PRODUCT MONOGRAPH

[Pr]TEVA-TICLOPIDINE

(ticlopidine hydrochloride)

250mg Tablets

Teva Standard

Inhibitor of platelet function

Teva Canada Limited
30 Novopharm Court,
Toronto, Ontario
Canada M1B 2K9
www.tevacanada.com

Date of Preparation:
November 17, 2011

Control#: 150008

PRODUCT MONOGRAPH

Pr TEVA-TICLOPIDINE

(ticlopidine hydrochloride)

Tablets

THERAPEUTIC CLASSIFICATION

Inhibitor of Platelet Function

ACTION AND CLINICAL PHARMACOLOGY

Ticlopidine hydrochloride is an inhibitor of platelet aggregation. It causes a time and dose dependent inhibition of platelet aggregation and release of platelet factors, as well as a prolongation of bleeding time. The drug has no significant *in vitro* activity.

The exact mechanism of action is not fully characterized, but does not involve inhibition of the prostacyclin/thromboxane pathways or platelet cAMP.

Ticlopidine hydrochloride interferes with platelet membrane function by inhibiting ADP induced platelet-fibrinogen binding and subsequent platelet-platelet interactions. The effect of ticlopidine hydrochloride on platelet function is irreversible.

Template bleeding time is usually prolonged by 2 to 5 fold of baseline values with the therapeutic dose of ticlopidine hydrochloride.

Upon discontinuation of ticlopidine hydrochloride dosing, bleeding time and other platelet function tests return to normal within 1 week in the majority of patients.

The correlation between ticlopidine hydrochloride plasma levels and activity is still under investigation. Much of the following data was obtained from older patients corresponding to the age of patients participating in clinical trials (mean age: 63 years).

After oral administration of the therapeutic dose of ticlopidine hydrochloride, rapid absorption occurs, with peak plasma levels occurring at approximately 2 hours after dosing. Absorption is at least 80% complete. Administration of ticlopidine hydrochloride after meals results in an increased (20%) level of ticlopidine hydrochloride in plasma.
Steady state plasma levels of ticlopidine hydrochloride in plasma are obtained after approximately 14 days of dosing at 250 mg b.i.d. The terminal elimination half-life is 4 to 5 days. However, inhibition of platelet aggregation is not correlated with plasma drug levels.

Ticlopidine hydrochloride binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins in a non-saturable manner.

Ticlopidine hydrochloride is metabolized extensively by the liver; no intact ticlopidine hydrochloride is detected in the urine. Unmetabolized ticlopidine hydrochloride is a minor component in plasma after a single dose, but at steady state, ticlopidine hydrochloride is the major component.

Impaired hepatic function resulted in higher than normal plasma levels of unchanged ticlopidine hydrochloride after single doses or after multiple doses.

Inhibition of platelet aggregation is detected within 2 days of administration with 250 mg b.i.d. Maximum platelet aggregation inhibition is achieved 8 to 11 days following dosing with 250 mg b.i.d.

A comparative, single-dose, two-way bioavailability study was performed on TEVA-TICLOPIDINE 250 mg tablets and TICLID® 250 mg tablets. The pharmacokinetic data

calculated for a single oral dose of 2 X 250 mg tablets (ticlopidine HCl tablet formulations TEVA-TICLOPIDINE versus TICLID®) under non-fasting conditions are in the following table.

Geometric Mean Arithmetic Mean (C.V.)				
	TEVA-TICLOPIDINE (2 X 250 mg)	TICLID®** (2 X 250 mg)	Ratio of Geometric Means (%)	90% Geometric Confidence Interval
AUC_{0-72} (ng·hr/mL)	6412 8223 (73)	6486 7761 (59)	98.9	84.46% - 108.01%
AUC_I (ng·hr/mL)	6954 9014 (76)	7249 8797 (60)	95.9	81.61% - 105.26%
C_{max} (ng/mL)	1626 1943 (65)	1694 1909 (51)	96.0	80.14% - 107.26%
T_{max}* (hr)	2.56 (0.70)	2.95 (0.75)	---	---
$T_{½}$* (hr)	21.4 (10)	27.6 (19)	---	---

*For the Tmax and $T_{½}$ parameters these are the arithmetic means (standard deviation)

**TICLID® 250 mg Tablets manufactured by Syntex Inc., Canada.

INDICATIONS AND CLINICAL USE

TEVA-TICLOPIDINE (ticlopidine hydrochloride) tablets are indicated for reduction of the risk of recurrent stroke for patients who have experienced at least one of the following events: complete thromboembolic stroke, minor stroke, reversible ischemic neurological deficit (RIND), or transient ischemic attack (TIA) including transient monocular blindness (TMB).

Because ticlopidine can cause life threatening thrombotic thrombocytopenic purpura (TTP) and other blood dyscrasias including neutropenia/agranulocytosis, and aplastic anemia (WARNINGS, Haematological Complications), ticlopidine should be reserved for patients who are intolerant or allergic to acetylsalicylic acid therapy, have failed acetylsalicylic acid therapy, and who are not suitable candidates for other antiplatelet therapy.

Considerations in the selection of stroke prevention therapy should include the patient's current medical status and history, and their ability to comply with the required blood monitoring instructions concerning the use of ticlopidine.

CONTRAINDICATIONS

TEVA-TICLOPIDINE (ticlopidine hydrochloride) is contraindicated in the following conditions:

1. Known hypersensitivity to drug or its excipients
2. Presence or history of hematopoietic disorders (such as neutropenia, thrombocytopenia or agranulocytosis).
3. Haemorrhagic diathesis or presence of haemostatic disorder.
4. Conditions associated with active bleeding, such as bleeding peptic ulcer or intracranial bleeding.
5. Severe liver dysfunction.

WARNINGS

Ticlopidine can cause life threatening thrombotic thrombocytopenic purpura (TTP) and other blood dyscrasias including neutropenia/agranulocytosis, and aplastic anemia (see WARNINGS, Haematological Complications and ADVERSE REACTIONS). Ticlopidine should be reserved only for patients at high risk of stroke (see INDICATION AND CLINICAL USE).

All patients should have a white blood cell count with a differential and platelet count performed at baseline, before treatment is initiated, followed by monitoring at weekly intervals, to the end of the third month of therapy with ticlopidine (see WARNINGS, Haematological Complications). If any evidence of TTP or neutropenia is seen, ticlopidine should be immediately discontinued. For the first 3 month of therapy, prescriptions of ticlopidine should be limited to a 14-day supply (see AVAILABILITY).

Hematological Complications

All forms of hematological adverse reactions are potentially fatal. Rarely, cases of pancytopenia, aplastic anemia or thrombocytopenia have been reported. Thrombotic thrombocytopenic purpura (TTP) is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction and fever. The signs and symptoms can occur in any order, in particular, clinical symptoms may procede laboratory findings by hours or days.

TTP was not seen during clinical trials but a number of cases (with fatal outcomes) have been reported to date through spontaneous worldwide post-marketing reporting. The estimated incidence of TTP in association with the use of ticlopidine for the prevention of stroke and for the prevention of thrombosis following coronary stent placement is one case per 1600 to 5000 patients treated (0.06% to 0.02%), while in the general population TTP is estimated to occur at a frequency of 3.7 cases per year per million persons (0.00037%). The median time to occurrence was 3 -4 weeks from the start of therapy, but a few cases occurred as soon as the same day of therapy, or more than 12 weeks after drug administration. Treatment consists of discontinuation of ticlopidine and plasmapheresis. Because platelet transfusions may accelerate thrombosis in patients with TTP on ticlopidine, they should be avoided.

About 2.4% of ticlopidine treated patients in clinical trials developed neutropenia (defined as an absolute neutrophil count (ANC) below $1.2x10^9$ cells/L). The incidence of severe neutropenia (ANC$<0.45x10^9$ cells/L) was 0.8%. Severe neutropenia occurs during the first 3 - 12 weeks of therapy, and may develop quickly over a few days. The bone marrow shows a reduction in myeloid precursors. The condition may be life-threatening. It is usually reversible, and the recovery occurs within 1 - 3 weeks after discontinuation of the drug but may take longer, on occasion.

In clinical trials, thrombocytopenia (defined as a platelet count of $<0.8x10^{11}$ cells/L) has been observed in 0.4% of ticlopidine patients. The incidence of thrombocytopenia in patients on ASA or placebo was 0.3% or 0.4% respectively. The thrombocytopenia may occur as an isolated

finding or in combination with neutropenia. Thrombocytopenia occurs during the first 3 - 12 weeks of therapy, and recovery usually occurs after drug discontinuation. All patients should have a white blood cell count with a differential and platelet count performed every week starting at baseline, before treatment is initiated, to the end of the third month of therapy with TEVA-TICLOPIDINE (ticlopidine hydrochloride). When the neutrophil count shows a declining trend or the neutrophil numbers have fallen below 30% of the baseline, the values should be confirmed. If the presence of neutropenia (ANC $<1.2x10^9$ cells/L) or thrombocytopenia ($<0.8x10^{11}$ cells/L) are confirmed, the drug should be discontinued and CBC with white cell differential and platlet count should be monitored until they return to normal. Because of the long plasma half-life of TEVA-TICLOPIDINE, it is recommended that any patient who discontinues TEVA-TICLOPIDINE for any reason within the first 90 days have an additional CBC with white cell differential count obtained two weeks after discontinuation of therapy. (See PRECAUTIONS)

Hemorrhagic Complications

Prolongation of bleeding time occurs in subjects treated with ticlopidine hydrochloride. Purpura and a few cases of more serious hemorrhagic events such as hematemesis, melena, hemothorax and intracranial bleeding have been reported. Patients must be instructed to watch for signs of bleeding disorders and to report any abnormality to their physician immediately. Ticlopidine hydrochloride therapy has to be stopped by the patient if a physician is not immediately available for consultation.

Anticoagulant/Antiplatelet Drugs

The use of heparins, oral anticoagulants and antiplatelet agents should be avoided as tolerance and safety of simultaneous administration with TEVA-TICLOPIDINE has not been established (see PRECAUTIONS- Drug Interactions). However, in exceptional cases of concomitant treatment, close clinical and laboratory monitoring is required.

Hepatic Abnormalities

Most patients receiving ticlopidine hydrochloride showed some increase of their alkaline phosphatase values above their baseline and in one-third the increase exceeded the upper reference range. In 6% the value was greater than twice the upper reference range. These increases in alkaline phosphatase were nonprogressive and asymptomatic. In clinical trials, 2 cases (0.1%) of cholestatic jaundice accompanied by elevated transaminases alkaline phosphatase, and bilirubin levels above 43 μmol/L have been observed. Both patients recovered promptly upon drug discontinuation. There have been rare reports of hepatitis during the first months of treatment from postmarketing experience. The course has generally been favourable after treatment was discontinued with recovery periods ranging from 4 - 239 days and a median of 30 days.

Pregnancy

The safety of ticlopidine hydrochloride in pregnancy has not been established. It should not be used in pregnant patients.

Pediatric Use

Safety in children has not been studied. Do not use in pediatric patients.

PRECAUTIONS

Selection of Patients

TEVA-TICLOPIDINE (ticlopidine hydrochloride) should be used only for the established indications (see INDICATIONS) and should not be given to patients with hematopoietic disorders, hemostatic disorders, patients suffering from conditions associated with active bleeding (see CONTRAINDICATIONS) and patients anticipating elective surgery. In clinical trials elderly patients tolerated the drug well, but safety in children and pregnant women have not been established.

Clinical Monitoring

All patients have to be carefully monitored for clinical signs and symptoms of adverse drug reactions (see ADVERSE EFFECTS). The signs and symptoms possibly related to neutropenia (fever, chills, sore throat, ulcerations in oral cavity), thrombocytopenia and abnormal hemostasis (prolonged or unusual bleeding, bruising, purpura, dark stool), jaundice (including dark urine, light colored stool) and allergic reactions should be explained to the patients who should be advised to stop medication and consult their physician immediately if any of these occur.

Laboratory Monitoring

All patients should have a white blood cell count with a differential and platelet count performed every week starting at baseline, before treatment is initiated, to the end of the third month of therapy with TEVA-TICLOPIDINE (ticlopidine hydrochloride). When the neutrophil count shows a declining trend or the neutrophil numbers have fallen below 30% of the baseline, the values should be confirmed. If the presence of neutropenia (ANC $<1.2 \times 10^9$ cells/L) or thrombocytopenia ($<0.8 \times 10^{11}$ cells/L), are confirmed, the drug should be discontinued. Because of the long plasma half-life of TEVA-TICLOPIDINE, it is recommended that any patient who discontinues TEVA-TICLOPIDINE for any reason within the first 90 days have an additional CBC with white cell differential count obtained two weeks after discontinuation of therapy (see WARNINGS). Thereafter, the WBC counts need only be repeated for symptoms or signs suggestive of neutropenia.

Liver function tests should be conducted during therapy with TEVA-TICLOPIDINE (ticlopidine hydrochloride) in response to signs and symptoms suggestive of hepatic dysfunction.

Elective Surgery

Ticlopidine hydrochloride should be discontinued 10 to 14 days prior to elective surgery or dental extraction and bleeding time and thrombocyte count performed before the procedure if clinically indicated.

Emergency Surgery

Prolonged bleeding during surgery may be a problem in ticlopidine hydrochloride treated patients. Transfusions of fresh platelets would be expected to improve hemostasis in such patients, but there are no data from clinical trials to confirm this expectation. There are data from clinical pharmacology trials that indicate treatment with glucocorticosteroids can normalize bleeding time in ticlopidine hydrochloride treated subjects, but there is no experience with ticlopidine hydrochloride treated surgical patients to show that such treatment improves hemostasis.

Specific Precautions

Liver: Ticlopidine hydrochloride is contraindicated in patients with severe liver dysfunction or cholestatic jaundice. Mild increase of alkaline phosphatase may be seen for the duration of the treatment and is inconsequential in the majority of patients (see WARNINGS and CONTRAINDICATIONS).

Kidneys: Ticlopidine hydrochloride has been well tolerated in patients with moderately decreased renal function. In severe renal disease, caution and close monitoring are recommended.

Gastrointestinal: Conditions associated with active bleeding, such as bleeding ulcers, constitute contraindication for ticlopidine hydrochloride. Clinical judgment and monitoring of stool for occult blood are required for patients with a history of ulcerative lesions.

Trauma: Ticlopidine hydrochloride should be discontinued temporarily until the danger of abnormal bleeding is eliminated. A single fatal case of intracranial bleeding following head trauma has been reported. The extent to which ticlopidine hydrochloride may have contributed to the severity of the bleeding is unknown.

Drug Interactions: Since ticlopidine hydrochloride is metabolized by the liver, dosing of TEVA-TICLOPIDINE or other drugs metabolized in the liver may require adjustment upon starting or stopping therapy.

The following table outlines the agents which have been concomitantly administered with ticlopidine hydrochloride and the observed interaction if any:

DRUG INTERACTIONS

AGENTS	OBSERVED INTERACTION
COMBINATIONS WITH INCREASED HAEMORRHAGIC RISK	
NSAIDs including ASA	The combined antithrombotic effect of ticlopidine hydrochloride and ASA or NSAIDS can lead to increased risk of haemorrhagic complications. If concomitant use of these drugs is necessary, close clinical and laboratory monitoring is required.
Heparins	Increased haemorrhagic risk due to combination of anticoagulant and platelet antiaggregant activity. If such drugs are necessary, close clinical and laboratory monitoring is required.
COMBINATIONS REQUIRING SPECIAL PRECAUTIONS	
Antipyrine and products metabolized by hepatic microsomal enzymes	30% increase in $t_{½}$ of antipyrine. Dose of products metabolized by hepatic microsomal enzymes to be adjusted when starting or stopping concomitant therapy with ticlopidine hydrochloride.
Theophylline	$t_{½}$ of theophylline increased from 8.6 to 12.2 hrs along with a comparable reduction in its total plasma clearance. Monitoring of plasma levels of theophylline followed by the theophylline dose adjustment is mandatory when treating patients concomitantly with ticlopidine hydrochloride and theophylline.
Digoxin	Approximately 15% reduction in digoxin plasma levels, (little of no change in digoxin's efficacy expected)

Cimetidine	Chronic administration of cimetidine induced a 50% reduction in clearance of a single dose of ticlopidine hydrochloride.
Antacids	20% decrease in ticlopidine hydrochloride plasma level when administered after antacids.
Phenytoin	*In vitro* studies demonstrated that ticlopidine hydrochloride does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of ticlopidine hydrochloride and its metabolites have not been studied *in vivo*. Caution should be exercised in coadministering this drug with ticlopidine hydrochloride and it may be useful to remeasure phenytoin blood concentrations.
Phenobarbital	No interaction reported.

Other Concomitant Therapy

Although specific interaction studies were not performed, in clinical studies, ticlopidine hydrochloride was used concomitantly with beta-blockers, calcium channel blockers and diuretics without evidence of clinically significantly adverse interactions.

In vitro studies demonstrated that ticlopidine hydrochloride is reversibly bound to plasma proteins (98%), but that it does not interact with plasma protein binding of propanolol, which is also highly protein bound in its basic form.

Cyclosporine blood levels should be monitored in case of coadministration with ticlopidine hydrochloride. In very rare instances, lowering of cylcosporine blood levels has been reported.

Use in Women

The safety of ticlopidine hydrochloride in pregnant women has not been established. Unless absolutely indicated, ticlopidine hydrochloride should not be prescribed to a pregnant woman (see WARNINGS; TOXICOLOGY - Fertility and Reproduction).

Lactating Women

Studies in rats have shown that ticlopidine hydrochloride is excreted in milk. Unless absolutely indicated, ticlopidine should not be prescribed to a lactating woman.

ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 1 to 5 years duration, discontinuation of ticlopidine hydrochloride due to one or more adverse effects was required in 20.9% of patients. In these same trials, ASA and placebo led to discontinuation in 14.5% and 6.7% of patients respectively.

The incidence rates of adverse reactions listed were derived from multicenter, controlled clinical trials comparing ticlopidine hydrochloride, placebo and acetylsalicylic acid over study periods of up to 5 years. The rates are based on adverse reactions considered probably drug-related by the investigator. Adverse experiences occurring in greater than 1% of patients treated with ticlopidine hydrochloride in controlled clinical trials are shown as follows:

PERCENT OF PATIENTS IN CONTROLLED STUDIES

EVENT	ticlopidine hydrochloride (n = 2048) incidence	ASA (n=1527) incidence	Placebo (n=536) incidence
Diarrhea	12.5 (6.3)*	5.2 (1.8)	4.5 (1.7)
Nausea	7.0 (2.6)	6.2 (1.9)	1.7 (0.9)
Dyspepsia	7.0 (1.1)	9.0 (2.0)	0.9 (0.2)
Rash	5.1 (3.4)	1.5 (0.8)	0.6 (0.9)
GI pain	3.7 (1.9)	5.6 (2.7)	1.3 (0.4)
Neutropenia	2.4[a] (1.3)	0.8 (0.1)	1.4 (0.4)
Purpura	2.2 (0.2)	1.6 (0.1)	0.0 (0.0)
Vomiting	1.9 (1.4)	1.4 (0.9)	0.9 (0.4)
Flatulence	1.5 (0.1)	1.4 (0.3)	0.0 (0.0)

Pruritus	1.3 (0.8)	0.3 (0.1)	0.0 (0.0)
Dizziness	1.1 (0.4)	0.5 (0.4)	0.0 (0.0)
Anorexia	1.0 (0.4)	0.5 (0.4)	0.0 (0.0)

* Percent of patients (in parentheses) discontinuing clinical trials due to event

[a] Includes 0.8% of severe neutropenia

The incidence of thrombocytopenia in these controlled studies was 0.4% in the ticlopidine hydrochloride and placebo groups of patients and 0.3% in the acetylsalicylic acid patient population.

The following rare events have been reported:

Pancytopenia, bone marrow aplasia, hemolytic anemia with reticulocytosis, thrombocytopenic thrombotic purpura, jaundice, allergic pneumonitis, systemic lupus (positive ANA), peripheral neuropathy, vasculitis, serum sickness, arthropathy, hepatitis, nephrotic syndrome, myositis angioedema (quincke edema), fever, hyponatremia, bleeding increased (spontaneous, post-traumatic or postoperative), cholestatic jaundice, colitis, erythema multiforme, hepatic necrosis, hepatocellular jaundice, peptic ulcer, Stevens-Johnson syndrome, renal failure, sepsis and hypersensitivity nephropathy.

Gastrointestinal: Ticlopidine hydrochloride therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. While most are mild and transient, when chronic or severe or accompanied by weight loss, fatigue and/or anorexia, it can also be indicative of colitis. The majority of the cases occur within the first 3 months of therapy. If the effect is persistent or severe, therapy should be discontinued. Typically events are resolved within 1-2 weeks thereafter.

Hemorrhagic: Ticlopidine hydrochloride has been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria, conjunctival hemorrhage, gastrointestinal bleeding and peri- and postoperative bleeding (see PRECAUTIONS- Emergency

Surgery). Intracerebral bleeding was rare in clinical trials with ticlopidine hydrochloride and was no more than that seen with comparator agents (acetylsalicylic acid, placebo).
Cutaneous: Ticlopidine hydrochloride has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within 3 months of initiation of therapy, with a mean time to onset of 11 days. If drug is discontinued, recovery should occur within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of more severe rashes.

Altered Laboratory Findings:
Hematological: Agranulocytosis, eosinophilia, neutropenia, pancytopenia, isolated thrombocytopenia (rarely accompanied by haemolytic anaemia), and thrombocytosis have been associated with ticlopidine hydrochloride administration (see WARNINGS).

Liver: Ticlopidine hydrochloride therapy has been accompanied by an increase in hepatic enzymes. In clinical trials, increases in alkaline phosphatase and transaminase levels (incidence greater than twice the upper limit of normal) were observed in both ticolpidine and placebo groups. Maximal changes occur within 1 to 4 months of therapy initiation (see WARNINGS). No progressive increases were observed in closely monitored clinical trials, but most patients with these abnormalities had therapy discontinued. Ticlopidine hydrochloride therapy has also been accompanied by a minor elevation of bilirubin and deviations in GGTP. One case of significant increase in γGT in an elderly patient was reported in the literature. γGT returned to normal upon discontinuation of ticlopidine hydrochloride therapy.

Cholesterol: Chronic ticlopidine hydrochloride therapy has been associated with increased serum cholesterol and triglycerides. Serum levels of HDL-C, LDL-C, VLDL-C, and triglycerides are increased 8 to 10% after 1 to 4 months of therapy. No further progressive elevations are seen with continuous therapy. The ratios of the lipoprotein subfractions (especially the ratio of HDL to LDL) remain unchanged. The effect is not correlated with age, sex, alcohol use or diabetes.

SYMPTOMS AND TREATMENT OF OVERDOSE

One case of deliberate overdosage with ticlopidine hydrochloride has been reported in a foreign postmarketing surveillance program. A 38 year old male took a single 6000 mg dose of ticlopidine hydrochloride (equivalent to 24 standard 250 mg tablets). The only abnormalities reported were increased bleeding time and increased SGPT. No special therapy was instituted and the patient recovered without sequelae. Based on animal studies, overdosage may result in severe gastrointestinal intolerance.

In the case of excessive bleeding after injury or surgery, standard supportive measures should be carried out if indicated, including gastric lavage, platelet transfusion and use of corticosteroids.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately

DOSAGE AND ADMINISTRATION

The recommended dose is 250 mg twice daily with food.

TEVA-TICLOPIDINE should be taken with meals to minimize gastrointestinal intolerance.

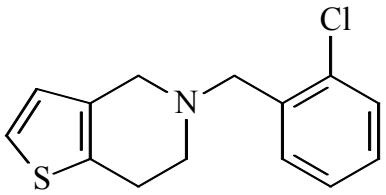
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: ticlopidine hydrochloride

Chemical Name 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno-(3,2-c) pyridine hydrochloride

Structural Formula:



· HCl

Molecular Formula: $C_{14}H_{14}ClNS \cdot HCl$ Molecular Weight: 300.25

Description: Ticlopidine hydrochloride is a white crystalline solid. Sparingly soluble in water, in ethanol, in methanol and chloroform; very slightly soluble in ethyl acetate; practically insoluble in ether. It has a pKa of 7.64 and the pH of a 2.5% aqueous solution at 25□C is between 3.5 - 4.5.

NONMEDICINAL INGREDIENTS:

Ticlopidine hydrochloride tablets contain: citric acid, corn starch, microcrystalline cellulose, magnesium stearate, povidone, and stearic acid powder. The film-coating consists of hydroxypropyl methylcellulose, hydroxypropylcellulose, polyethylene glycol, talc, titanium dioxide and triethyl citrate.

STABILITY AND STORAGE RECOMMENDATIONS:

Store blister packs between 15°-25°C and bottles between 15°- 30°C. Dispense in light resistant containers. Blister packs should not be exposed to light.

AVAILABILITY

TEVA-TICLOPIDINE (ticlopidine hydrochloride) 250 mg tablets are white to off white, oval shaped, film coated tablets engraved with "**N**" on one side and "**250**" on the other side. They are

available bottles of 100 tablets and in boxes of 28 tablets (2 blisters of 14 tablets) and 56 tablets (4 blisters of 14 tablets). For the first 3 months of therapy, only request or dispense the 14 days supply of tablets (see Precautions).

TEVA-TICLOPIDINE - PATIENT PACKAGE INSERT

PLEASE READ CAREFULLY

You have been prescribed TEVA-TICLOPIDINE by your doctor. Reading this information can help you learn about TEVA-TICLOPIDINE and how to make this medicine work best for you. If you have any questions after reading this information, speak with your doctor or pharmacist.

What is TEVA-TICLOPIDINE?

TEVA-TICLOPIDINE is a product name for the prescription drug ticlopidine. Each film-coated tablet of TEVA-TICLOPIDINE contains 250 mg of ticlopidine hydrochloride, the active ingredient. It also contains additional (non-medicinal or inactive) ingredients. These are: citric acid, corn starch, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol / macrogol, povidone, sodium starch glycolate, stearic acid, talc, titanium dioxide and triethyl citrate. Ticlopidine reduces the ability of blood clotting cells (platelets) to stick to each other and to the walls of blood vessels. This action reduces the tendency of blood to clot in unwanted places such as in narrowed blood vessels.

What is TEVA-TICLOPIDINE used for?

TEVA-TICLOPIDINE is usually prescribed to patients who have had a previous stroke or who experienced one or more warning episodes indicating an increased risk of stroke, such as transient ischemic attacks, ischemic neurological changes or minor strokes. A stroke occurs when a clot (or thrombus) forms in a blood vessel in the brain, or forms in another part of the body and breaks off and then travels to the brain (embolus). In clinical trials, ticlopidine hydrochloride has been shown to decrease both the stroke mortality and the occurrence of repeat stroke in such patients.

What should you tell your doctor before you start taking TEVA-TICLOPIDINE?

Before beginning treatment with TEVA-TICLOPIDINE, make sure your doctor knows if:

- you ever had a bad reaction to TEVA-TICLOPIDINE or any of its inactive ingredients
- you have a history of blood disorders such as low white blood cell counts (neutropenia), low platelets (thrombocytopenia) or lack of white blood cells (agranulocytosis)
- you have active bleeding problems such as stomach or intestinal ulcers, intracranial (within the head) bleeding
- you have severe liver disease
- you are pregnant, plan on becoming pregnant, or are breast-feeding a child
- you are taking any other medicines (including those not prescribed by your doctor). TEVA-TICLOPIDINE is known to interfere with some other drugs.

This information will help your doctor and you decide whether you should use TEVA-TICLOPIDINE, and what extra care may need to be taken while you are on the medication.

How should TEVA-TICLOPIDINE be taken?

Your doctor has prescribed TEVA-TICLOPIDINE after carefully studying your case. Other

people may not benefit from taking this medicine, even though their problems may seem similar to yours. Do not give your TEVA-TICLOPIDINE to anyone else.

TEVA-TICLOPIDINE is intended for oral use only. The usual dosage is two tablets daily with meals throughout the course of treatment.

TEVA-TICLOPIDINE has been prescribed to you to be used strictly as directed by your **doctor**. As certain adverse reactions may occur in some patients (see below), you will have to be carefully monitored by your doctor for their signs and symptoms especially for the first three months you are on TEVA-TICLOPIDINE. If you stop taking TEVA-TICLOPIDINE for any reason within the first 3 months, you will still need to have your blood tested for an additional two weeks after you have stopped taking TEVA-TICLOPIDINE.

You will also be required to have a blood test (to measure your blood count and some biochemical indicators) before you start taking ticlopidine and then every week for the first three months you are on ticlopidine.

It is also very important that you report to your doctor immediately if you noticed:
- **any sign of infection** such as fever, chills, sore throat, ulcers in the mouth, etc.
- **abnormal bleeding and bruising or dark stool**
- signs of **jaundice** (yellow eyes or skin, dark urine or light coloured stool).
- signs of fever, weakness, difficulty speaking or seizures
- **skin rash**
- persistent **diarrhea**

as they could be signs of side effects.

If your doctor is not immediately available, discontinue the medication until he/she can be consulted with.

If you are to have any surgery or dental extraction, **inform the surgeon or dentist that you are on TEVA-TICLOPIDINE**, which may cause prolonged bleeding.

Taking other medicines:
TEVA-TICLOPIDINE may alter your response to some medications; therefore, you should tell your doctor if you are presently taking any other medications. Your doctor will determine whether medications should be discontinued or if close monitoring or adjustments to the dosage or schedule are necessary. In particular, inform your doctor if you are taking any of the following medications: heparins, oral anticoagulants, antiplatelet drugs, non-steroidal anti-inflammatory drugs or acetylsalicylic acid and derivatives, theophylline, digoxin, phenobarbital, phenytoin or cyclosporine.

What are the possible unwanted effects of TEVA-TICLOPIDINE?
About 20% of patients will experience some side-effects caused by TEVA-TICLOPIDINE. Most side effects develop during the first three months of treatment and they usually disappear within 1-2 weeks after TEVA-TICLOPIDINE is stopped. The potentially more serious adverse reactions are the following:

- Decreased white blood count occurs in about 2% of patients on TEVA-TICLOPIDINE treatment. This condition will cause reduced resistance to infection. Regular blood tests are necessary to detect this side effect early and stop the medication. In less than 1% of patients, the white blood count can drop to very low levels, but discontinuation of TEVA-TICLOPIDINE therapy will almost always result in complete recovery.

- Thrombotic thrombocytopenic purpura (TTP) is a serious blood disorder. TTP can occur in some patients taking ticlopidine. TTP can sometimes be associated with serious consequences such as a large fall in platelet count or red blood cell count measured in your blood tests, kidney problems, fever, hallucinations, headaches and confusion, or changes in consciousness.

- Increased bleeding tendency manifested by prolonged bleeding from traumatic or surgical wounds, bruising, bleeding into gastrointestinal tract (manifested by black stool), etc. occurs rarely, in less than 1% of patients, but has to be watched for if you have a history of bleeding disorders, gastroduodenal ulcers, etc. (discuss your medical history with your physician), or if you are about to have a surgical procedure (do not forget to inform the surgeon or dentist).

- Very rarely jaundice and/or liver failure, usually reversible upon withdrawal of TEVA-TICLOPIDINE, have been reported.

More common side-effects are upset stomach - (to minimize this possibility, **always take TEVA-TICLOPIDINE with meals**), diarrhea, and skin rashes.

Your doctor may wish to do routine blood tests from time to time as TEVA-TICLOPIDINE may alter blood counts, blood flow (hemostasis) or liver tests.

As with any drug, the possibility of an unexpected, previously unknown, potentially serious adverse reaction can never be ruled out. Report any other undesirable or unpleasant effects not mentioned in this leaflet to your doctor.

What should you do in case of an overdose or accidental taking of TEVA-TICLOPIDINE?
Contact you doctor and/or poison control centre immediately if you suspect you have taken an overdose or someone else accidentally takes your TEVA-TICLOPIDINE. If you are unable to contact them, go to a hospital emergency department for medical help.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

How should this product be stored?
- Keep out of the reach of children.
- Store blister packs between 15°-25°C and bottles between 15°- 30°C. Protect from light.
- Do not use this medicine after the expiry date on the package.

WARNING

Use only as directed.

This insert does not provide all known information about TEVA-TICLOPIDINE. If you do not understand this information, or have any questions or concerns about your treatment, please speak with your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Teva Canada Limited at:
1-800-268-4127 ext. 5005 (English)
1-877-777-9117 (French)
or druginfo@tevacanada.com

This leaflet was prepared by:
Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

Last revised: November 17, 2011

PHARMACOLOGY

Ticlopidine hydrochloride is a new chemical entity with a mechanism of platelet aggregation inhibition different from other available antithrombotic agents.

Primary Pharmacology

1. *Ex vivo/ in vivo* studies

The administration of ticlopidine hydrochloride to intact animals results in inhibition of platelet aggregation activity that is dose- and time-dependent. For *ex vivo* aggregation induced by ADP, ID50 values less than 50 mg/kg were found for ticlopidine hydrochloride in the mouse, rat, monkey, baboon and human (ID50=the dose of ticlopidine hydrochloride needed to produce a 50% inhibition of *ex vivo* ADP induced platelet aggregation). These data are shown in the table below:

Species	ID_{50} mg/kg	Route	Treatment duration	Inducer
rat	31	p.o.	1 dose	ADP
	44	p.o.	1 dose	ADP
	22	p.o.	1 dose	Collegen
Mouse	~10	p.o.	3 days	ADP
Guinea Pig	~300	p.o.	1 dose	ADP
	~300	p.o.	1 dose	Collegen
	>100	p.o.	3 days	ADP
Rabbit	~50	p.o.	7 days	ADP
Dog	<50	p.o.	3 days	ADP
Pig	100	p.o.	3 days	ADP
Rhesus Monkey	>10	p.o.	5 days	ADP
Baboon	<100	p.o.	1 dose	ADP

	<100	p.o.	3 days	ADP
	<25	p.o.	2-3 days	ADP
Man	<10	p.o.	5-8 days	ADP

Ticlopidine hydrochloride is effective whether administered orally, intravenously or subcutaneously. Ticlopidine hydrochloride inhibits aggregation stimulated by a variety of inducers. The inhibition of aggregation *ex vivo* occurs at plasma levels of ticlopidine hydrochloride far below those required for *in vitro* inhibition. The inhibitory effects of ticlopidine hydrochloride are long-lasting (>24 hrs). In order to restore aggregation rapidly, administration of normal platelets is required.

When aggregation inducers are administered to intact animals, transient thrombocytopenia or mortality occurs. Ticlopidine hydrochloride protects mice, rats and rabbits from thrombocytopenia or death induced by ADP, collagen, liquoid (sodium polyanethol sulfate) and other agents when the challenge was given subsequently to ticlopidine hydrochloride dosing.

2. *In vitro* studies

In vitro studies have shown that ticlopidine hydrochloride is a relatively weak inhibitor of platelet aggregation, regardless of the species whose platelet-rich plasma (PRP) is used. The concentration required for inhibition of aggregation *in vitro* are several hundred-fold higher than the peak plasma levels found *in vivo.* When ticlopidine hydrochloride was studied in the PRP of rats, rabbits and humans, the IC50 values for inhibition of aggregation induced by ADP were about 1 mM whereas concentrations of ticlopidine hydrochloride in plasma after therapeutic doses (250 mg B.I.D.) are in the range of 1 to 5 μM.

3. Thrombosis Models

Ticlopidine hydrochloride inhibits thrombus formation in several *in vivo* thrombosis models which are considered to be platelet dependent (see page 19). In the rat, single oral doses of ticlopidine hydrochloride as low as 5 mg/kg inhibit the formation of thrombus in an AV shunt while acetylsalicylic acid in doses as high as 300 mg/kg fails to inhibit thrombosis in this model.

Ticlopidine hydrochloride, given for three days, inhibits thrombus formation induced by dental clips inserted in the inferior *vena cava*, by ligation of the *vena cava* and by insertion of a silk thread in a shunt between the carotid artery and jugular vein. In rabbits treated with ticlopidine hydrochloride, thrombus formation is inhibited in a glass extracorporeal shunt between the dorsal aorta and inferior *vena cava*. When given to dogs, ticlopidine hydrochloride prevents thrombus formation during dialysis and reduces thrombus formation after electrical stimulation of the femoral vein. Thrombosis in dogs with implanted Gore-Tex grafts is reduced by prior treatment of the animals with ticlopidine hydrochloride.

Thus, ticlopidine hydrochloride is effective in reducing or preventing thrombosis in rats, rabbits, dogs and baboons in several different models. The efficacy of ticlopidine hydrochloride in these thrombosis models supports the concept that the compound possesses utility in the treatment of human thrombotic disorders.

4. Platelet Survival

Beta-aminopropionitrile, when given to rats, decreases the platelet half-life. Treatment with 10 mg/kg/day, p.o. of ticlopidine hydrochloride for 7 days, normalizes platelet half-life in this model. Ticlopidine at 25 mg/kg, p.o. completely normalized platelet survival in baboons fitted with AV cannulae after 3 days of treatment. Thus, ticlopidine hydrochloride treatment decreases the enhanced platelet consumption generated in these models.

5. Platelet Retention and Adherence

Platelet adherence plays an important role in both thrombosis and atherosclerosis. Treatment of animals and humans with ticlopidine hydrochloride resulted in the inhibition of retention of platelets to glass beads. Platelets from rabbits treated with ticlopidine hydrochloride displayed reduced adherence to a subcellular matrix from cultured endothelial cells. When de-endothelialized carotid arteries of rats dosed with ticlopidine hydrochloride were compared with de-endothelialized arteries from control animals, an approximately 50% reduction in adherence of platelets to the de-endothelialized carotid artery was found; this effect was associated with a 50% reduction in myointimal proliferation.

6. Atherosclerosis Models

Ticlopidine hydrochloride was tested in two models of angioplasty in rabbits with mixed results. No difference in intimal hyperplasia between control and ticlopidine-treated (50 mg/kg/day, p.o.) Dutch belted rabbits were observed for 14 days after balloon induced endothelial damage of the iliac arteries. However, when the endothelial cells of the aorta were removed by balloon catherterization in New Zealand white rabbits, 30 and 60 days after ballooning, ticlopidine hydrochloride-treated (50 mg/kg/day, p.o.) animals showed 46% and 32%, reduction, respectively, in intimal proliferation when compared to controls.

7. Coagulation, Fibrinolysis and Bleeding Time

Ticlopidine hydrochloride has no effect on the classical coagulation or fibrinolytic systems. Analysis of several experiments in which coagulation was induced by aortic pieces from ticlopidine hydrochloride-treated rats, indicates there is a prolongation of coagulation time and this is observed only in the presence of platelets. As expected for an agent which inhibited platelet aggregation, prolongation of bleeding times is observed in several animal models as well as in humans.

8. Physical Properties of Blood

Ticlopidine hydrochloride was shown in rats to decrease blood viscosity (at doses of 200 mg/kg) under various shear conditions and to increase erythrocyte deformability (at doses of 30 or 300 mg/kg).

9. Fibrinogen Binding

Fibrinogen is required for normal human platelet function *in vivo* and *in vitro.* Fibrionogen binds to platelets when they are stimulated. It has been established that the fibrinogen molecules bound to the platelet as a result of platelet stimulation are directly involved in the platelet aggregation response. The primary mediator of fibrinogen binding to platelets is ADP. Studies on the effects of ticlopidine hydrochloride and several other platelet aggregation inhibitors on fibrinogen binding revealed that ticlopidine hydrochloride displays unique effects. Neither acetylsalicylic acid nor the prostaglandins, PG12 and PGE1 when added to PRP, inhibit fibrinogen binding. Ticlopidine hydrochloride when added *in vitro* is also inactive. However,

after dosing to both animals and humans (Fig. 1), ticlopidine hydrochloride inhibits fibrinogen binding. The inhibition was irreversible for the life of the platelets.

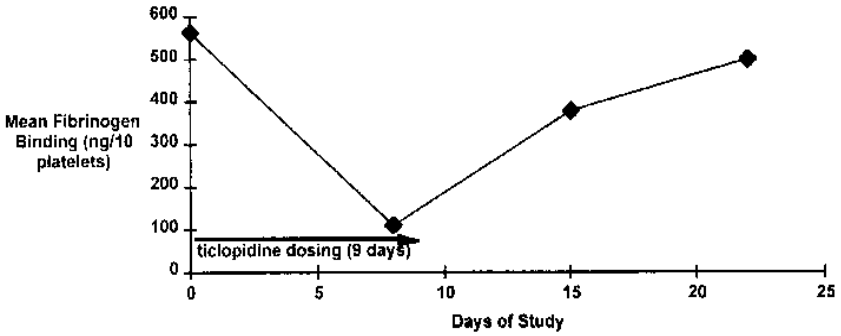


Figure 1: The inhibition of fibrinogen binding to human platelets stimulated by ADP after ticlopidine treatment of healthy volunteers.

10. Mechanism of Action

The mechanism of action of ticlopidine is still unknown. It does not inhibit the cyclooxygenase enzyme system.

Small but significant cAMP elevations have been noted in platelets from ticlopidine hydrochloride-treated animals and humans. However, the lack of an effect of an adenylate cyclase inhibitor on the inhibition by ticlopidine hydrochloride casts doubt on the relevance of cAMP elevation to the mechanism of action of ticlopidine hydrochloride.

The above data indicate that ticlopidine hydrochloride does not act via prostaglandin or cAMP dependent pathways. However, there is some evidence that ticlopidine acts by inhibition of the ADP-mediated pathways of platelet aggregation. The initial rate of ADP-induced aggregation is independent of products released from platelet granules and products of the platelet cyclooxygenase pathway. Ticlopidine hydrochloride treatment of human volunteers results in inhibition of the rate of ADP-induced aggregation (Fig. 2). Another of the actions of ADP is to promote the binding of fibrinogen to specific receptors on the platelet membrane, which is necessary for platelet-platelet adherence during aggregation. As shown in Figure 1, ticlopidine

hydrochloride inhibits the ADP-stimulated binding of fibrinogen to human platelets, providing further evidence for the inhibition of ADP-mediated mechanisms by ticlopidine hydrochloride.

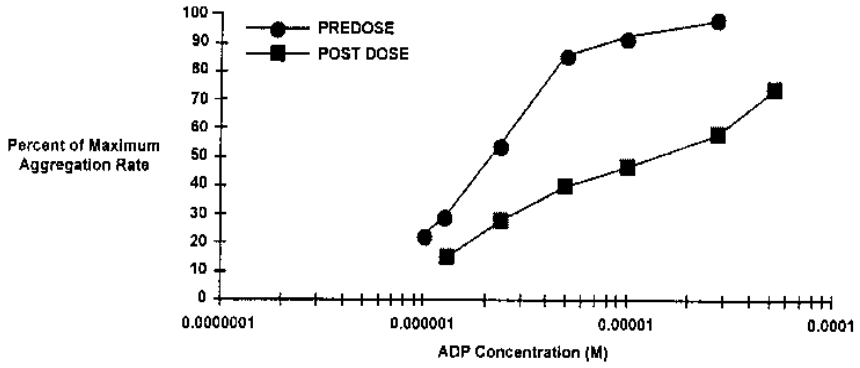


Figure 2: Inhibition of initial rate of human platelet aggregation: ADP dose response effects.

The observation that ticlopidine hydrochloride is essentially inactive when added directly to suspensions of platelets has resulted in speculation that the platelet inhibitory activity of ticlopidine hydrochloride is mediated by a metabolite. However, inhibition of platelet aggregation does not appear to be mediated by circulating metabolites in plasma. Addition of plasma from animals or humans treated with ticlopidine hydrochloride to platelets from untreated individuals do not inhibit platelet aggregation, indicating that circulating levels of ticlopidine hydrochloride or its metabolites does not directly inhibit platelet aggregation. 2-Hydroxy ticlopidine hydrochloride (2-HT) is the only identified metabolite of ticlopidine hydrochloride which significantly inhibits platelet aggregation after oral administration. However, 2-HT is also relatively inactive in vitro against platelets and has not been detected (<0.05 mg/mL) in plasma of rats, mice, rhesus monkeys, baboons or humans given oral doses of ticlopidine. The metabolism of ticlopidine hydrochloride to 2-HT may represent an initial step which results in formation of an active metabolite.

Although a number of studies have examined the effects of agents which alter drug metabolism on the platelet inhibitory activity of ticlopidine hydrochloride, the results of these studies are equivocal. The role of metabolism of ticlopidine hydrochloride in the development of inhibition of platelet aggregation remains unclear but it is unlikely to be due to a circulating metabolite.

Based on the above, certain characteristics of ticlopidine's mechanism of action have been established .

Characteristics of Ticlopidine Hydrochloride's Mechanism of Action

- Not a cyclooxygenase inhibitor (no inhibition of PGI_2 formation)
- Not phosphodiesterase inhibitor.
- Action not dependent on cAMP elevation.
- Action not dependent of prostaglandin formation.
- Action is irreversible for the life of the platelet.
- No metabolite directly responsible for ticlopidine's action has been identified.
- Inhibits fibrinogen binding.
- Evidence suggests ticlopidine hydrochloride primarily inhibits ADP effects

Although the mechanism by which ticlopidine hydrochloride inhibits the ADP-mediated pathway for platelet aggregation is not yet known, it is clear from the evidence that ticlopidine exerts its inhibition of platelet aggregation induced by a variety of stimulants by inhibiting the ADP component of the aggregation pathway. Ticlopidine hydrochloride therefore, represents an antiplatelet agent with a mechanism of action distinct from that of other available antithrombotic agents.

Clinical Pharmacology

The effect of ticlopidine hydrochloride on platelet function is irreversible as shown both by inhibition of fibrinogen binding after washing and by inhibition of platelet aggregation after resuspension of platelets in buffered medium.

At the therapeutic dose, ADP-induced platelet aggregation is inhibited by 50-70%. Lower total daily doses of 375 and 250 mg result in 30-60% and 25-50% inhibition of platelet aggregation, respectively.
Following on oral dose of radioactive ticlopidine hydrochloride administered in solution, 60% of the radioactivity was recovered in the urine and 23% in the feces. Ticlopidine hydrochloride is metabolized extensively by the liver. Unmetabolized ticlopidine hydrochloride is a minor component in plasma after a single dose, but at steady state, ticlopidine hydrochloride is the major component.

Patients with normal, mildly or moderately impaired renal function were studied for pharmacokinetic and platelet pharmacodynamic effects of ticlopidine given as 250 mg B.I.D. for 11 days. Concentrations of unchanged ticlopidine were measured after a single 250 mg dose and after the final 250 mg dose on day 11 in subjects with normal (creatinine clearance Ccr=80-150 mL/min), mildly impaired (Ccr=50-80 mL/min) and moderately impaired (Ccr=20-50 mL/min) renal function. There was a pattern of increasing AUC values and decreasing plasma clearance with increasing renal impairment. There were no statistical differences in ADP-induced aggregation. Bleeding times showed significant prolongation only in the moderately impaired patients.

The effect of decreased hepatic function on the pharmacokinetics of ticlopidine hydrochloride was studied in 17 patients with advanced cirrhosis. The average plasma concentration of ticlopidine in these subjects was slightly higher than that seen in normal subjects of similar age.

General Pharmacology
At the commonly used therapeutic dose, ticlopidine hydrochloride has no known significant pharmacological action in man other than inhibition of platelet function.

Ticlopidine hydrochloride has no appreciable CNS effects in mice or rats. It does not affect behavior in the mouse or modify stereotypy or food intake in rats. Ticlopidine hydrochloride is inactive in animal models of inflammation that detect cyclooxygenase activity, in accord with the demonstrated lack of cyclooxygenase inhibition in platelets. Ticlopidine hydrochloride has no

known effect on immunologic function in animal models and displays no activity in antiviral screens. Ticlopidine hydrochloride does not inhibit tumor cells in culture but did show occasional ability to reduce metastasis induced by injection of tumor cells in mouse and rat models. Ticlopidine hydrochloride does, however, prolong the time to hyperacute renal xenograft rejection in both rabbits and cats.

Ticlopidine hydrochloride produces rapid, transient, dose-related decreases in mean blood pressure of less than 5 min duration following intravenous administration to anesthetized rats. Subsequent to oral ticlopidine hydrochloride administration in spontaneously hypertensive rats, non-dose-related decreases in systolic blood pressure are observed and the duration exceeds 24 hr. Intracoronary administration of ticlopidine hydrochloride in the Langendorff dog heart preparation produces dose-related increases in coronary blood flow with no increase in heart rate or myocardial oxygen consumption. In the open-chest anesthetized dog, intravenous ticlopidine hydrochloride produces rapid non-dose-related decreases in mean blood pressure and increases in aortic blood flow of 0.5-1.0 min duration. At the highest dose, coronary blood flow is increased for more than 15 min. In tracheal-cannulated, spontaneously breathing dogs, intravenous ticlopidine produces rapid dose-related increases in respiratory rate with no effect on depth of respiration. Non-dose-related decreases in mean blood pressure are accompanied by small but significant increases in heart rate. Renal and femoral arterial blood flow increases of short duration occurred. No cardiac depression or ECG changes were reported.

In rats diarrhea is seen at doses which produced platelet inhibitory responses. Ticlopidine hydrochloride reduces the gastric ulceration and bleeding which developed after rats were subjected to cold restraint stress.

At a high oral dose (500 mg/kg), ticlopidine hydrochloride significantly elevates blood glucose levels in rats. After prolonged dosing at a lower dose (200 mg/kg/day for 6 wk), no changes in blood glucose levels are seen. Ticlopidine hydrochloride competitively inhibits hepatic drug-metabolizing enzymes after single doses but induces cytochromes P-450 and b5 after prolonged dosing to rats and mice. The effects of ticlopidine hydrochloride on barbiturate-induced loss-of-righting reflex and sleep prolongation were in keeping with the observed effects on the liver

drug-metabolizing enzymes. The possible role of ticlopidine in the induction of drug metabolizing enzymes in humans is still under investigation.

TOXICOLOGY

Preclinical toxicity studies were conducted with ticlopidine hydrochloride to evaluate the systemic, reproductive, carcinogenic, immunogenic, and the genotoxic effects of ticlopidine hydrochloride.

Acute Toxicity

Clinical changes observed in rats and mice include piloerection, hypothermia, hypopnea and ptosis. Observations in baboons include emesis, diarrhea and yellow-colored urine. Necropsy in rats and mice revealed lung congestion.

SPECIES	ROUTE	DURATION	DOSES	CONCLUSIONS
mouse (ddY)	Oral (gavage)	single-dose (7-day)	500, 600, 750, 825, 900, 1000, 1500	Most died within 48 hours. LD_{50} = 850 mg/kg (males) LD_{50} = 600 mg/kg (females) Nonlethal dose >750 mg/kg (males) and 500 mg/kg (females)
mouse	Oral (gavage)	single-dose (12-day)	500,1000, 1500	Most died within 24 hours. LD_{50} = 825 mg/kg Nonlethal dose = 500 mg/kg
mouse (Swiss)	Oral (gavage)	single-dose (8-day)	250, 500, 750, 1000, 1500	Most died within 48 hours. LD_{50} = 777 mg/kg Nonlethal dose = 250 mg/kg
mouse (ddY)	i.v.	single-dose (7-day)	70, 80, 90, 100	Deaths occured within 30 min. LD_{50} = 88 mg/kg (males) LD_{50} = 91 mg/kg (females) Nonlethal dose = 70 mg/kg
mouse (Swiss)	i.v.	single-dose (8-day)	25, 50, 75, 100	LD_{50} = 51 mg/kg (females) Nonlethal dose = 25 mg/kg
mouse	I.P.	single-dose (12-day)	100, 200, 300, 400, 800	Most died within 72 hours. LD_{50} = 225 mg/kg Nonlethal dose = 100 mg/kg

mouse	S.C.	single-dose (7-day)	800, 1000, 1200, 1500, 1700, 2000, 3000, 3200, 3500, 4000	Most died within 72 hours. LD50 = 3270 (males) mg/kg LD50 = 1250 (females) mg/kg Nonlethal dose: Males = 2000 mg/kg Females = 800 mg/kg
rat	oral (gavage)	single-dose (12-day)	1000, 1500, 2000, 3000	Most died within 48 hours. LD50 = 1500 mg/kg Nonlethal dose= 1000 mg/kg
rat (Sprague Dawley)	oral (gavage)	single-dose (8-day)	1000, 1500, 2000, 3000, 4000, 5000	LD50 = 1938 mg/kg Nonlethal dose= 1500 mg/kg
rat (Wistar)	i.v.	single-dose (7-day)	60, 65, 70, 75, 80, 100	Most died within 30 minutes LD50 = 70 mg/kg (males) LD50 = 79 mg/kg (females) Nonlethal dose= 60 mg/kg
rat (Wistar) males only	i.v.	single-dose (3-day)	40, 50, 55 60, 75	LD50 = 55 mg/kg (males) Nonlethal dose= 40 mg/kg
rat	I.P.	single-dose (12-day)	100, 200, 400, 800	Most died within 24 hours. LD50 = 500 mg/kg Nonlethal dose= 200 mg/kg
rat	S.C.	single-dose (7-day)	5000	Nonlethal dose> 5000 mg/kg
Baboon (Papio cynocephalus)	oral (gavage	single-dose (14-day)	1500, 3000, 6000	Emesis within 30 minutes Nonlethal dose > 6000 mg/kg
Baboon (Papio cynocephalus)	I.P.	single-dose (14-day)	500, 1000	Most died within 24 hours. LD50 = 500 - 1000 mg/kg Nonlethal dose < 500 mg/kg

Subchronic Toxicity

SPECIES	ROUTE	DURATION	DOSES	CONCLUSIONS
rat (Sprague Dawley)	oral (gavage)	4 weeks (6 days/ week)	0, 40, 150, 600	Daily oral administration of 600 mg/kg for 1 month were toxic while 150 mg/kg were nontoxic.

rat (Sprague Dawley)	oral (gavage)	4 weeks with 2 and 4 week recovery periods	0, 600	Changes following oral administration of 600 mg/kg essentially reversible.
rat (Sprague Dawley)	oral (gavage)	4 weeks	0, 1000	At 100 mg/kg daily dose, lethalities within 1 week.
rat (Sprague Dawley)	oral (gavage)	2 weeks	0, 600	The homogenous eosinophilic material in hepatocytes was characteristic of smooth endoplasmic reticulum.
dog	oral (hard gelatin capsules)	Dose titration (3 week)	0, 25, 50, 100 (each dose given for 5 days)	Nontoxic dose ² 100 mg/kg for 5 days.

Clinical changes in rats included salivation, sedation, urinary incontinence, decrease in body weight, decrease blood cell count and increased serum cholesterol.

Chronic Toxicity

SPECIES	ROUTE	DURATION	DOSES	CONCLUSIONS
rat (Sprague Dawley)	oral (gavage)	6 months 6 days/week with a 3-month interim sacrifice.	0, 10, 30, 100, 300	Daily oral ticlopidine for 6 months, nontoxic dose was 30 mg/kg/day and 100 mg/kg/day was toxic.
rat (Sprague Dawley)	oral (gavage)	18 months with interim sacrifice after 6 months	0, 30, 100, 300	Oral ticlopidine for 18 months, nontoxic dose was 30 mg/kg/day and toxic dose was 100 mg/kg/day.
Baboon (Papio cynocephalus)	oral (gavage)	12 months with interim sacrifice at 6 months	0, 30, 75, 125 (187.5 up to week 4 and 125 thereafter)	Oral ticlopidine for at least 12 months: 30 mg/kg/day was nontoxic and 75 mg/kg/day was toxic.

Chronic oral toxicity studies were conducted in rats for 6 and 18 months. At 30 mg/kg/day. mild salivation and yellow urine was observed. At higher doses: salivation, urinary incontinence, decrease in weight gain, mild anemia, increases in blood cholesterol and liver

weight, inhibition of platelet aggregation and higher morbidity were observed. The nontoxic dose was 30 mg/kg/day and the toxic dose was 100 mg/kg/day.

Baboons treated for 12 months exhibited salivation, emesis, greenish-yellow urine, decreased weight gain and inhibition of platelet aggregation at doses of 75 mg/kg/day or higher.

Carcinogenicity

No carcinogenic effects were observed in mice treated with ticlopidine for 18 months. Rats treated for 24 months with ticlopidine did not exhibit carcinogenic effects either

Reproduction and Teratology

At doses as high as 320 mg/kg/day, rats did not exhibit teratogenicity. At 400 mg/kg/day, embryo/fetotoxicity was seen, but there were no adverse effects on the reproductive performance of the offspring. Administration of 200 mg/kg/day or less was not teratogenic in the rabbit. Maternal toxicity was present at 100 and 200 mg/kg/day.

Oral doses of less than 190 mg/kg/day of ticlopidine during the perinatal and postnatal period had no adverse effects in rats. At 400 mg/kg/day, ticlopidine was toxic to dams and was accompanied by decreases in pup survival and pup weights.

Genotoxicity

Genotoxicity studies showed no mutagenic activity in Salmonella typhimurium, mice or chinese hamsters.

REFERENCES

1. Bruno JJ, Molony BA.; Ticlopidine. In: Scriabine A., ed. New Drugs Annual: Cardiovascular Drugs. New York, Raven Press, 1983; 295-331

2. Flores-Runk P, Raasch RH. Ticlopidine and antiplatelet therapy. Ann Pharmacotherapy 1993; 27: 1091-1098.

3. Panak E, et al. Ticlopidine: A promise for the prevention and treatment of thrombosis and its complications. Haemostasis 1983; 13(Suppl. 1): 1-54

4. Saltiel E, Ward A. Ticlopidine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in platelet-dependent disease states. Drugs 1987; 34: 222-262.

5. Shah H, Fratis A et al. Effect of food and antacid on absorption of orally administered ticlopidine hydrochloride. J Clin Pharmacol 1990; 30: 733-736.

6. USP DI Drug Information for the Health Care Professional, 16th Edition 1996. United States Pharmacopeial Convention Inc. 1996; pp 2883-2887.

7. Ticlid® (ticlopidine hydrochloride) 250 mg tablets Product Monograph. February 25, 2003, Hoffmann-La Roche Ltd., Mississauga, Ontario.

8. PDR 48th Edition. Physician's Desk Reference. 1994. Oradell, NJ, USA. pp. 2370-2372.

9. A two-way, single-dose non-fasting bioavailability study of ticlopidine HCl 100 mg tablets in normal, healthy, non-smoking male volunteers (Study No. 1589-1). November 1995. Data on file at Teva Canada Limited.