe hepatic patients because of probable increase in exposure. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins.

WARNING 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
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
Patients treated with Ticagrelor may develop dyspnea. Dyspnea is usually mild to moderate in intensity and often resolves during continued treatment, but lead to drug discontinuation
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.

Moderate Hepatic Impairment
Only limited information is available for use in patients with moderate hepatic impairment. Dose adjustments are not recommended but ticagrelor should be used with caution.

Bradyarrhythmias
Ticagrelor can cause ventricular pauses. Bradyarrhythmias including AV block have been

reported in the postmarketing setting. Ticagrelor should be used with caution in patients with a history of sick sinus syndrome, 2nd or 3rd degree AV block or bradycardia-related syncope not protected by a pacemaker.

Effects on ability to drive and use machines
Ticagrelor has no or negligible influence on the ability to drive and use machines. During treatment with ticagrelor, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

ADVERSE REACTIONS

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

[a] e.g. bleeding from bladder cancer, gastric cancer, colon cancer
[b] e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis
[c] Identified in post-marketing experience
[d] Frequencies derived from lab observations (Uric acid increases to >upper limit of normal from baseline below or within reference range. Creatinine increases of >50% from baseline.) and not crude adverse event report frequency.
[e] e.g. conjunctival, retinal, intraocular bleeding
[f] e.g. epistaxis, haemoptysis
[g] e.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage
[h] e.g. ecchymosis, skin haemorrhage, petechiae
[i] e.g. haemarthrosis, muscle haemorrhage
[j] e.g. haematuria, cystitis haemorrhagic
[k] e.g. vaginal haemorrhage, haematospermia, postmenopausal haemorrhage
[l] e.g. contusion, traumatic haematoma, traumatic haemorrhage

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.

USE IN SPECIAL POPULATIONS

Pregnancy
US FDA 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. 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.

Pediatrics
The safety and effectiveness of Ticagrelor in pediatric patients have not been established.

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

Renal impairment
No dosage adjustment is needed in patients with renal impairment. No data is available for patients receiving dialysis.

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.

OVER DOSAGE
Ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity may be dose-limiting. Other clinically meaningful adverse reactions which may occur with overdose include dyspnea, gastrointestinal effects (nausea, vomiting, diarrhea) and ventricular pauses. In the event of an overdose, the above potential adverse reactions could occur and ECG monitoring should be considered.
There is currently no known 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

PRESENTATION
Anplag 60mg: Pack of 14 Tablets.
Anplag 90mg: Pack of 20 Tablets.

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, report at reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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