

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-253

PRINTED LABELING

NDC 0228-2613-06

PUREPAC

**TICLOPIDINE
HYDROCHLORIDE
TABLETS
250 mg**

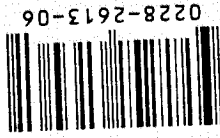
USUAL DOSAGE: One tablet two times a day.
See package insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F).

IMPORTANT: Dispense enclosed Patient Information Leaflet with prescription.

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA

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250 mg
light-resistant container as defined in USP *Light-Resistant Container* (21 CFR 312.62).
NDC 0228-2613-06
Lot No. 666 20 1999
SAMPLE

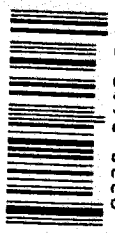


NDC 0228-2613-06
**TICLOPIDINE
HYDROCHLORIDE**



250 mg
light-resistant container as defined in USP *Light-Resistant Container* (21 CFR 312.62).
NDC 0228-2613-06
Lot No. 666 20 1999

SAMPLE



NDC 0228-2613-06

NDC 0228-2613-06

PUREPAC

**TICLOPIDINE
HYDROCHLORIDE
TABLETS**

250 mg

USUAL DOSAGE: One tablet two times a day.
See package insert for full prescribing information.
Store at controlled room temperature (20°-25°C) (59°-68°F).
IMPORTANT: Dispense enclosed Patient Information Leaflet with prescription.

Manufactured by
TICLOPIDINE PHARMACEUTICAL CO.
Eli Lilly, Inc.
Greenfield, IN 47120 USA



Each unit contains
one (1) tablet.
250 mg
light resistant container as defined in
the USP

NOTE: It is essential that CBCs (including platelet count) be performed every two weeks during the first three months of therapy with ticlopidine hydrochloride (see accompanying insert).

Lot No.

21

SAMPLE



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**IMPORTANT INFORMATION
ABOUT TICLOPIDINE
HYDROCHLORIDE
TABLETS**

Revised — August 1998

The information in this leaflet is intended to help you use ticlopidine hydrochloride safely. Please read the leaflet carefully. Although it does not contain all the detailed medical information that is provided to your doctor, it provides facts about ticlopidine hydrochloride that are important for you to know. If you still have questions after reading this leaflet or if you have questions at any time during your treatment with ticlopidine hydrochloride, check with your doctor.

Special Warning for Users of Ticlopidine Hydrochloride/Necessary Blood Tests: Ticlopidine hydrochloride is recommended to help reduce your risk of having a stroke, but only for patients who have had a stroke or early stroke warning symptoms while on aspirin, or for those who have these symptoms but are intolerant or allergic to aspirin.

Ticlopidine hydrochloride is not prescribed for those who can take aspirin to prevent a stroke because ticlopidine hydrochloride can cause life-threatening blood problems. **Getting your blood tests done and reporting symptoms to your doctor as soon as possible can avoid serious complications.**

The white cells of the blood that fight infection may drop to dangerous levels

(a condition called neutropenia). This occurs in about 2.4% (1 in 40) of people on ticlopidine. You should be on the lookout for signs of infection such as fever, chills or sore throat. If this problem is caught early, it can almost always be reversed, but if undetected it can be fatal.

Another problem that has occurred in some patients taking ticlopidine is a decrease in cells called platelets (a condition called thrombocytopenia). This may occur as part of a syndrome that includes injury to red blood cells, causing anemia, kidney abnormalities, neurologic changes and fever. This condition is called TTP and can be fatal.

Things you should watch for as possible early signs of TTP are yellow skin or eye color, pinpoint dots (rash) on the skin, pale color, fever, weakness on a side of the body, or dark urine. If any of these occur, contact your doctor immediately.

Both complications occur most frequently in the first 90 days after ticlopidine hydrochloride is started. To make sure you don't develop either of these problems, your doctor will arrange for you to have your blood tested before you start taking ticlopidine hydrochloride and then every 2 weeks for the first 3 months you are on ticlopidine hydrochloride. If detected, neutropenia and thrombocytopenia can almost always be reversed. It is essential that you keep your appointments for the blood tests and that you call your doctor immediately if you have any indication that you may have TTP or neutropenia. If you stop taking ticlopidine hydrochloride for any

reason within the first 3 months, you will still need to have your blood tested for an additional 2 weeks after you have stopped taking ticlopidine hydrochloride.

Other Warnings and Precautions: A few people may develop jaundice while being treated with ticlopidine hydrochloride. The signs of jaundice are yellowing of the skin or the whites of the eyes or consistent darkening of the urine or lightening in the color of the stools. These symptoms should be reported to your physician promptly. If any of the symptoms described above for neutropenia, TTP or jaundice occur, contact your doctor immediately.

Ticlopidine hydrochloride should be used only as directed by your doctor. Do not give ticlopidine hydrochloride to anyone else. **Keep ticlopidine hydrochloride out of reach of children!**

Some people may have such side effects as diarrhea, skin rash, stomach or intestinal discomfort. If any of these problems are persistent, or if you are concerned about them, bring them to your doctor's attention.

It may take longer than usual to stop bleeding when taking ticlopidine hydrochloride. Tell your doctor if you have any more bleeding or bruising than usual, and, if you have emergency surgery, be sure to let your doctor or dentist know that you are taking ticlopidine hydrochloride. Also, tell your doctor well in advance of any planned surgery (including tooth extraction), because he or she may recommend that you stop taking ticlopidine hydrochloride temporarily.

How Ticlopidine Hydrochloride Works:

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, then travels to the brain (an embolus). In both cases the blood supply to part of the brain is blocked and that part of the brain is damaged. Ticlopidine hydrochloride works by making the blood less likely to clot, although not so much less that it causes you to become likely to bleed, unless you have a bleeding disorder or some injury (such as a bleeding ulcer of the stomach or intestine) that is especially likely to bleed.

Who Should Not Take Ticlopidine Hydrochloride? Contact your doctor immediately and **do not take ticlopidine hydrochloride if:**

- you have an allergic reaction to ticlopidine hydrochloride
- you have a blood disorder or a serious bleeding problem, such as a bleeding stomach ulcer
- you have previously been told you had TTP
- you have severe liver disease or other liver problems
- you are pregnant or you are planning to become pregnant
- you are breastfeeding

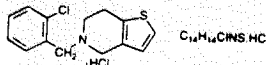
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Revised — August 1998

TICLOPIDINE HYDROCHLORIDE TABLETS

Revised — August 1999

WARNING:
 Ticlopidine hydrochloride can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis and thrombotic thrombocytopenic purpura (TTP).
Neutropenia/Agranulocytosis: Among 2646 patients in clinical trials, there were 98 cases (2.4%) of neutropenia (less than 1200 neutrophils/mm³), and the neutrophil count was below 400/mm³ in 17 of these patients (0.6% of the total population).
TTP: One case of thrombotic thrombocytopenic purpura was reported during clinical trials. Based on postmarketing data, US physicians reported about 100 cases between 1992 and 1997. Based on an estimate of total population exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated TTP may be as high as one case in every 2000 to 4000 patients exposed.
Monitoring of Clinical and Hematologic Status: Severe hematological adverse reactions may occur within a few days of the start of therapy. The incidence of TTP peaks after about 3 to 4 weeks of therapy and neutropenia peaks at approximately 4 to 6 weeks with both declining thereafter. Only a few cases have arisen after more than 3 months of treatment.
 Hematological adverse reactions cannot be reliably predicted by any identified demographic or clinical characteristics. During the first 3 months of treatment, patients receiving ticlopidine hydrochloride must, therefore, be hematologically and clinically monitored for evidence of neutropenia or TTP. If any such evidence is seen, ticlopidine hydrochloride should be immediately discontinued. The detection and treatment of ticlopidine-associated hematological adverse reactions are further described under **WARNINGS**.

DESCRIPTION:
 Ticlopidine hydrochloride is a platelet aggregation inhibitor. Chemically it is 5-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydro- [3,2-c] pyridine hydrochloride. The structural formula is



Ticlopidine hydrochloride is a white crystalline solid. It is freely soluble in water and self-buffers to a pH of 3.6. It also dissolves freely in methanol; is sparingly soluble in methylene chloride and ethanol; slightly soluble in acetone and insoluble in a buffer solution of pH 6.3. It has a molecular weight of 300.75.
 Ticlopidine hydrochloride tablets for oral administration contain 250 mg of ticlopidine hydrochloride. In addition, each tablet contains the following inactive ingredients: calcium stearate, colloidal silicon dioxide, croscarmellose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, maltodextrin, microcrystalline cellulose, polyethylene glycol, polyethylene glycol, titanium dioxide, and tracetin.

CLINICAL PHARMACOLOGY:
Mechanism of Action: When taken orally, ticlopidine hydrochloride causes a time- and dose-dependent inhibition of both platelet aggregation and release of platelet granule constituents, as well as a prolongation of bleeding time. The intact drug has no significant *in vitro* activity at the concentrations attained *in vivo*, and activity of ticlopidine has been isolated.
 Ticlopidine hydrochloride, after oral ingestion, interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions. The effect on platelet function is reversible for the life of the platelet, as shown both by persistent inhibition of hydrogen bonding after washing platelets *ex vivo* and by inhibition of platelet aggregation after resuspension of platelets in buffered medium.

Pharmacokinetics and Metabolism: After oral administration of a single 250-mg dose, ticlopidine hydrochloride is rapidly absorbed with peak plasma levels occurring at approximately 2 hours after dosing and increase in the AUC of ticlopidine.
 Ticlopidine hydrochloride displays nonlinear pharmacokinetics and clearance decreases markedly on repeated dosing. In older volunteers, the apparent half-life of ticlopidine after a single 250-mg dose is about 12.6 hours, with renal dosing at 250 mg bid, the terminal elimination half-life rises to 4 to 5 days and steady-state levels of ticlopidine hydrochloride in plasma are obtained after approximately 14 to 21 days.

Ticlopidine hydrochloride binds reversibly (58%) to plasma proteins, mainly to serum albumin and lipoproteins. The binding to albumin and lipoproteins is nonsaturable over a wide concentration range. Ticlopidine also binds to alpha₁-acid glycoprotein. At concentrations attained with the recommended dose, only 15% or less of ticlopidine in plasma is bound to this protein.
 Ticlopidine hydrochloride is metabolized extensively by the liver; only trace amounts of intact drug are detected in the urine. Following an oral dose of radioactive ticlopidine hydrochloride administered in solution, 60% of the radioactivity is recovered in the urine and 23% in the feces. Approximately 1/3 of the dose excreted in the feces is intact ticlopidine hydrochloride, possibly excreted in the bile. Ticlopidine hydrochloride is a minor component in plasma (5%) after a single dose, but at steady-state is the major component (15%). Approximately 40% to 50% of the radioactive metabolites circulating in plasma are covalently bound to plasma proteins, probably by acylation.

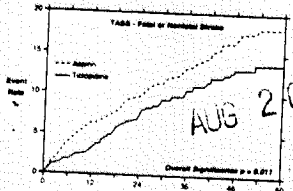
Clearance of ticlopidine decreases with age. Steady-state trough values in elderly patients (mean age 70 years) are about twice those in younger volunteer populations.
Hepatically Impaired Patients: The effect of decreased hepatic function on the pharmacokinetics of ticlopidine hydrochloride was studied in 17 patients with advanced cirrhosis. The average plasma concentration of ticlopidine in these subjects was slightly higher than that seen in older subjects in a separate trial (see **CONTRAINDICATIONS**).

Renally Impaired Patients: Patients with mildly (CrCl 50 to 80 mL/min) or moderately (CrCl 20 to 50 mL/min) impaired renal function were compared to normal subjects (CrCl 80 to 150 mL/min) in a study of the pharmacokinetic and platelet pharmacodynamic effects of ticlopidine hydrochloride (250 mg bid) for 11 days. Final 250-mg dose on Day 11.
 AUC values of ticlopidine increased by 28% and 60% in mild and moderately impaired patients, respectively, and plasma clearance decreased by 37% and 52%, respectively, but there were no statistically significant differences in ADP-induced platelet aggregation. In this small study (26 patients), bleeding times showed significant prolongation only in the moderately impaired patients.

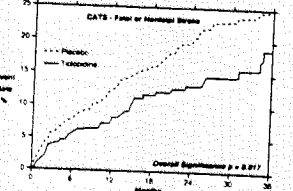
Pharmacodynamics: In healthy volunteers over the age of 50, substantial inhibition (over 50%) of ADP-induced platelet aggregation is detected within 4 days after administration of ticlopidine hydrochloride 250 mg bid, and maximum platelet aggregation inhibition (60% to 70%) is achieved after 8 to 11 days. Lower doses cause less, and more delayed, platelet aggregation inhibition, while doses above 250 mg bid give little additional effect on platelet aggregation but an increased rate of adverse effects. The dose of 250 mg bid is the only dose that has been evaluated in controlled clinical trials.
 After discontinuation of ticlopidine hydrochloride, bleeding time and other platelet function tests return to the normal within 2 weeks, in the majority of patients.
 At the recommended therapeutic dose (250 mg bid), ticlopidine hydrochloride has no known significant pharmacological actions in man other than inhibition of platelet function and prolongation of the bleeding time.

CLINICAL TRIALS:
 The effect of ticlopidine on the risk of stroke and cardiovascular events was studied in two multicenter, randomized, double-blind trials.

1. Study in Patients Experiencing Stroke Precursors: In a trial comparing ticlopidine and aspirin (The Ticlopidine Aspirin Stroke Study or TASS), 3069 patients (1987 men, 1082 women) who had experienced such stroke precursors as transient ischemic attack (TIA), transient monocular blindness, amaurosis fugax, 650 mg bid. The study was designed to follow patients for at least 2 years and up to 5 years.
 Over the duration of the study, ticlopidine hydrochloride significantly reduced the risk of fatal and nonfatal stroke by 24% (p = 0.01) from 18.1 to 13.8 per 100 patients followed for 5 years, compared to aspirin. During the first year, when the risk of stroke is greatest, the reduction in risk of stroke (fatal and nonfatal) compared to aspirin was 48%; the reduction was similar in men and women.



2. Study in Patients Who Had a Completed Atherothrombotic Stroke: In a trial comparing ticlopidine with placebo (The Canadian American Ticlopidine Study of CATS), 1073 patients who had experienced a previous atherothrombotic stroke were treated with ticlopidine hydrochloride 250 mg bid or placebo for up to 3 years.
 Ticlopidine hydrochloride significantly reduced the overall risk of stroke by 24% (p = 0.01) from 24.6 to 18.6 per 100 patients followed for 3 years, compared to placebo. During the first year, the reduction in risk of fatal and nonfatal stroke over placebo was 33%.



INDICATIONS AND USAGE:
 Ticlopidine hydrochloride is indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke.
 Because ticlopidine hydrochloride is associated with a risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP) and neutropenia/agranulocytosis (see **BOXED WARNING** and **WARNINGS**), ticlopidine hydrochloride should be reserved for patients with age-related atherosclerosis.

bleeding from trauma, surgery or pathological conditions. If it is desired to eliminate the antiplatelet effects of ticlopidine hydrochloride prior to elective surgery, the drug should be discontinued 10 to 14 days prior to surgery. Several controlled clinical studies have found increased surgical blood loss in patients undergoing surgery during treatment with ticlopidine. In TASS and CATS it was recommended that patients have ticlopidine discontinued prior to elective surgery. Several hundred patients underwent surgery during the trials, and no excessive surgical bleeding was reported.

Prolonged bleeding time is normalized within 2 hours after administration of 20 mg methylgladonine IV. Platelet transfusions may also be used to reverse the effect of ticlopidine hydrochloride on bleeding. Because platelet transfusions may accelerate thrombosis in patients with TTP on ticlopidine they should, if possible, be avoided.

GI Bleeding: Ticlopidine hydrochloride prolongs template bleeding time. The drug should be used with caution in patients who have lesions with a propensity to bleed such as ulcers. Drugs that might induce such lesions should be used with caution in patients on ticlopidine hydrochloride (see **CONTRAINDICATIONS**).

Use in Hepatically Impaired Patients: Since ticlopidine is metabolized by the liver, dosing of ticlopidine hydrochloride or other drugs metabolized in the liver may require adjustment upon starting or stopping concomitant therapy. Because of limited experience in patients with severe hepatic disease, who may have bleeding diatheses, the use of ticlopidine hydrochloride is not recommended in this population (see **CLINICAL PHARMACOLOGY AND CONTRAINDICATIONS**).

Use in Renally Impaired Patients: There is limited experience in patients with renal impairment. Decreased plasma clearance, increased AUC values and prolonged bleeding times can occur in renally impaired patients. In controlled clinical trials, no unexpected problems have been encountered in patients having mild renal impairment, and there is no experience with dosage adjustment in patients with greater degrees of renal impairment. Nevertheless, for renally impaired patients, it may be necessary to reduce the dosage of ticlopidine or discontinue it altogether if hemorrhagic or hematopoietic problems are encountered (see **CLINICAL PHARMACOLOGY**).

Information for the Patient (see PPI): Patients should be told that a decrease in the number of white blood cells (neutropenia) or platelets (thrombocytopenia) can occur with ticlopidine hydrochloride, especially during the first 3 months of treatment and that neutropenia, if it is severe, can result in an increased risk of infection. They should be told it is critically important to obtain the scheduled blood tests to detect neutropenia or thrombocytopenia. Patients should also be reminded to contact their physicians if they experience any indication of infection such as fever, chills, or sore throat, any of which might be a consequence of neutropenia. Thrombocytopenia may be part of a syndrome called TTP. Symptoms and signs of TTP such as fever, weakness, difficulty speaking, seizures, vomiting of skin or eyes, dark or bloody urine, pallor or petechiae (pinpoint hemorrhagic spots on the skin), should be reported immediately.

All patients should be told that it may take them longer than usual to stop bleeding when they take ticlopidine hydrochloride and that they should report any unusual bleeding to their physician. Patients should tell physicians and dentists that they are taking ticlopidine hydrochloride before any surgery is scheduled and before any new drug is prescribed.

Patients should be told to promptly report side effects of ticlopidine hydrochloride such as severe or persistent diarrhea, skin rashes or subcutaneous bleeding or any signs of cholestasis, such as yellow skin or sclera, dark urine, or light-colored stools.

Patients should be told to take ticlopidine hydrochloride with food or just after eating in order to minimize gastrointestinal discomfort.

Laboratory Tests: Liver Function: Ticlopidine hydrochloride therapy has been associated with elevations of alkaline phosphatase and transaminases, which generally occurred within 1 to 4 months of therapy initiation. In controlled clinical trials, the incidence of elevated alkaline phosphatase (greater than two times upper limit of normal) was 7.6% in ticlopidine patients, 6% in placebo patients and 2.5% in aspirin patients. The incidence of elevated AST (SGOT) (greater than two times upper limit of normal) was 3.1% in ticlopidine patients, 4% in placebo patients and 2.1% in aspirin patients. No progressive increases were observed in closely monitored clinical trials (eg, no transaminase greater than 10 times the upper limit of normal was seen), but most patients with these abnormalities had therapy discontinued. Occasionally patients had developed minor elevations in bilirubin.

Based on postmarketing and clinical trial experience, liver function testing, including SGPT and GGT, should be considered whenever liver dysfunction is suspected, particularly during the first 4 months of treatment.

Drug Interactions: Therapeutic doses of ticlopidine hydrochloride caused a 30% increase in the plasma half-life of antipyrine and may cause analogous effects on similarly metabolized drugs. Therefore, the dose of drugs metabolized by hepatic microsomal enzymes with low therapeutic ratios or being given to patients with hepatic impairment may require adjustment to maintain optimal therapeutic blood levels when starting or stopping concomitant therapy with ticlopidine. Studies of specific drug interactions yielded the following results.

Aspirin and Other NSAIDs: Ticlopidine potentiates the effect of aspirin or other NSAIDs on platelet aggregation. The safety of concomitant use of ticlopidine with aspirin or other NSAIDs has not been established. Aspirin did not modify the ticlopidine-mediated inhibition of ADP-induced platelet aggregation, but ticlopidine potentiated the effect of aspirin on collagen-induced platelet aggregation. Concomitant use of aspirin and ticlopidine is not recommended (see **PRECAUTIONS - GI Bleeding**).

Antacids: Administration of ticlopidine hydrochloride after antacids resulted in an 18% decrease in plasma levels of ticlopidine.

Cimetidine: Chronic administration of cimetidine reduced the clearance of a single dose of ticlopidine hydrochloride by 50%.

Digoxin: Coadministration of ticlopidine hydrochloride with digoxin resulted in a slight decrease (approximately 15%) in digoxin plasma levels. Little or no change in therapeutic efficacy of digoxin would be expected.

Theophylline: In normal volunteers, concomitant administration of ticlopidine hydrochloride resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 hours and a comparable reduction in total plasma clearance of theophylline.

Platelet Aggregation: In 6 normal volunteers, the inhibitory effects of ticlopidine hydrochloride on platelet aggregation were not altered by chronic administration of phenobarbital.

Phenytoin: *In vitro* studies demonstrated that ticlopidine does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of ticlopidine and its metabolites have not been studied *in vivo*. Several cases of elevated phenytoin plasma levels with associated somnolence and lethargy have been reported following coadministration with ticlopidine hydrochloride. Caution should be exercised in coadministering this drug with ticlopidine hydrochloride, and it may be useful to remeasure phenytoin blood concentrations.

Propranolol: *In vitro* studies demonstrated that ticlopidine does not alter the plasma protein binding of propranolol. However, the protein binding interactions of ticlopidine and its metabolites have not been studied *in vivo*. Caution should be exercised in coadministering this drug with ticlopidine hydrochloride.

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 (see **PRECAUTIONS**).

Food Interaction: The oral bioavailability of ticlopidine is increased by 20% when taken after a meal. Administration of ticlopidine hydrochloride with food is recommended to maximize gastrointestinal tolerance. In controlled trials, ticlopidine hydrochloride was taken with meals.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year oral carcinogenicity study in rats, ticlopidine at daily doses of up to 100 mg/kg (610 mg/m²) was not tumorigenic. For a 70-kg person (1.73m² body surface area) the dose represents 14 times the recommended clinical dose on a mg/kg basis and two times the clinical dose on body surface area basis. In a 78-week oral carcinogenicity study in mice, ticlopidine at daily doses up to 275 mg/kg (1180 mg/m²) was not tumorigenic. The dose represents 40 times the recommended clinical dose on a mg/kg basis and four times the clinical dose on body surface area basis. Ticlopidine was not mutagenic *in vitro* in the Ames test, rat hepatocyte DNA-repair assay, or the Chinese-hamster fibroblast chromosomal aberration test, or *in vivo* in the mouse spermatozoal morphology test, the Chinese-hamster micronucleus test, or the Chinese-hamster bone-marrow-cell sister-chromatid exchange test. Ticlopidine was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg/day.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Teratology studies have been conducted in mice (doses up to 200 mg/kg/day), rats (doses up to 400 mg/kg/day), and rabbits (doses up to 200 mg/kg/day). Doses of 400 mg/kg in rats, 200 mg/kg/day in mice and 100 mg/kg in rabbits produced maternal toxicity as well as fetal toxicity, but there was no evidence of a teratogenic potential of ticlopidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Studies in rats have shown ticlopidine is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ticlopidine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Clearance of ticlopidine is somewhat lower in elderly patients and lower levels are increased. The major clinical trials with ticlopidine hydrochloride were conducted in an elderly population with an average age of 64 years. Of the total number of patients in the therapeutic trials, 45% of patients were over 65 years old and 12% were over 75 years old. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS: Adverse reactions were relatively frequent with over 50% of patients reporting at least one. Most (30% to 40%) involved the gastrointestinal tract. Most adverse effects are mild, but 21% of patients discontinued therapy because of an adverse event, principally diarrhea, rash, nausea, vomiting, GI pain and neutropenia. Most adverse effects occur early in the course of treatment, but a new onset of adverse effects can occur after several months.

The incidence rates of adverse events listed in the following table were derived from multicenter, controlled clinical trials described above comparing ticlopidine hydrochloride, placebo and aspirin over study periods of up to 5.8 years. Adverse events considered by the investigator to be probably drug-related that occurred in at least 1% of patients treated with ticlopidine hydrochloride are shown in the following table.

Percent of Patients With Adverse Events in Controlled Studies

Event	Ticlopidine Hydrochloride (n=2048) Incidence	Aspirin (n=1527) Incidence	Placebo (n=536) Incidence
Any Event	60.0 (29.9)	53.2 (74.3)	34.3 (6.1)
Diarrhea	12.5 (6.3)	5.2 (1.8)	4.5 (1.7)
Nausea	7.0 (2.6)	6.2 (1.9)	7.0 (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)	1.1 (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 (0.3)	0.0 (0.0)
Abnormal Liver Function test	1.0 (0.7)	0.3 (0.3)	0.0 (0.0)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Hematological: Neutropenia/thrombocytopenia (TTP, see **BOXED WARNING AND WARNINGS**), agranulocytosis, eosinophilia, pancytopenia, thrombocytosis and bone-marrow depression have been reported.

Gastrointestinal: Ticlopidine hydrochloride therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild, but about 13% of patients discontinued therapy because of these. They usually occur within 3 months of initiation of therapy and typically are resolved within 1 to 2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued. In some cases of severe or bloody diarrhea, colitis was later diagnosed.

Hemorrhagic:

Diarrhea	12 (16.3)	5 (11.8)	7 (10.5)
Nausea	7 (12.6)	6 (11.9)	17 (10.5)
Dyspepsia	7 (11.1)	9 (10.2)	9 (10.2)
Rash	5 (13.4)	15 (10.8)	0 (10.9)
GI Pain	3 (7.9)	5 (6.7)	1 (3.0)
Neutropenia	2 (11.3)	0 (10.1)	1 (10.4)
Purpura	2 (10.2)	1 (6.1)	0 (10.0)
Vomiting	1 (1.4)	1 (0.9)	0 (10.4)
Flatulence	1 (5.0)	1 (4.0)	0 (10.0)
Pruritus	1 (3.0)	0 (3.1)	0 (10.0)
Dizziness	1 (1.0)	0 (5.0)	0 (10.0)
Anorexia	1 (1.0)	0 (5.0)	0 (10.0)
Abnormal Liver Function test	1 (0.7)	0 (3.0)	0 (10.0)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Hematological: Neutropenia, thrombocytopenia, TTP (see **BOXED WARNING** and **WARNINGS**), agranulocytosis, eosinophilia, pancytopenia, thrombocytosis and bone-marrow depression have been reported.

Cardiovascular: Ticlopidine hydrochloride therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild but about 13% of patients discontinued therapy because of these. They usually occur within 3 months of initiation of therapy and typically are resolved within 1 to 2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued. In some cases of severe or bloody diarrhea, colitis was later diagnosed.

Hemorrhagic: Ticlopidine hydrochloride has been associated with increased bleeding, spontaneous posttraumatic bleeding and pericardial bleeding including but not limited to gastrointestinal bleeding. It has also been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria and conjunctival hemorrhage.

Intracerebral bleeding was rare in clinical trials with ticlopidine hydrochloride, with an incidence no greater than that seen with comparator agents (ticlopidine 0.5%, aspirin 0.6%, placebo 0.75%). It has also been reported postmarketing.

Rash: Ticlopidine 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 onset time of 31 days. If drug is discontinued, recovery occurs within several days. Milder rashes do not recur on drug challenge. There have been rare reports of severe rashes, including Stevens-Johnson syndrome, erythema multiforme and exfoliative dermatitis.

Less Frequent Adverse Reactions (Probably Related): Clinical adverse experiences occurring in 0.5% to 1% of patients in the controlled trials include:

Digestive System: GI fullness
Skin and Appendages: urticaria
Nervous System: headache
Body as a Whole: asthenia, pain
Hemostatic System: epistaxis
Special Senses: tinnitus

In addition, rarer, relatively serious events have also been reported from postmarketing experience: Hemolytic anemia with reticulocytosis, aplastic anemia, immune thrombocytopenia, hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis, peptic ulcer, renal failure, nephrotic syndrome, hyponatremia, vasculitis, sepsis, angiodema, allergic onychomycosis, systemic lupus (positive ANA), peripheral neuropathy, serum sickness, arthropathy and myositis.

OVERDOSAGE:

One case of deliberate overdosage with ticlopidine hydrochloride has been reported by 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. Single oral doses of ticlopidine at 1600 mg/kg and 500 mg/kg were lethal to rats and mice, respectively. Symptoms of acute toxicity were GI hemorrhage, convulsions, hypothermia, dyspnea, loss of equilibrium and abnormal gait.

DOSEAGE AND ADMINISTRATION:

The recommended dose of ticlopidine hydrochloride is 250 mg bid taken with food. Other doses have not been studied in controlled trials for these indications.

HOW SUPPLIED:

Ticlopidine Hydrochloride Tablets are supplied as follows:
250 mg — Each unscored, white, oval, film-coated tablet debossed with "P" on one side and "61" on the other contains 250 mg of Ticlopidine Hydrochloride. Tablets are supplied in bottles of 30 (NDC 0228-2613-03), 60 (NDC 0228-2613-06), and 100 (NDC 0228-2613-11).

Dispense in a light, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).

Only

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Enzabett, NJ 07207 USA

40-8823

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PHARMACIST — DETACH HERE AND GIVE PATIENT INFORMATION SHEET TO PATIENT

Reason within the first 3 months, you will still need to have your blood tested. If you have any of the following symptoms, stop taking ticlopidine hydrochloride immediately and call your doctor.

Other Warnings and Precautions: A few people may develop purple skin while being treated with ticlopidine hydrochloride. If the signs of purpura (redness or swelling of the skin) or conjunctivitis (redness of the eyes or consistent tearing of the eyes or lightening of the color of the skin), these symptoms should be reported to your doctor immediately. If you experience any of the symptoms described above for neutropenia, TTP or heparin-induced thrombocytopenia (HIT), contact your doctor immediately.

Ticlopidine hydrochloride should be used only as directed by your doctor. Do not give ticlopidine hydrochloride to anyone else. Do not take more than the recommended dose. Do not take more than 2 tablets a day. Do not take more than 2 tablets a day. Do not take more than 2 tablets a day.

Some people may have such side effects as diarrhea, skin rash, stomach or rectal discomfort. If any of these symptoms occur, contact your doctor immediately. Do not take more than 2 tablets a day.

If you have any of the following symptoms, stop taking ticlopidine hydrochloride immediately and call your doctor:

- you have a change in your stool (blood in your stool, black or tarry stools, or stools that are very dark)
- you have a change in your urine (blood in your urine, or urine that is very dark)
- you have a change in your vomit (blood in your vomit, or vomit that is very dark)
- you have a change in your sputum (blood in your sputum, or sputum that is very dark)
- you have a change in your sweat (blood in your sweat, or sweat that is very dark)
- you have a change in your tears (blood in your tears, or tears that are very dark)
- you have a change in your saliva (blood in your saliva, or saliva that is very dark)
- you have a change in your nasal mucus (blood in your nasal mucus, or nasal mucus that is very dark)
- you have a change in your menstrual blood (blood in your menstrual blood, or menstrual blood that is very dark)
- you have a change in your urine (blood in your urine, or urine that is very dark)
- you have a change in your vomit (blood in your vomit, or vomit that is very dark)
- you have a change in your sputum (blood in your sputum, or sputum that is very dark)
- you have a change in your sweat (blood in your sweat, or sweat that is very dark)
- you have a change in your tears (blood in your tears, or tears that are very dark)
- you have a change in your saliva (blood in your saliva, or saliva that is very dark)
- you have a change in your nasal mucus (blood in your nasal mucus, or nasal mucus that is very dark)
- you have a change in your menstrual blood (blood in your menstrual blood, or menstrual blood that is very dark)

How Ticlopidine Hydrochloride Works: A clot (or thrombus) is a mass of blood cells that has clotted together. It can form in the heart or in any part of the body and break off, then travel to the brain, the lungs, or other parts of the body. Ticlopidine hydrochloride works by making the blood less likely to clot. Ticlopidine hydrochloride may also help to prevent blood clots from forming in the arteries. Ticlopidine hydrochloride may also help to prevent blood clots from forming in the veins. Ticlopidine hydrochloride may also help to prevent blood clots from forming in the arteries. Ticlopidine hydrochloride may also help to prevent blood clots from forming in the veins.

Who Should Not Take Ticlopidine Hydrochloride: Contact your doctor immediately and do not take ticlopidine hydrochloride if:

- you have an allergic reaction to ticlopidine hydrochloride or any of its ingredients
- you have a blood disorder or a serious bleeding problem, such as a bleeding stomach ulcer
- you have previously been told you had TTP (thrombotic thrombocytopenic purpura)
- you have an allergic reaction to ticlopidine hydrochloride or any of its ingredients
- you have a blood disorder or a serious bleeding problem, such as a bleeding stomach ulcer
- you have previously been told you had TTP (thrombotic thrombocytopenic purpura)

Who Should Take Ticlopidine Hydrochloride: Contact your doctor immediately and do not take ticlopidine hydrochloride if:

- you are pregnant or you are planning to become pregnant
- you are breastfeeding or you are planning to breastfeed
- you are taking any other medicine

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