

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**75161**

**DRAFT FINAL PRINTED LABELING**

# TICLOPIDINE HYDROCHLORIDE TABLETS

R<sub>x</sub> only

## WARNING

Ticlopidine hydrochloride can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis and thrombotic thrombocytopenic purpura (TTP).

### Neutropenia/Agranulocytosis

Among 2048 patients in clinical trials, there were 50 cases (2.4%) of neutropenia (less than 1200 neutrophils/mm<sup>3</sup>), and the neutrophil count was below 450/mm<sup>3</sup> in 17 of these patients (0.8% 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 estimated patient 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 Hematological Status

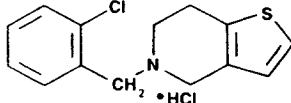
Severe hematological adverse reactions may occur within a few days of the start of therapy. The incidence of TTP peaks after about 3 to 4 weeks of therapy and neutropenia peaks at approximately 4 to 6 weeks with both declining thereafter. Only a few cases have arisen after more than 3 months of treatment.

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-tetrahydrothieno [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 300.25.

Each tablet, for oral administration, contains 250 mg of ticlopidine hydrochloride. In addition, each tablet contains the following inactive ingredients: ammonium chloride, magnesium stearate, microcrystalline cellulose, povidone, starch (corn), and stearic acid. The white film coating contains hydroxypropylmethyl cellulose, lactose monohydrate, titanium dioxide and triacetin.

## 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 although analysis of urine and plasma indicates at least twenty metabolites, no metabolite which accounts for the 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 irreversible for the life of the platelet, as shown both by persistent inhibition of fibrinogen binding 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 is extensively metabolized. Absorption is greater than 80%. Administration after meals results in a 20% increase in the AUC of ticlopidine.

Ticlopidine hydrochloride displays non-linear 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 repeat 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 (98%) 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 alpha-1 acid glycoprotein. At concentrations attained with the recommended dose, only 15% or less 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 mild (Cr 50 to 80 mL/min) or moderately (Cr 20 to 50 mL/min) impaired renal function were compared to normal subjects (Cr 80 to 150 mL/min) in a study of the pharmacokinetic and platelet pharmacodynamic effects of ticlopidine hydrochloride (250 mg bid) for 11 days. Concentrations of unchanged ticlopidine hydrochloride were measured after a single 250 mg dose and after the 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 normal within two 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.

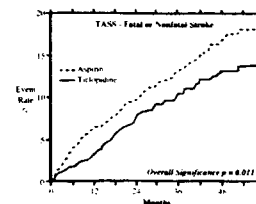
## CLINICAL TRIALS

The effect of ticlopidine on the risk of stroke and cardiovascular events was studied in two multi-center, 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), reversible ischemic neurological deficit or minor stroke, were randomized to ticlopidine 250 mg bid or aspirin 650 mg bid. The study was designed to follow patients for at least 2 years and up to 5 years.

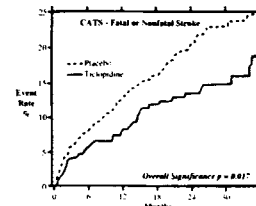
Over the duration of the study, ticlopidine hydrochloride significantly reduced the risk of fatal and nonfatal stroke by 24% ( $p = .011$ ) from 18.1 to 13.8 per 100 patients followed for five years, compared to aspirin. During the first year, when the risk of stroke is greatest, the reduction in risk 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, or 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% ( $p = .017$ ) from 24.6 to 18.6 per 100 patients followed for three 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 tablets are 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 who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.

## CONTRAINDICATIONS

The use of ticlopidine hydrochloride is contraindicated in the following conditions:

- Hypersensitivity to the drug.
- Presence of hematopoietic disorders such as neutropenia and thrombocytopenia or a past history of TTP.
- Presence of a hemostatic disorder or active pathological bleeding (such as bleeding peptic ulcer or intracranial bleeding).
- Patients with severe liver impairment.

## WARNINGS

### Hematological Adverse Reactions

#### NEUTROPENIA

Neutropenia may occur suddenly. Bone-marrow examination typically shows a reduction in myeloid precursors. After withdrawal of ticlopidine, the neutrophil count usually rises to  $> 1200/mm^3$  within 1 to 3 weeks.

#### THROMBOCYTOPENIA

Rarely, thrombocytopenia may occur in isolation or together with neutropenia.

#### THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. The signs and symptoms can occur in any order; in particular, clinical symptoms may precede laboratory findings by hours or days. With prompt treatment (often including plasmapheresis), 70% to 80% of patients will survive with minimal or no sequelae. Because platelet transfusions may accelerate thrombosis in patients with TTP on ticlopidine, they should, if possible, be avoided.

### MONITORING FOR HEMATOLOGIC ADVERSE REACTIONS

Starting just before initiating treatment and continuing through the third month of therapy, patients receiving ticlopidine hydrochloride must be monitored every 2 weeks. Because of ticlopidine's long plasma half-life, patients who discontinue ticlopidine during this 3-month period should continue to be monitored for 2 weeks after discontinuation. More frequent monitoring, and monitoring after the first 3 months of therapy, is necessary only in patients with clinical signs (e.g., signs or symptoms suggestive of infection) or laboratory signs (e.g., neutrophil count less than 70% of the baseline count, decrease in hematocrit or platelet count) that suggest incipient hematological adverse reactions.

Clinically, fever might suggest either neutropenia or TTP. TTP might also be suggested by weakness, pallor, petechiae or purpura, dark urine (due to blood, bile pigments, or hemoglobin) or jaundice, or neurological changes. Patients should be told to discontinue ticlopidine hydrochloride and to contact the physician immediately upon the occurrence of any of these findings.

Laboratory monitoring should include a complete blood count, with special attention to the absolute neutrophil count (WBC x % neutrophils), platelet count, and the appearance of the peripheral smear. Ticlopidine is occasionally associated with thrombocytopenia unrelated to TTP. Any acute, unexplained reduction in hemoglobin or platelet count should prompt further investigation for a diagnosis of TTP, and the appearance of schistocytes (fragmented RBCs) on the smear should be treated as presumptive evidence of TTP. If there are laboratory signs of TTP, or if the neutrophil count is confirmed to be  $< 1200/mm^3$ , then the drug should be discontinued.

### Other Hematological Effects

Rare cases of agranulocytosis, pancytopenia or aplastic anemia have been reported in postmarketing experience, some of which have been fatal. All forms of hematological adverse reactions are potentially fatal.

### Cholesterol Elevation

Ticlopidine hydrochloride therapy causes increased serum cholesterol and triglycerides. Serum total cholesterol levels are increased 8 to 10% within 1 month of therapy and persist at that level. The ratios of the lipoprotein subfractions are unchanged.

### Anticoagulant Drugs

The tolerance and safety of coadministration of ticlopidine hydrochloride with heparin, oral anticoagulants, or fibrinolytic agents have not been established. If a patient is switched from an anticoagulant or fibrinolytic drug to ticlopidine hydrochloride, the former drug should be discontinued prior to ticlopidine hydrochloride administration.

## PRECAUTIONS

### General

Ticlopidine hydrochloride should be used with caution in patients who may be at risk of increased 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 methylprednisolone 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).



# Ticlopidine

## Hydrochloride Tablets

SEP 13 1999

### IMPORTANT INFORMATION ABOUT TICLOPIDINE HCl Tablets

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 colour, pinpoint dots (rash) on the skin, pale colour, 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 colour 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:

**Genpharm Inc.**  
Toronto, Canada  
M8Z 2S6  
1-800-661-7134

Printed in Canada.

004-616 REV.#01

August 1998

**TICLOPIDINE HCl**  
**TABLET**  
**250 mg**

LOT: XXXXXX Exp.: XX.XXXX

Mfg. By:  
Genpharm Inc.  
Toronto, Canada  
M8Z 2S6

13 1999

**TICLOPIDINE HCl**  
**TABLET**  
**250 mg**

LOT: XXXXXX Exp.: XX.XXXX

Mfg. By:  
Genpharm Inc.  
Toronto, Canada  
M8Z 2S6

**TICLOPIDINE HCl**  
**TABLET**  
**250 mg**

LOT: XXXXXX Exp.: XX.XXXX

Mfg. By:  
Genpharm Inc.  
Toronto, Canada  
M8Z 2S6

13 1999

**TICLOPIDINE HCl**  
**TABLET**  
**250 mg**

LOT: XXXXXX Exp.: XX.XXXX

Mfg. By:  
Genpharm Inc.  
Toronto, Canada  
M8Z 2S6

Each tablet contains: Ticlopidine HCl 250 mg

**USUAL DOSAGE:** For dosage recommendations and other important prescribing information, read accompanying insert.

**NOTE:** It is essential that CBCs (including platelet count) and white cell differentials be performed every two weeks, starting at baseline before treatment is initiated to the end of the third month of therapy with ticlopidine hydrochloride. (See accompanying insert).

**Important:** Dispense enclosed Patient Package insert with prescription.

Store at controlled room temperature 15° to 30°C (59°-86°F).

Dispense in a tight, light-resistant container.

002-360 REV# 00

NDC 55567-054-13

30  
Tablets

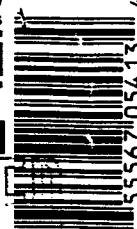
**TICLOPIDINE HCl**

Tablets

**250 mg**

Caution: Federal law prohibits dispensing without prescription.

Manufactured by:  
**GENPHARM INC.**  
Toronto, Canada  
M8Z 2S6  
1-800-661-7134



SEP 15 1999

**Each Tablet Contains:**  
Ticlopidine HCl 250 mg

**USUAL DOSAGE:** For dosage recommendations and other important prescribing information, read accompanying insert.

**Note:** It is essential that CBC's (including platelet count) and white cell differentials be performed every two weeks, starting at baseline before treatment is initiated to the end of the third month of therapy with ticlopidine hydrochloride (see accompanying insert).

**Important:** Dispense enclosed Patient Package Insert with prescription. Store at controlled room temperature 15°- 30°C (59°- 86°F). Dispense in a tight light-resistant container.

**Package Not Child Resistant**  
003-682 REV# 00

NDC 55567-054-25

500  
Tablets

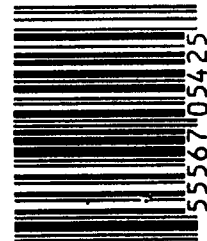
**TICLOPIDINE HCl**

Tablets

**250 mg**

**Caution:** Federal law prohibits dispensing without prescription

Manufactured by:  
**GENPHARM INC.**  
Toronto, Canada  
M8Z 2S6  
1-800-661-7134



SEP 13 1998

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NDC 55567-054-07

98 Tablets  
Unit Dose

**TICLOPIDINE HCl**

Tablets

**250 mg**

Caution: Federal law prohibits dispensing  
without prescription

GENPHARM INC.

7 Blister Strips  
of 14 Tablets

Each Tablet Contains: Ticlopidine HCl 250 mg

USUAL DOSAGE: One tablet two times a day with meals. See package insert for full  
prescribing information.

NOTE TO DISPENSER: Please provide a patient package insert when the blister pack  
is dispensed.

Note: It is essential that CBC's (including platelet  
count) and white cell differentials be performed every  
two weeks, starting at baseline before treatment is  
initiated to the end of the third month of therapy with  
ticlopidine hydrochloride (see accompanying insert).

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

This package is not child resistant. The tablets in this  
package are intended for institutional in-patient use. If  
dispensed for out-patient use, an appropriate safety  
closure should be provided.



NDC 55567-054-07

**TICLOPIDINE HCl**

Tablets

**250 mg**

98 Tablets  
Unit Dose

APPROVED

NDC 55567-054-07

98 Tablets  
Unit Dose

**TICLOPIDINE HCl**

Tablets

250 mg

Caution: Federal law prohibits dispensing  
without prescription

GENPHARM INC.

7 Blister Strips  
of 14 Tablets

NDC 55567-054-07

98 Tablets  
Unit Dose

**TICLOPIDINE HCl**

Tablets

250 mg

Caution: Federal law prohibits dispensing  
without prescription



Manufactured by:  
**GENPHARM INC.**  
Toronto, Canada M8Z 2S6  
1-800-661-7134

7 Blister Strips  
of 14 Tablets