PRODUCT MONOGRAPH

Ticlopidine
(ticlopidine hydrochloride)

250 mg Tablets

Inhibitor of Platelet Function

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PRODUCT MONOGRAPH

TICLOPIDINE
(ticlopidine hydrochloride)

250 mg Tablets

THERAPEUTIC CLASSIFICATION

Inhibitor of Platelet Function

ACTION AND CLINICAL PHARMACOLOGY

Ticlopidine (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 two to five-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 one 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 bid. The terminal elimination half-life is 4-5 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 dose or after multiple doses.

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

COMPARATIVE BIOAVAILABILITY STUDY

A single dose, comparative, randomized, two-way, blinded, fed, crossover bioavailability study of Ticlopidine (ticlopidine hydrochloride) 250 mg tablets against the Canadian Reference Product, Ticlid® 250 mg tablets in normal, healthy, male volunteers was conducted. The pharmacokinetic data calculated for Ticlopidine and Ticlid® are presented below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA
TICLOPIDINE HYDROCHLORIDE
(1 x 250 mg)
From Measured Data

Parameter	Geometric Mean (CV%) Arithmetic Mean (CV%)		Ratio (%) of Geometric Means	90% Confidence Interval
	TICLOPIDINE	TICLID®*		
AUC_T (ng.hr/mL)	1259.87 (72.5) 1494.0 (55.1)	1252.10 (65.3) 1439.5 (46.5)	100.7	93.3% – 108.8%
AUC_I (ng.hr/mL)	1401.83 (57.4) 1595.5 (51.2)	1378.27 (54.0) 1536.3 (43.2)	100.0	92.4% – 108.1%
AUC_{0-72} (ng.hr/mL)	1267.03 (69.3) 1485.7 (53.3)	1259.78 (62.7) 1434.8 (44.7)	100.7	93.7% – 108.2%
C_{max} (ng/mL)	424.19 (71.5) 495.17 (48.9)	470.08 (64.6) 539.10 (45.7)	90.2	80.0% - 101.7%
T_{max}(h)**	1.641 (41.5)	1.882 (30.4)	N/A	N/A
$T_{½}$ (h)**	20.421 (34.3)	20.918 (37.3)	N/A	N/A

* Ticlid®, Hoffmann-La Roche Ltd., Mississauga, Ontario, Canada
** Given as arithmetic means (CV%)
N/A = Not Applicable

INDICATIONS AND CLINICAL USE

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, Rreversible Ischemic Neurological Deficit (RIND), or Transient Ischemic attack (TIA) including Transient Monocular Blindness (TMB).

Because ticlopdine 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 (ASA) therapy, have failed acetylsalicylic acid (ASA) 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

Ticlopidine (ticlopidine hydrochloride) is contraindicated in the following conditions:

1. Known hypersensitivity to drug or its excipients.
2. Presence of haematopoietic disorders (such as neutropenia and/or thrombocytopenia)
3. Presence of haemostatic disorder.

4. Conditions associated with active bleeding, such as bleeding peptic ulcer or intracranial bleeding.

5. Severe liver dysfunction.

WARNINGS

Ticlopdine can cause life threatening thrombotic thrombocytopenic purpura (TTP) and other blood dyscrasias including neutropenia/agranulocytosis, and aplastic anemia (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).

Haematological Complications

All forms of haematological adverse reactions are potentially fatal. Rarely, cases of pancytopenia, aplastic anemia or thrombocytopenia, have been reported. Thrombotic thrombocytopenic purpura (TTP) is characterized by thromboctytopenia, 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 precede 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 1.2 x 10^9 cells/L). The incidence of severe neutropenia (ANC <0.45 x 10^9 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 $<0.8 \times 10^{11}$ 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 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 and CBC with white cell differential and platelet count should be monitored until they return to normal. Because of the long plasma half-life of ticlopidine hydrochloride, it is recommended that any patient who discontinues 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 therapy has to be stopped by the patient if a physician is not immediately available for consultation.

Anticoagulant Drugs

Should be avoided as tolerance and safety of simultaneous administration with ticlopidine hydrochloride has not been established.

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, two 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.

Pregnancy

The safety of Ticlopidine 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

Ticlopidine (ticlopidine hydrochloride) should be used only for the established indications (see INDICATIONS) and should not be given to patients with haematopoietic disorders, haemostatic 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 REACTIONS). 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 coloured 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 a platelet count performed every week starting at baseline, before treatment is initiated, to the end of the third month of therapy with Ticlopidine. When the neutrophil count shows a declining trend or the neutrophil numbers have fallen below 30% of the baseline, the value 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 ticlopidine hydrochloride, it is recommended that any patient who discontinues Ticlopidine for any reason within the first 90 days, have an additional CBC with white cell differential 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 Ticlopidine in response to signs and symptoms suggestive of hepatic disfunction.

Elective Surgery

Ticlopidine 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 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 treated subjects, but there is no experience with ticlopidine 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 System: Conditions associated with active bleeding, such as bleeding ulcers, constitute contraindication for ticlopidine hydrochloride. Clinical judgement 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 is metabolized by the liver, dosing of (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:

AGENTS	OBSERVED INTERACTION
NSAIDs including ASA	Ticlopidine potentiates the effect of ASA or NSAIDs on platelet aggregation. The safety of use of ticlopidine with ASA or NSAIDs is not established.
Antipyrine and products metabolized by hepatic microsomal enzymes	30% increase in $t_{1/2}$ of antipyrine. Dose of products metabolized by hepatic microsomal enzymes to be adjusted when starting or stopping concomitant therapy with ticlopidine hydrochloride.
Theophylline	$t_{1/2}$ of theophylline increased from 8.6 to 12.2 hr along with a comparable reduction in its total plasma clearance.
Digoxin	Approximately 15% reduction in digoxin plasma levels, (little or 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 plasma level when administered after antacids.
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 significant adverse interactions.

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 in the following table were derived from multicenter, controlled clinical trials comparing ticlopidine HCl, placebo, and ASA 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 one percent of patients treated with ticlopidine hydrochloride in controlled clinical trials are shown in the Table below.

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 (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

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 ASA patient population.

The following rare events have been reported and their relationship to ticlopidine hydrochloride is uncertain

Pancytopenia, 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, 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, and sepsis.

Gastrointestinal

Ticlopidine hydrochloride therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild and transient in nature and occur within 3 months of initiation of therapy. Typically, events are resolved within 1-2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued.

Hemorrhagic

Ticlopidine hydrochloride has been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria, conjunctival hemorrhage, gastrointestinal bleeding, and postoperative bleeding.

Intracerebral bleeding was rare in clinical trials with ticlopidine hydrochloride, and was no more than that seen with comparator agents (ASA, placebo).

Rash

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

Haematological: Agranulocytosis, eosinophilia, neutropenia, pancytopenia, thrombocytopenia, and thrombocytosis have been associated with ticlopidine hydrochloride administration (see WARNINGS).

Liver: Ticlopidine hydrochloride therapy has been associated with elevations of alkaline phosphatase (See WARNINGS). Maximal changes occur within 1-4 months of therapy initiation. No further progressive increases are seen with continuous therapy. Occasionally patients developed deviations in bilirubin, SGOT, SGPT, and GGTP.

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 8-10% after 1-4 months of therapy. No further progressive elevations are seen with continuous therapy. The ratios of the lipoprotein subfractions are unchanged. The effect is not correlated with age, sex, alcohol use, or diabetes.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

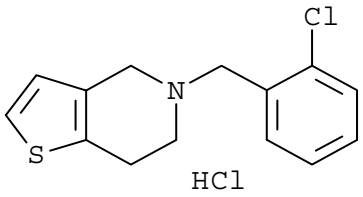
The recommended dose of Ticlopidine (ticlopidine hydrochloride) is 250 mg twice daily with food.

Ticlopidine should be taken with meals to minimize gastrointestinal intolerance.

PHARMACEUTICAL INFORMATION

Ticlopidine Hydrochloride Drug Substance

Structural Formula



Molecular Weight 300.25

Chemical Name The IUPAC chemical name of ticlopidine hydrochloride 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno-(3,2-c) pyridine hydrochloride.

Description

Ticlopidine hydrochloride is a white or almost white crystalline powder, sparingly soluble in water and in ethanol; very slightly soluble in ethyl acetate; practically insoluble in ether

pKa: 7.64

Composition

Ticlopidine (ticlopidine hydrochloride) tablets are provided, as white film coated tablets containing ticlopidine hydrochloride, povidone, corn starch, ammonium chloride, purified water, stearic acid, magnesium stearate and microcrystalline cellulose. The coating suspension consists of purified water and opadry white (ie. lactose monohydrate, hydroxypropyl methylcellulose, titanium dioxide and triacetin).

Stability and Storage Recommendations

Store at room temperature, 15°-30° C. Ticlopidine tablets should be dispensed in light resistant containers. Blister packs should not be exposed to light or excessive moisture.

AVAILABILITY OF DOSAGE FORMS

Ticlopidine (ticlopidine hydrochloride) 250 mg tablets are white, biconvex, film-coated, oval-shaped tablets with "G" on one side and T250" on the other. The tablets are available in cartons of 28 (2 x 14) tablets, and, in bottles of 100's.

For the first 3 months of therapy, only request or dispense the 14 days supply of tablets (see PRECAUTIONS).

TICLOPIDINE - PATIENT PACKAGE INSERT

PLEASE READ CAREFULLY

You have been prescribed Ticlopidine by your doctor. Reading this information can help you learn about 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 Ticlopidine?

TICLOPIDINE is a product name for the prescription drug ticlopidine. Each film-coated tablet of TICLOPIDINE contains 250 mg of ticlopidine hydrochloride, the active ingredient. It also contains additional (non-medicinal or inactive) ingredients. povidone, corn starch, ammonium chloride, purified water, stearic acid, magnesium stearate and microcrystalline cellulose. The coating suspension consists of purified water and opadry white (ie. lactose monohydrate, hydroxypropyl methylcellulose, titanium dioxide and triacetin). 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 TICLOPIDINE used for?

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 has been shown to decrease stroke mortality in patients.

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

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

- you ever had a bad reaction to 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). TICLOPIDINE is known to interfere with some other drugs.

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

How should TICLOPIDINE be taken?

Your doctor has prescribed 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 TICLOPIDINE to anyone else.

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

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 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**. If you stop taking 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 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 TICLOPIDINE**, which may cause prolonged bleeding.

Taking other medicines:

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 (ASA) and derivatives, theophylline, digoxin, phenobarbital, phenytoin or cyclosporine.

What are the possible unwanted effects of TICLOPIDINE?

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

- Decreased white blood count occurs in about 2% of patients on 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 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 TICLOPIDINE, have been reported.

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

Your doctor may wish to do routine blood tests from time to time as 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 TICLOPIDINE?

Contact you doctor and/or poison control centre immediately if you suspect you have taken an overdose or someone else accidentally takes your 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 at room temperature (15 - 30° C). Protect from light.

· Do not use this medicine after the expiry date on the package.

WARNING

Use only as directed.

Keep out of reach of children.

This insert does not provide all known information about 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, ON K1A 0K9

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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, ID_{50} values less than 50 mg/kg were found for ticlopidine hydrochloride in the mouse, rat, monkey, baboon and human (ID_{50} = the dose of ticlopidine hydrochloride needed to produce a 50 percent inhibition of *ex vivo* ADP induced platelet aggregation). These data are shown in Table 1 below:

Table 1
Comparison of Platelet Aggregation Inhibition Effects of Ticlopidine

Species	ID50 mg/kg	Route	Treatment Duration	Inducer
Rat	31	po	1 dose	ADP
	44	po	1 dose	ADP
	22	po	1 dose	Collagen
Mouse	approx 10	po	3 days	ADP
Guinea Pig	approx 300	po	1 dose	ADP
	approx 300	po	1 dose	Collagen
	> 100	po	3 days	ADP
Rabbit	approx 50	po	7 days	ADP
Dog	< 50	po	3 days	ADP
Pig	100	po	3 days	ADP
Rhesus Monkey	> 10	po	5 days	ADP
Baboon	< 100	po	1 dose	ADP
	< 100	po	3 days	ADP
	< 25	po	2-3 days	ADP
Man	< 10	po	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 concentrations 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 IC_{50} values for inhibition of aggregation induced by ADP were about 1 mM whereas concentrations of ticlopidine hydrochloride in plasma after therapeutic doses (250 mg BID) are in the range of 1 to 5 mcM (Fig.1).

3. Thrombosis Models

Ticlopidine hydrochloride inhibits thrombus formation in several *in vivo* thrombosis models which are considered to be platelet dependent (Table 2). 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 (ASA) 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.

Table 2

Ticlopidine Hydrochloride: Minimum Effect Doses (MED)
***In Vivo* Effects: Platelet Stimuli and Thrombosis Models**

Table 2

Ticlopidine Hydrochloride: Minimum Effect Doses (MED)
***In Vivo* Effects: Platelet Stimuli and Thrombosis Models**

Species	MED mg/kg	Route	No. of Doses	Challenge Agent	Endpoint
Mouse	< 30	iv	Single	ADP	Mortality
	< 100	po	Single	ADP	Mortality
	30	po	Single	Collagen	Mortality
Rat	< 125	po	Single	ADP	Mortality
	Approx 100	po	Single	Collagen	Platelet
	100	po	4 days	Collagen	Count
	200	po	4 days	Liquoid	Lung
	200	po	4 days	Endotoxin	Thrombi
	Approx 25	iv	Single	Lactic Acid	Platelet
	50	po	Single	Lactic Acid	Count
	3	po	Single	Laurate	Platelet
	10	po	7 days	APN	Count
	200	po	3 days	Clip	Lung
	5	po	Single	AV Shunt	Emboli
	< 100	po	3 days	Silk Thread	Lung
	150	po	3 days	Vena Cava Ligation	Emboli
					Gangrene
					Platelet Survival
					Thrombus
					Thrombus
					Thrombus
					Thrombus
Guinea Pig	100	po	3 days	ADP	Platelet Count
Rabbit	50	iv	Single	Laurate	Platelet
	200	po	Single	IIa/EPI	Count
	100	po	5 days	Glass Shunt	Lung
					Thrombi
					Thrombus
Dog		po	Single	Dialyzer	Pressure
		po	Single	Electrical	Drop
	100	po	3 days prior	Gore-Tex Grafts	Thrombus
	83				Graft Patency
	100				

Table 2 **Ticlopidine Hydrochloride: Minimum Effect Doses (MED)** ***In Vivo* Effects: Platelet Stimuli and Thrombosis Models**					
Baboon	100	po	4 days prior	Electrical Damage	Thrombus Morphology
	25	po	3 days	AV Shunt	Platelet Survival

4. Platelet Survival

Beta-aminopropionitrile, when given to rats, decreases the platelet half-life. Treatment with 10 mg/kg/day, po of ticlopidine hydrochloride for 7 days, normalizes platelet half life in this model. Ticlopidine at 25 mg/kg, po 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, po) 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 catheterization in New Zealand white rabbits, 30 and 60 days after ballooning, ticlopidine hydrochloride-treated (50 mg/kg/day, po) 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 also indicates that ticlopidine has no effect on PF-3 availability. However, when coagulation is induced by aortic pieces from ticlopidine hydrochloride-treated rats, 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*. Fibrinogen 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 (ASA) nor the prostaglandins, PGI_2 and PGE; when added to PRP, inhibit fibrinogen binding. Ticlopidine hydrochloride when added *in vitro* is also inactive. However, after dosing to both animals and humans, ticlopidine hydrochloride inhibits fibrinogen binding. The inhibition was irreversible for the life of the platelets.

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. 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. 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.

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 mcg/mL) in plasma of rats, mice, rhesus monkeys, baboons, or humans given oral dose 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 (Table 3).

Table 3

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 on 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 an 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. Approximately 40-50% of the radioactive metabolites circulating in plasma are covalently bound to plasma proteins.

Patients with normal, mildly or moderately impaired renal function were studied for pharmacokinetic and platelet pharmacodynamic effects of ticlopidine hydrochloride given as 250 mg BID 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 C_{cr}=80-150 mL/min), mildly impaired (C_{cr}=50-80 mL/min) and moderately impaired (C_{cr}=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 actions in man other than inhibition of platelet function.

Ticlopidine hydrochloride has no appreciable CNS effects in mice or rats. It does not affect behaviour 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 tumour cells in culture but did show occasional ability to reduce metastasis induced by injection of tumour 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. A tabular summary of these studies is on the following pages.

ACUTE TOXICITY

SPECIES (N/GROUP)	ROUTE	DURATION (OBSERV. PERIOD)	DOSES (MG/KG)	RESULTS	CONCLUSIONS
Mouse (ddY) (10/sex)	Oral (gavage)	Single dose (7-day)	500, 600 750, 825 900, 1000, 1500	Most deaths occurred within 48 hours. Piloerection, hypothermia, prostration, and hypopnea were noted prior to death. Necropsy revealed gastric bleeding in several dead mice.	The oral LD_{50} value was 850 mg/kg, respectively for males and females. The nonlethal oral dose was less than 750 mg/kg for males and 500 mg/kg for females.
Mouse (strain, sex unknown) (20-40)	Oral (gavage)	Single dose (12-day)	500, 1000, 1500	Most deaths occurred within 24 hours. There were no special findings in major organs at autopsy.	The oral LD_{50} value (males and females combined) was 825 mg/kg. The nonlethal oral dose was less than 500 mg/kg.
Mouse (Swiss) (5/sex)	Oral (gavage)	Single dose (8-day)	250, 500, 750, 1000, 1250	Most deaths occurred by 48 hours. Dose-related observations at 500 mg/kg and higher doses included piloerection, prostration, decreased activity, ptosis, and abnormal gait. Principal postmortem findings were hemorrhagic stomach, intestines, and lungs, and congested subungular tissue.	The oral LD_{50} value (males and females combined) was 777 mg/kg. The nonlethal oral dose was 250 mg/kg.
Mouse (ddY) (10/sex)	I.V.	Single dose (7-day)	70, 80, 90, 100	Deaths occurred within 30 minutes. Convulsions and dyspnea were noted prior to death. Necropsy revealed lung congestion in some of the dead mice.	The i.v. LD_{50} value was 88 mg/kg for males and 91 mg/kg for females. The nonlethal i.v. dose was 70 mg/kg for females and less than 70 mg/kg for males.
Mouse (Swiss) (10 females)	I.V.	Single dose (8-day)	25, 50, 75, 100	At 25 mg/kg , mice exhibited exophthalmia, and gasping. At higher doses, disordered running, loss of equilibrium, clonic convulsions, leaping, and death in respiratory arrest were noted.	The i.v. LD_{50} value in female mice was 51 mg/kg. The nonlethal i.v. dose was 25 mg/kg.

ACUTE TOXICITY (Continued)					
SPECIES (N/GROUP)	**ROUTE**	**DURATION (OBSERV. PERIOD)**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Mouse (Strain, sex unknown) (20)	I.P.	Single dose (12-day)	100, 200, 300, 400, 800	Most deaths occurred within 72 hours. At autopsy, there were no special findings in the major organs.	The i.p. LD_{50} value (males and females combined) was 225 mg/kg. The nonlethal i.p. dose was 100 mg/kg.
Mouse (ddY) (10/sex)	S.C.	Single dose (7-day)	800, 1000, 1200, 1500, 1700, 2000, 3000, 3200, 3500, 4000	Most deaths occurred within 72 hours. Piloerection and hypopnea were noted before death. Necrosis around the injection site was prominent in most animals.	The s.c. LD_{50} value was 3270 mg/kg for males and 1250 mg/kg for females. The nonlethal s.c. dose was 2000 mg/kg in males and less than 800 mg/kg in females.
Rat (Wistar) (10/sex)	Oral (gavage)	Single dose (7-day)	1440, 1600, 1720, 2080, 2290, 2500, 3000	Most deaths occurred within 48 hours. Prior to death, animals showed sedation, abnormal gait, piloerection, chromodacryorrhea, lacrimation, nasal bloody discharge, hypopnea, and hypothermia. Necropsy revealed gastric and intestinal bleeding in dead rats.	The oral LD_{50} value was 1780 mg/kg for males and 1800 mg/kg for females. The nonlethal oral dose was 1440 mg/kg.
Rat (Strain unknown) (10-20/sex)	Oral (gavage)	Single dose (12-day)	1000, 1500, 2000, 3000	Most deaths occurred within 48 hours. At autopsy, there were no special findings in the major organs.	The oral LD_{50} value (males and females combined) was 1500 mg/kg. The nonlethal oral dose was less than 1000 mg/kg in males and was 1000 mg/kg in females.
Rat (Sprague Dawley) (5/sex)	Oral (gavage)	Single dose (8-day)	1000, 1500, 2000, 3000, 4000, 5000	Clinical changes included regurgitation, decreased activity, piloerection, ptosis, hypopnea, bloody lacrimation, and ataxia. Principal necropsy findings were distended stomach and hemorrhage in stomach and lungs.	The oral LD_{50} value (males and females combined) was 1938 mg/kg. The nonlethal oral dose was 1500 mg/kg.
Rat (Wistar) (10/sex)	I.V.	Single dose (7-day)	60, 65, 70, 75, 80, 100	Deaths occurred within 30 minutes. Prior to death, tonic convulsions and dyspnea were noted. Necropsy revealed lung congestion in some of the dead rats.	The i.v. LD_{50} value was 70 mg/kg for males and 79 mg/kg for females. The nonlethal i.v. dose was less than 60 mg/kg for males and 60 mg/kg for females.
Rat (Wistar) (10 males)	I.V.	Single dose (3-day)	40, 50, 55, 60, 75	Clinical changes were excitation, decreased activity, prostration, lateral decubitus, and convulsions.	The i.v. LD_{50} value in male rats were 55 mg/kg. The nonlethal i.v. dose was 40 mg/kg in males.
Rat (Strain unknown) (10/sex)	I.P.	Single dose (12-day)	100, 200, 400, 800	Deaths occurred within 24 hours. At autopsy, there were no special findings in the major organs.	The i.p. LD_{50} value (males and females combined) was 500 mg/kg. The nonlethal i.p. dose was 200 mg/kg.

ACUTE TOXICITY (Continued)					
SPECIES (N/GROUP)	**ROUTE**	**DURATION (OBSERV. PERIOD)**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Rat (Wistar) (10/sex)	S.C.	Single dose (7-day)	5000	Animals showed piloerection, nasal discharge, weakness, and necrosis at injection site.	The nonlethal s.c. dose for males and females was greater than 5000 mg/kg.
Baboon (Papio- cyno-cephalus) (1/sex)	Oral (gavage)	Single dose (14-day)	1500, 3000, 6000	Emesis occurred in all animals within 30 minutes after dosing. Additional clinical changes were salivation, diarrhea, and yellow-coloured urine.	The nonlethal oral dose in baboons was greater than 6000 mg/kg.
Baboon (Papio- cyno-cephalus) (2/sex)	I.P.	Single dose (14-day)	500, 1000	Clinical changes included yellow-coloured urine, prostration, emesis, tremors, incoordination, salivation, torpidity, clonic convulsions, and hyperexcitability. Deaths occurred within 24 hours. Necropsy revealed accumulation of serous fluid in the peritoneal cavity, and congestion of lungs, liver, kidney, and the alimentary canal.	The i.p. LD_{50} value was estimated to be between 500 mg/kg and 1000 mg/kg. The nonlethal i.p. dose was less than 500 mg/kg in males and 500 mg/kg in females.

SUBCHRONIC TOXICITY					
SPECIES (N/GROUP)	**ROUTE**	**DURATION**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Rat (Sprague Dawley) (10/sex)	Oral (gavage)	4 weeks (6 days/week)	0, 40, 150, 600	Changes that were present predominantly at 600 mg/kg were: Salivation, lacrimation, bloody nasal discharge, lack of huddling behaviour, sedation, and urinary incontinence. Decrease in body weight, food intake, and water consumption. Decreases in red cell count, haemoglobin, haematocrit, and platelet count Increases in serum cholesterol and total protein. Decreases in urinary sodium, potassium, and pH. Increases in liver, kidney, and adrenal weights, and decreased thymus weight. Hemosiderin deposition in spleen, centrolobular hypertrophy with eosinophilic material in hepatocytes, acidophilic droplets in proximal tubular cells, and a slight decrease in thymocytes in thymic cortex.	Daily oral administration of 600 mg/kg/day for 1 month was toxic to the rat while doses of 150 mg/kg/day were nontoxic.
Rat (Sprague Dawley) (15/sex)	Oral (gavage)	4 weeks with 2 and 4-week recovery periods each on 5/sex	0, 600	In rats sacrificed at end of 1 month of treatment, the findings at 600 mg/kg/day were essentially similar to those of the previous 1-month toxicity study (AT 2419). In treated rats evaluated at 2 and 4 weeks post-treatment, the changes, except for hemosiderin deposition in spleen, were reversible.	Changes seen in the rat following continued oral administration of 600 mg/kg/day were essentially reversible upon cessation of treatment.
Rat (Sprague Dawley) (5-10/sex)	Oral (gavage)	4 weeks	0, 1000	Clinical changes included salivation, lacrimation, bloody nasal discharge, lack of huddling behaviour, sedation, urinary incontinence, hypothermia, and respiratory depression. Eight of 10 males and 8 of 10 females given 1000 mg/kg/day died within 1 week. In surviving animals, the clinical pathologic and the histopathologic changes were similar to the rats given 600 mg/kg/day for 1 month (AT 2419).	Daily oral doses of 1000 mg/kg/day caused lethalities in the rat within 1 week.

SUBCHRONIC TOXICITY (Continued)					
SPECIES (N/GROUP)	**ROUTE**	**DURATION**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Rat (Sprague Dawley) (3 males)	Oral (gavage)	2 weeks	0, 600	Light microscopy of the liver revealed centrolobular hepatocytic hypertrophy with homogeneous eosinophilic material in hepatocytes. Electron microscopy revealed marked proliferation of smooth endoplasmic reticulum in hepatocytes.	The homogeneous eosinophilic material in hepatocytes observed in ticlopidine-treated rats was characterized as proliferation of smooth endoplasmic reticulum.
Rat (Wistar) (15/sex)	Oral (gavage)	6 weeks 5 days/week with a 2-week recovery period on 5/sex/group	0, 50, 200	In high-dose females, a slight increase in blood cholesterol and a decrease in hepatic triglycerides were present. The liver and the adrenal weights were elevated in treated rats. No treatment-related histopathologic alterations were present.	Daily oral dose of 50 mg/kg/day for 6 weeks was nontoxic to the rat while a dose of 200 mg/kg /day was slightly toxic.
Dog (2 males)	Oral (Hard gelatin capsules)	Dose-titration (3-weeks)	0, 25, 50, 100, (Each dose given for 5 days)	No treatment-related changes in clinical condition, ECG, hematology, and blood chemistry were present.	Daily oral doses up to and including 100 mg/kg/day for 5 days were nontoxic to the dog.

CHRONIC TOXICITY					
SPECIES (N/GROUP)	**ROUTE**	**DURATION**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Rat (Sprague Dawley) (15/sex)	Oral (gavage)	6 months 6 days/week with a 3-month interim sacrifice on 4-5/sex/group	0, 10, 30, 100, 300	At 30 mg/kg, mild salivation and yellow urine were present. At higher doses, the principal findings were: Salivation, lack of grooming, urinary incontinence, and yellow urine. Decreased weight gain and increased water intake. Mild anemia Increase in blood cholesterol, total protein, and phosphorus, and decreases in sugar, GOT, and GPT. Increases in urinary volume, sodium, potassium, chloride, and protein. Increased liver weight. Centrolobular hepatocytic hypertrophy with eosinophilic material in hepatocytes, and presence of eosinophilic granules/golden-brown pigments in tubular epithelium and casts in the kidney.	In rats given ticlopidine orally for 6 months, the nontoxic dose was 30 mg/kg/day and the toxic dose was 100 mg/kg/day.

Rat (Sprague Dawley) (35/sex)	Oral (gavage)	18 months with interim sacrifice after 6 months on 10/sex/group	0, 30, 100, 300	At 100 and/or 300 mg/kg/day, principal changes were: Salivation, reduced grooming, aversion to handling, decreases in weight gain and food intake, increased water consumption, and higher mortality. Increases in serum cholesterol, total protein, and alkaline phosphatase, and decreased serum glucose. Inhibition of platelet aggregation. Increased liver weight, and controlobular hepatocytic hypertrophy with eosinophilic material in hepatocytes (proliferation of smooth endoplasmic reticulum). The extent of hepatic changes were similar at 6 and 18-month sacrifices. The hepatic changes were reversible in rats given a 5 week recovery period after 6 months of treatment.	In rats given ticlopidine orally for 18 months, the nontoxic dose was 30 mg/kg/day and the toxic dose was 100 mg/kg/day.

CHRONIC TOXICITY (Continued)					
SPECIES (N/GROUP)	**ROUTE**	**DURATION**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Baboon (Papio cyno-cephalus) (5/sex)	Oral (gavage)	12 months with interim sacrifice at 6 months on 2/sex/group	0, 30, 75, 125, (187.5 up to week 4 and 125 thereafter)	At 75 mg/kg/day and higher doses, the principal changes were: Salivation, emesis, greenish yellow-coloured urine, cough, inappetence, inactivity, and decreased weight gain. Inhibition of platelet aggregation. Increased liver, kidney, and adrenal weights. Elevated levels of hepatic cytochrome P-450 and microsomal protein. Distension of blood sinusoids in the adrenal medulla.	In baboons given ticlopidine orally for at least 12 months the nontoxic dose was 30 mg/kg/day, and the toxic dose was 75 mg/kg/day.

CARCINOGENICITY					
SPECIES (N/GROUP)	**ROUTE**	**DURATION**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Mouse (C57B1/10J) <u>Control</u> 156/sex for 18 months 28/sex for interim sacrifice <u>Treated</u> 52/sex for 18 months 28/sex for interim sacrifice	Oral (via diet)	18 months	0, 25, 135, 275	The body weights of high-dose males were lower than controls. The liver weights were elevated in mid- and high- dose animals. Non-neoplastic histologic changes were present in the liver (periacinar hepatocytic hypertrophy) and in the kidney (increased incidence of protein-filled tubules and renal pelvic calculi) of the mid and/or high-dose animals. There was no evidence of neoplasia attributable to the test compound.	Dietary administration of ticlopidine hydrochloride at doses of 25, 135 and 275 mg/kg of body weight per day for 18 months was not carcinogenic in the mouse.

Rat (Sprague Dawley) Control 150/sex for 24 months 35/sex for interim sacrifice Treated 50/sex for 24 months 35/sex for interim sacrifice	Oral (via diet)	24 months	0, 10, 30, 100	The body weights and the food intakes were lower for high-dose animals compared with controls. No differences were noted in the survival distribution for males, while in females there was evidence of increased survival with increasing dose. Non-neoplastic histologic changes were present in the liver of mid and/or high-dose animals, and those included hepatocytic hypertrophy and hepatocytic vacuolation. There was no evidence of neoplasia attributable to the test compound.	Dietary administration of ticlopidine hydrochloride at doses of 10, 30, and 100 mg/kg of body weight per day for 24 months was not carcinogenic in the rat.

SPECIAL TOXICITY STUDIES

	SPECIES (N/GROUP)	**ROUTE**	**DURATION**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Antigenicity	Guinea pig (4-10 females)	Oral/S.C.	Systemic anaphylaxis Passive cutaneous anaphylaxis (PCA)		No symptoms of systemic anaphylaxis and no PCA reaction were present.	Ticlopidine hydrochloride did not elicit sensitization activity in systemic anaphylaxis and PCA tests in guinea pigs.
Myelotoxicity	Mouse (C3H) (4 males)	Oral (gavage)	5 days	75, 150, 300	Ticlopidine did not induce any decrease either in the number of bone marrow cells or in the bone marrow pluripotential cells.	Ticlopidine was not toxic to bone marrow pluripotential stem cells in mice.
Hematotoxicity	Baboon (papio papio) (3/sex)	Oral (gavage)	8-75 days survivors necropsied between study days 94 and 99	0 (vehicle) Ticlopidine 200 (day 1 to 75) 400/300 (day 1 to 17) PCR 3787 200 (day 1 to 75) 400/300 (day 1 to 33) 3 x 150 (day 73 to 80)	Mortalities with ticlopidine were: 4 of 6 at 200 mg/kg between days 18 and 23; and 6 of 6 at 400/300 mg/kg between days 5 and 17. Reticulopenia was present in found dead or sacrificed animals. With PCR 3787, no deaths at 200 or 3 x 150 mg/kg; and 2 of 6 died at 400/300 mg/kg between days 28 and 30. Hematologic changes were present at 400/300 mg/kg.	No significant haematologic or bone marrow were present in the baboon at daily oral doses of 200 mg/kg of ticlopidine (lethal dose) or PCR 3787. Mortality and haematologic changes were present at 400/300 mg/kg of PCR 3787.

Hematotoxicity	Baboon (Papio papio) 2/sex control 8/sex ticlopidine	Oral (gavage)	18 days	0 (vehicle) 125	Four females given ticlopidine died or were sacrificed because of poor clinical condition and 1 male died from intercurrent disease. Haematologic and bone marrow evaluations showed slight and transient anemia, reticulopenia, and neutropenia, increased heterophagy of haematopoietic cells, and heterogeneity of granules in eosinophilic leukocytes. Slight thymic involution and slight nephropathy were also present.	Daily oral doses of 125 mg/kg of ticlopidine were highly toxic to the baboon. Slight changes were present in haematology and bone marrow at the toxic dose.
Hematotoxicity	Baboon (Papio papio) (1/sex)	Oral (gavage)	32 days	0 (vehicle) Ticlopidine 30 75 125 Chloramphenicol (given I.M.) 30 75 125 Thiamphenicol 30 75 125	Mortalities occurred at 125 mg/kg of ticlopidine or thiamphenicol. Slight anemia was present in animals given ticlopidine while thrombopenia and/or anemia were present in animals given thiamphenicol or chloramphenicol. In the bone marrow, areas of cytolysis and vacuolated myelocytes were present with all test compounds, and macrophagocytosis of erythroblasts and abnormal granules and lipids in eosinophilic leukocytes with ticlopidine at 125 mg/kg/day.	Daily oral doses of 125 mg of ticlopidine was highly toxic to the baboon. Slight changes were present in haematology and bone marrow at toxic doses of ticlopidine. Similar changes also occurred with thiamphenicol and chloramphenicol.

SPECIAL TOXICITY STUDIES (Continued)

	SPECIES (N/GROUP)	**ROUTE**	**DURATION**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Effects on gastric mucosa	Rat (Sprague Dawley) (35-39 males)	Oral (gavage)	2, 5, and 10 days	100, 200, 400	After 2 days of treatment, ticlopidine-treated rats had less severe lesions and a lower ulcer index than animals in the phenylbutazone group (100 mg/kg/day). After 5 and 10 days of treatment, the results of ticlopidine-treated rats were similar or close to those found in control animals.	In rats, ticlopidine was much better tolerated by the gastric mucosa than phenylbutazone.

Gastric & hepatic tolerance	Rat (Wistar) (5/sex)	Oral (gavage)	4 days	0, 100, 400	At 100 mg/kg/day, the blood cholesterol was elevated. At 400 mg/kg/day the changes were: elevated blood cholesterol, elevated SGPT, increased liver weight, decreased thymus weight and a higher incidence of hepatic steatosis.	In fasted rats given ticlopidine orally for 4 days elevated blood cholesterol was noted at 100 mg/kg/day, while elevated levels of blood cholesterol and SGPT, increased liver weight, and probable hepatic steatosis were present at 400 mg/kg/day.
Effects on rat liver	Rat (Alderly Park strain) (6 males)	Oral (gavage)	3 and 18 days	0, 20, 100	Phenobarbitone (20 and 100 mg/kg/day) was used as positive control. The principal results were decreased hexobarbitone sleeping time, increased cytochrome P-450 and b5, and centrolobular hepatocytic changes.	The hepatic effects with ticlopidine in the rat represent a phenobarbitone-like pharmacologic effect and not hepatotoxicity.
Decomposition product toxicity	Rat (Sprague Dawley) (6/sex)	Oral (gavage)	2 weeks	DE-41608 50, 200, 800 DE-4160 800	No adverse effects with DE-41608 at 50 and 200 mg/kg/day. At 800 mg/kg/day, the toxicity profile of DE-41608 was similar to that of DE-4160 (ticlopidine). Both compounds caused lethalities.	The decomposition product of ticlopidine (DE-41608) was nontoxic to the rat at oral doses of 50 and 200 mg/kg/day for 2 weeks. Both DE-4160 and DE-41608 caused lethalities in rats at 800 mg/kg/day.

FERTILITY AND REPRODUCTION					
SPECIES (N/GROUP)	**ROUTE**	**DURATION**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Rat (Sprague Dawley) (30/sex)	Oral (gavage)	Male and female reproduction	0, 20, 80, 320,	The mating performance and pregnancy rate were comparable. A tendency for slight increase in fetal weight and the degree of ossification were present in treated groups. No treatment-related external, skeletal, and visceral changes were present in fetuses.	At doses as high as 320 mg/kg/day, there were no adverse effects on the reproductive capacity of male and female rats and there was no evidence of teratogenicity.
Rat (CD) (30/sex)	Oral (gavage)	Male and female reproduction	0, 50, 100, 400	At 400 mg/kg/day, the observations were: Increase in resorptions, decrease in litter size, and decreases in F1 pup survival and body weight. No adverse effects on the reproductive performance of the F1 offspring were present.	At doses of 50, 100, and 400 mg/kg/day, there were no adverse effects on the reproductive performances of male and female rats. At 400 mg/kg/day, embryo/fetotoxicity was seen, but there was no adverse effects on the reproductive performance of the offspring.

TERATOLOGY					
SPECIES (N/GROUP)	**ROUTE**	**DURATION**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Mouse (OF1) (29-45 females)	Oral (gavage)	Teratology	0, 50, 100, 200	At 200 mg/kg/day, a decreased litter size and an increase in resorptions were present. No treatment-related external, skeletal, and visceral changes were present in fetuses.	Oral administration of 50, 100, and 200 mg/kg/day during organogenesis was not teratogenic in the mouse. Maternal/embryo-toxicity was present at 200 mg/kg/day.
Rat (Sprague Dawley) (32-35 females)	Oral (gavage)	Teratology and Female Reproduction	0, 20, 90, 400	At 400 mg/kg/day, an increase in resorptions and a decrease in fetal weight were present. No treatment -related external, skeletal, and visceral changes were present in fetuses. No adverse effects on parturition and the fertility of the offspring were present.	At oral doses of 20, 90, and 400 mg/kg/day, there were no evidence of teratogenicity and no adverse effects on the fertility of the offspring. Maternal/embryo-toxicity was present at 400 mg/kg/day.
Rat (Sprague Dawley) (23-25 females)	Oral (gavage)	Teratology	0, 50, 140, 400	The fetal weight was decreased at 400 mg/kg/day. No treatment-related external, skeletal and visceral changes were present in fetuses.	Oral administration of 50, 140 and 400 mg/kg/day during organogenesis was not teratogenic in the rat. Maternal toxicity was present at 400 mg/kg/day.
Rabbit (Japanese White) (15 females)	Oral (gavage)	Teratology	0, 50, 100, 200	At 100 and 200 mg/kg/day, decreased weight gain and food intake were present. No treatment-related external, skeletal and visceral changes were present in fetuses.	Oral administration of 50, 100, and 200 mg/kg/day during organogenesis was not teratogenic in the rabbit. Maternal toxicity was present at 100 and 200 mg/kg/day.
Rabbit (New Zealand White) (13-14 females)	Oral (Gavage)	Teratology	0, 50, 100, 200	At 200 mg/kg/day, there was anorexia and decreased weight gain. No treatment-related external, skeletal, and visceral changes were present in fetuses.	Oral administration of 50, 100, and 200 mg/kg/day during organogenesis was not teratogenic in the rabbit. Maternal toxicity was present at 200 mg/kg/day.

PERINATAL AND POSTNATAL REPRODUCTION					
SPECIES (N/GROUP)	**ROUTE**	**DURATION**	**DOSES (MG/KG)**	**RESULTS**	**CONCLUSIONS**
Rat (Sprague Dawley) (22 females)	Oral (gavage)	Perinatal/Postnatal Reproduction	0, 50, 100, 400	At 400 mg/kg/day, the principal changes were: decreased weight gain in dams, probable mortality (7 of 22 dams died), increased number of dead pups at birth and decrease in live litter size, pup viability, and pup weight.	Oral administration at 50 and 100 mg/kg/day during the perinatal and the 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.
Rat (Sprague Dawley) (23-26 females)	Oral (gavage)	Perinatal/Postnatal Reproduction	0, 20, 90, 190, 400	At 400 mg/kg/day, the principal changes were: decreased weight gain in dams, slight increase in gestation period, decreased live litter size, increased number of pups born dead, and decreases in the postnatal survival and the weight of the pups. No adverse effects on the postnatal developmental/behavioural tests and the reproductive capacity of the offspring were present.	Oral administration of 20, 90, and 190 mg/kg/day during the perinatal and the 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					
SPECIES	**ROUTE**	**DURATION**	**DOSES (MG/KG/DAY)**	**RESULTS**	**CONCLUSIONS**
Bacillus subtillis, Salmonella typhimurium (with and without activation), Escherichia coli (with and without activation), and Chinese hamster lung fibroblasts (D-6 cell)				The in vitro assays were all negative.	No mutagenic activity in B. subtillis, S. typhimurium (with and without activation), E. coli (with and without activation), and Chinese hamster culture cells.
Salmonella typhimurium (with and without activation)				The in vitro assays were all negative.	No mutagenic activity in S. typhimurium (with and without activation).
Salmonella typhimurium (with and without activation) Rat hepatocyte primary culture-DNA repair assay				The in vitro assays were all negative.	No mutagenic activity in S. typhimurium (with and without activation), and hepatocyte primary culture cells.
Salmonella typhimurium and Escherichia coli (with and without activation)				The in vitro assays were all negative.	No mutagenic activity in S. typhimurium and E. coli (with and without activation).
Salmonella typhimurium and Escherichia coli (with and without activation): N-oxide metabolite				The in vitro assays were all negative.	No mutagenic activity with N-oxide metabolite in S. typhimurium and E. coli (with and without activation).
Mouse (C57/CBA)	I.P.	5 days	17.5, 37.5, 75, 150	No significant increase in the frequency of abnormal spermatozoids.	No mutagenic activity in an in vivo assay that evaluated morphology of spermatozoids in the mouse.
Chinese Hamster (cricetulus griseus)	Oral (gavage)	One or two daily doses	137.5, 275	No increases either in the amount of sister chromatid exchange or in structural chromosome abnormalities.	No mutagenic activity in an in vivo assay that evaluated sister chromatid exchange and chromosome abnormalities in Chinese hamster bone marrow.

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