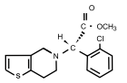
FRONT

FRELET
(CLOPIDOGREL 75 MG)

DESCRIPTION
Frelet (clopidogrel bisulfate) is a thienopyridine class inhibitor of P2Y12 ADP platelet receptors. Chemically it is methyl (+)- (S)-α- (2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5 (4H)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is C16H16ClNO2SH2SO4 and its molecular weight is 419.9.

The structural formula is as follows:



Clopidogrel bisulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°

Frelet for oral administration is provided as either pink, round, biconvex, debossed, film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base or pink, oblong, debossed film-coated tablets containing 391.5 mg of clopidogrel bisulfate which is the molar equivalent of 300 mg of clopidogrel base.

LIST OF EXCIPIENTS

1. Clopidrogrel Bisulphate USP
2. Maize Starch BP
3. Microcrystalline Cellulose BP
4. Lactose BP
5. Povidone K30 BP
6. Isopropyl Alcohol BP
7. Purified Talc BP
8. Colloidal Anhydrous Silica BP
9. Magnesium Stearate BP
10. Hypromellose E15 BP
11. Titanium dioxide BP
12. Red Oxide of Iron IHS
13. Dichloromethane BP

INDICATIONS
Acute Coronary Syndrome (ACS)

· For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], including patients who are to be managed medically and those who are to be managed with coronary revascularization, Frelet has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.
· For patients with ST-elevation myocardial infarction (STEMI), Frelet has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary percutaneous coronary intervention is unknown.

The optimal duration of Frelet therapy in ACS is unknown.

Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, Frelet has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

DOSAGE AND ADMINISTRATION
Acute Coronary Syndrome

Frelet can be administered with or without food [see CLINICAL PHARMACOLOGY]
· For patients with non-ST-elevation ACS (UA/NSTEMI), initiate Frelet with a single 300 mg oral loading dose and then continue at 75 mg once daily. Initiate aspirin (75-325 mg once daily) and continue in combination with Frelet.
· For patients with STEMI, the recommended dose of Frelet is 75 mg once daily orally, administered in combination with aspirin (75-325 mg once daily), with or without thrombolytics. Frelet may be initiated with or without a loading dose.

Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

The recommended daily dose of Frelet is 75 mg once daily orally, with or without food

SIDE EFFECTS
The following serious adverse reactions are discussed below and elsewhere in the labeling:
· Bleeding [see WARNINGS AND PRECAUTIONS]
· Thrombotic thrombocytopenic purpura [see WARNINGS AND PRECAUTIONS]

Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions and durations of follow up, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Frelet has been evaluated for safety in more than 54,000 patients, including over 21,000 patients treated for 1 year or more. The clinically important adverse reactions observed in trials comparing Frelet plus aspirin to placebo plus aspirin and trials comparing Frelet alone to aspirin alone are discussed below.

Bleeding
CURE

In CURE, Frelet use with aspirin was associated with an increase in major bleeding (primarily gastrointestinal and at puncture sites) compared to placebo with aspirin (see Table 1). The incidence of intracranial hemorrhage (0.1%) and fatal bleeding (0.2%) were the same in both groups. Other bleeding events that were reported more frequently in the clopidogrel group were epistaxis, hematuria, and bruise.

The overall incidence of bleeding is described in Table 1.

Table 1: CURE Incidence of Bleeding Complications (% patients)

Major bleeding †	3.7‡	2.7 §	0.001
Life-threatening bleeding	2.2	1.8	0.13
Fatal	0.2	0.2	
5 g/dL hemoglobin drop	0.9	0.9	
Requiring surgical intervention	0.7	0.7	

Event	Frelet (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)	p-value
Hemorrhagic strokes	0.1	0.1	
Requiring inotropes	0.5	0.5	
Requiring transfusion (≥ 4units)	1.2	1.0	
Other major bleeding	1.6	1.0	0.005
Significantly disabling	0.4	0.3	
Intraocular bleeding with significant loss of vision	0.05	0.03	
Requiring 2-3 units of blood	1.3	0.9	
Minor bleeding	5.1	2.4	< 0.001

* Other standard therapies were used as appropriate.
† Life-threatening and other major bleeding.
‡ Major bleeding event rate for Frelet + aspirin was dose-dependent on aspirin: < 100 mg = 2.6%; 100-200 mg = 3.5%; > 200 mg = 4.9% Major bleeding event rates for Frelet + aspirin by age were: < 65 years = 2.5%, ≥ 65 to < 75 years = 4.1%, ≥ 75years = 5.9%
§ Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: < 100 mg = 2.0%; 100-200 mg = 2.3%; > 200 mg = 4.0% Major bleeding event rates for placebo + aspirin by age were: < 65 years = 2.1%, ≥ 65 to < 75 years = 3.1%, ≥ 75 years = 3.6%
Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin or low molecular weight heparin (LMWH), and the rate of bleeding in these patients was similar to the overall results.

COMMIT
In COMMIT, similar rates of major bleeding were observed in the Frelet and placebo groups, both of which also received aspirin (see Table 2).

Table 2: Incidence of Bleeding Events in COMMIT (% patients)

Type of bleeding	Frelet (+ aspirin) (n=22961)	Placebo (+ aspirin) (n=22891)	p-value
Major* noncerebral or cerebral bleeding**	0.6	0.5	0.59
Major noncerebral	0.4	0.3	0.48
Fatal	0.2	0.2	0.90
Hemorrhagic stroke	0.2	0.2	0.91
Fatal	0.2	0.2	0.81
Other noncerebral bleeding (non-major)	3.6	3.1	0.005
Any noncerebral bleeding	3.9	3.4	0.004

* Major bleeds were cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.
** The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for Frelet +

CAPRIE (Frelet vs. Aspirin)

In CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2.0% in those taking Frelet vs. 2.7% in those taking aspirin; bleeding requiring hospitalization occurred in 0.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for Frelet compared to 0.5% for aspirin.

Other bleeding events that were reported more frequently in the Frelet group were epistaxis and hematoma.

Other Adverse Events

In CURE and CHARISMA, which compared Frelet plus aspirin to aspirin alone, there was no difference in the rate of adverse events (other than bleeding) between Frelet and placebo.

In CAPRIE, which compared Frelet to aspirin, pruritus was more frequently reported in those taking Frelet. No other difference in the rate of adverse events (other than bleeding) was reported.

Common side effects
· Blood and lymphatic system disorders: Agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP)
· Gastrointestinal disorders: Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis
· General disorders and administration site condition: Fever, hemorrhage of operative wound
· Hepato-biliary disorders: Acute liver failure, hepatitis (non-infectious), abnormal liver function test
· Immune system disorders: Hypersensitivity reactions, anaphylactoid reactions, serum sickness
· Musculoskeletal, connective tissue and bone disorders: Musculoskeletal bleeding, myalgia, arthralgia, arthritis
· Nervous system disorders: Taste disorders, fatal intracranial bleeding
· Eye disorders: Eye (conjunctival, ocular, retinal) bleeding
· Psychiatric disorders: Confusion, hallucinations
· Respiratory, thoracic and mediastinal disorders: Bronchospasm, interstitial pneumonitis, respiratory tract bleeding
· Renal and urinary disorders: Glomerulopathy, increased creatinine levels
· Skin and subcutaneous tissue disorders: Maculopapular or erythematous rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, erythema multiforme, skin bleeding, lichen planus
· Vascular disorders: Vasculitis, hypotension

WARNINGS
Included as part of the PRECAUTIONS section.

PRECAUTIONS

Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is due to an active metabolite.

BACK

The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 [see Boxed Warning] and by concomitant medications that interfere with CYP2C19. Avoid concomitant use of Frelet and strong or moderate CYP2C19 inhibitors.

Omeprazole, a moderate CYP2C19 inhibitor, has been shown to reduce the pharmacological activity of Frelet if given concomitantly or if given 12 hours apart. Consider using another acid-reducing agent with less CYP2C19 inhibitory activity. Pantoprazole, a weak CYP2C19 inhibitor, had less effect on the pharmacological activity of Frelet than omeprazole [see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION].

General Risk of Bleeding

Thienopyridines, including Frelet, increase the risk of bleeding. If a patient is to undergo surgery and an antiplatelet effect is not desired, discontinue Frelet five days prior to surgery. In patients who stopped therapy more than five days prior to CABG the rates of major bleeding were similar (event rate 4.4% Frelet + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of CABG, the major bleeding rate was 9.6% for Frelet + aspirin, and 6.3% for placebo + aspirin.

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of clopidogrel's active metabolite is short, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.

Discontinuation of Frelet

Avoid lapses in therapy, and if Frelet must be temporarily discontinued, restart as soon as possible. Premature discontinuation of Frelet may increase the risk of cardiovascular events.

Patients with Recent Transient Ischcmic Attack (TIA) or Stroke

In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and Frelet has not been shown to be more effective than Frelet alone, but the combination has been shown to increase major bleeding.

Thrombotic Thrombocytopenic Purpura (TTP)

TTP, sometimes fatal, has been reported following use of Frelet, sometimes after a short exposure (< 2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever

POSSIBLE DRUG/FOOD INTERACTIONS:

CYP2C19 Inhibitors

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of certain drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition

Proton Pump Inhibitors (PPI)

Avoid concomitant use of Plavix with omeprazole or esomeprazole. In clinical studies, omeprazole was shown to reduce the antiplatelet activity of Plavix when given concomitantly or 12 hours apart. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established. A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with Plavix. Consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite. Dexlansoprazole, lansoprazole and pantoprazole had less effect on the antiplatelet activity of Plavix than did omeprazole or esomeprazole

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Coadministration of Plavix and NSAIDs increases the risk of gastrointestinal bleeding.

Warfarin (CYP2C9 Substrates)

Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of Plavix with warfarin increases the risk of bleeding because of independent effects on hemostasis.
However, at high concentrations in vitro, clopidogrel inhibits CYP2C9.

SSRIs And SNRIs

Since selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) affect platelet activation, the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding.

Nonclinical Toxicology
Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures > 25 times that in humans at the recommended daily dose of 75 mg.

Clopidogrel was not genotoxic in four in vitro tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one in vivo test (micronucleus test by oral route in mice).

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m2 basis).

Use In Specific Populations
Pregnancy
Pregnancy Category B

Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day, respectively (65 and 78 times the recommended daily human dose, respectively, on a mg/m2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, Frelet should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is 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 clopidogrel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Geriatric Use

Of the total number of subjects in the CAPRIE and CURE controlled clinical studies, approximately 50% of patients treated with Frelet were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with Frelet were 60 years and older, 26% of whom were 70 years and older.

The observed risk of thrombotic events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Figures 2 and 5 for the CURE and COMMIT trials, respectively [see Clinical Studies]. The observed risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Tables 1 and 2 for the CURE and COMMIT trials, respectively [see ADVERSE REACTIONS]. No dosage adjustment is necessary in elderly patients.

Renal Impairment

Experience is limited in patients with severe and moderate renal impairment [see CLINICAL PHARMACOLOGY].

Hepatic Impairment

No dosage adjustment is necessary in patients with hepatic impairment [see CLINICAL PHARMACOLOGY].

OVERDOSE

Platelet inhibition by Frelet is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting, prostration, difficult breathing, and gastrointestinal hemorrhage in animals.

Based on biological plausibility, platelet transfusion may restore clotting ability.

CONTRAINDICATIONS
Active Bleeding

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

Hypersensitivity

Frelet is contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to clopidogrel or any component of the product [see ADVERSE REACTIONS].

CLINICAL PHARMACOLOGY
Mechanism of Action

Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets.

Pharmacodynamics

Clopidogrel must be metabolized by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. This action is irreversible. Consequently, platelets exposed to clopidogrel's active metabolite are affected for the remainder of their lifespan (about 7 to 10 days). Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Frelet. Repeated doses of 75 mg Frelet per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg Frelet per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Geriatric Patients

Elderly (≥ 75 years) and young healthy subjects had similar effects on platelet aggregation.

Renally-Impaired Patients

After repeated doses of 75 mg Frelet per day, patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) and moderate renal impairment (creatinine clearance from 30 to 60 mL/min) showed low (25%) inhibition of ADP-induced platelet aggregation.

Hepatically-Impaired Patients

After repeated doses of 75 mg Frelet per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects.

Gender

In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women.

Pharmacokinctics

Clopidogrel is a prodrug and is metabolized to a pharmacologically active metabolite and inactive metabolites.

Absorption

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Effect of Food

Frelet can be administered with or without food. In a study in healthy male subjects when Frelet 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was reduced by less than 9%. The active metabolite AUC0-24 was unchanged in the presence of food, while there was a 57% decrease in active metabolite Cmax. Similar results were observed when a Frelet 300 mg loading dose was administered with a high-fat breakfast.

Metabolism

Clopidogrel is extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes. Cytochromes first oxidize clopidogrel to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. This metabolic pathway is mediated by CYP2C19, CYP3A, CYP2B6 and CYP1A2. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.

The Cmax of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose. Cmax occurs approximately 30 to 60 minutes after dosing. In the 75 to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: increasing the dose by a factor of four results in 2.0- and 2.7-fold increases in Cmax and AUC, respectively.

Elimination

Following an oral dose of 14C-labeled clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post-dosing. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The half-life of the active metabolite is about 30 minutes.

STORAGE CONDITION : Store below 25°C. Protect from light & moisture

SHELF LIFE : 24 months

DATE OF PUBLICATION/REVIEW: 21.03.2014

Manufactured at : **ATOZ Pharmaceuticals Pvt. Ltd.**
12, Balaji Nagar, Ambattur, Chennai - 600 053. INDIA.

Marketed by:

Innocia Lifesciences Pvt. Ltd.
Block - A, No. 12, Balaji Nagar, Ambattur, Chennai - 600 053. INDIA.

PIAG36