CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75161

DRAFT FINAL PRINTED LABELING
TICLOPIDINE HYDROCHLORIDE TABLETS

**INDICATIONS AND USAGE**

Ticlopidine hydrochloride tablets are indicated to reduce the risk of thrombotic stroke (first or non-first) in patients who have experienced prior stroke or transient ischemic attack (TIA), and who have an increased risk of experiencing another stroke. It is not known whether ticlopidine hydrochloride is effective in reducing the risk of non-thrombotic stroke.

**CONTRAINDICATIONS**

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

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

**WARNINGS**

**Hematologic Adverse Reactions**

Neutropenia may occur suddenly. Bone marrow examination typically shows a reduction in myeloid precursor cells. After withdrawal of ticlopidine, the neutrophil count usually rises to >1000/mm³ within 1-4 weeks.

**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 addition, there may be fever, malaise, lethargy, and other nonspecific symptoms. TTP may be associated with monoclonal gammopathy or paroxysmal nocturnal hemoglobinuria.

**Monitoring and Hematologic Adverse Reactions**

Staging just prior to initiating therapy and continuing throughout the first month of therapy, patients receiving ticlopidine hydrochloride must be monitored weekly. Ticlopidine hydrochloride should be discontinued immediately if signs of aplastic anemia or myelodepression are observed. Therapy should be discontinued if neutropenia develops.

**Hepatic Impairment**

Patients with mild liver disease (Child-Pugh score of 5-6) or moderate liver disease (Child-Pugh score of 7-9) may experience a higher incidence of adverse effects. Laboratory monitoring should be performed as clinically indicated. The drug should be used with caution in patients with severe liver impairment (Child-Pugh score of 10 or more). Therapy should be discontinued if severe liver impairment occurs.

**Pharmacokinetics**

Ticlopidine is rapidly absorbed following oral administration, with peak plasma levels occurring within 2-4 hours after dosing. Ticlopidine is extensively metabolized in the liver. The primary metabolites are 4-hydroxyticlopidine, 5-hydroxyticlopidine, and 5-hydroxy-4-hydroxylated ticlopidine. Ticlopidine is extensively metabolized in the liver, and the primary metabolites are 4-hydroxyticlopidine, 5-hydroxyticlopidine, and 5-hydroxy-4-hydroxylated ticlopidine. Ticlopidine is extensively metabolized in the liver, and the primary metabolites are 4-hydroxyticlopidine, 5-hydroxyticlopidine, and 5-hydroxy-4-hydroxylated ticlopidine.

**Use in Renally Impaired Patients**

Ticlopidine is primarily eliminated by renal excretion. The clearance of ticlopidine is decreased in patients with renal impairment. However, the drug can be used in patients with mild to moderate renal impairment. However, the drug can be used in patients with mild to moderate renal impairment. However, the drug can be used in patients with mild to moderate renal impairment. However, the drug can be used in patients with mild to moderate renal impairment. However, the drug can be used in patients with mild to moderate renal impairment. However, the drug can be used in patients with mild to moderate renal impairment. However, the drug can be used in patients with mild to moderate renal impairment. However, the drug can be used in patients with mild to moderate renal impairment.
Information for the Patient (see Patient Package Insert [PPI])

Patients should be told that a decrease in the number of white blood cells (neutropenia) or platelets (thrombocytopenia) may occur during treatment with ticlopidine hydrochloride. If either of these decreases is severe, treatment should be discontinued. Patients should be instructed to contact their physician if for any reason they notice any indication of infection such as fever, chills, or sore throat, any difficulty breathing, unusual bleeding or bruising, or pain, redness, or swelling at the site of injection or intravenous infusion. If any of these symptoms persist or worsen, patients should contact their physician immediately.

All patients should be told that they may see fewer and smaller red blood cells than normal (anemia) and that they should report any unusual bleeding to their physician. Patients should be instructed that they could be taking ticlopidine hydrochloride for several months, and therefore, they must take their medicine as directed. They should be advised to contact their physician if their condition does not improve or gets worse.

Patients should be told to report promptly side effects of ticlopidine hydrochloride such as severe or persistent diarrhea, skin rashes, or any unusual bleeding or bruising after taking ticlopidine hydrochloride for 3 days, and any side effects that occur during the first 30 days of therapy because these reactions may occur more commonly during this period. All patients should be told to take ticlopidine hydrochloride with food or just after eating in order to minimize gastrointestinal discomfort.

Laboratory Test

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 elevations of alkaline phosphatase (2 to 2.5 times upper limits of normal) was 3% in ticlopidine patients. In patients taking aspirin, 3 to 5% of ticlopidine patients had elevations of alkaline phosphatase and 1 to 2% had elevations of transaminases. Four ticlopidine patients had elevations of alkaline phosphatase levels greater than 5 times the upper limit of normal. However, in patients with ticlopidine therapy, the incidence of these elevations was lower. If any of these tests indicate the need to discontinue therapy, the physician should be consulted.

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

Drug Interactions

Some drugs are affected by the use of ticlopidine hydrochloride. These interactions may affect the effectiveness of a ticlopidine hydrochloride regimen or affect the levels of other drugs being taken by the patient. The physician should be consulted if drug interactions are noted during therapy.

ANTACIDS

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

CONTRAINDICATIONS

Chronic administration of omeprazole reduced the clearance of a single dose of ticlopidine hydrochloride by 50%

DISCUSSION

The use of antacids to reduce the peak plasma levels of ticlopidine hydrochloride is recommended.

ANTICOAGULANTS

Anticoagulants, including warfarin, may interfere with the metabolism of ticlopidine hydrochloride and affect the prothrombin time. These drugs should be avoided if possible.

Ticlopidine hydrochloride increases the risk of bleeding. Patients on anticoagulant therapy should be monitored closely.

OTHER CONCOMITANT THERAPY

Food Interactions

Food has little effect on the plasma levels or its metabolism and ticlopidine therapy has been studied in vivo. Caution should be exercised in concomitantly using this drug with ticlopidine hydrochloride.

Carbohydrate, Monoglyceride and Impairment of Fertility

In 1-year studies, in rats and rabbits, ticlopidine hydrochloride had no effect on fertility or on the number of live births. In rats, daily doses of up to 100 mg/kg (400 mg/kg) was not toxic. In rabbits, daily doses of up to 200 mg/kg (800 mg/kg) was not toxic. Therefore, ticlopidine is not considered a human teratogen. In studies in rabbits, ticlopidine hydrochloride did not impair fertility or cause fetal abnormalities.

Carcinogenesis, Mutagenesis and Impairment of Fertility

In 1-year studies in rats, ticlopidine hydrochloride did not produce any increase in tumors. The incidence of tumors was not increased in rats or mice given multiple doses of ticlopidine hydrochloride up to 30 mg/kg body weight for 2 years. In the rat, ticlopidine hydrochloride did not induce tumors in any of the 3 strains of tests mice used. In mice, ticlopidine hydrochloride did not induce tumors at doses up to 275 mg/kg (1180 mg/kg) was not toxic. The incidence of tumors was not increased in rabbits given intraperitoneal or subcutaneous injections of ticlopidine hydrochloride in animals. In rabbits, the incidence of tumors was not increased in the rat or mouse. The incidence of tumors was not increased in mice given intraperitoneal or subcutaneous injections of ticlopidine hydrochloride for 2 years. Therefore, ticlopidine is not considered a human teratogen. In studies in rabbits, ticlopidine hydrochloride did not impair fertility or cause fetal abnormalities.

Dosage and Administration

Administration of ticlopidine hydrochloride tablets is 250 mg bid taken with food. Other doses have not been studied in clinical trials for these indications.

Special Warnings for Use of Ticlopidine Hydrochloride/Neonatal Blood Tests

Ticlopidine hydrochloride is recommended for patients under 18 years of age for ticlopidine hydrochloride-related adverse reactions. Caution is advised for children aged 1 to 6 years. A larger dose is required for children aged 6 to 12 years. Caution is advised for children aged 12 years and older. A smaller dose is required for children aged 12 years and older.

Neonatal Blood Tests

Ticlopidine hydrochloride has been associated with increased bleeding, spontaneous post-traumatic haemorrhage, and premature delivery. Neonatal blood tests should be performed at birth to determine if the mother was taking ticlopidine hydrochloride. These tests may be positive even in the absence of symptoms and may persist for several months. If these tests are positive, the physician should be consulted.

Ticlopidine hydrochloride has been reported to cause neonatal bleeding. Neonatal blood tests should be performed before and after delivery. These tests may be positive even in the absence of symptoms and may persist for several months. If these tests are positive, the physician should be consulted.

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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 2R8
1-800-661-7134

Printed in Canada.
004-616  REV #01  August 1998
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).


Caution: Federal law prohibits dispensing without prescription

Manufactured by: GENPHARM INC.
Toronto, Canada M6Z 2S6
1-800-661-7134

NDC 55567-054-25
500 Tablets
TICLOPIDINE HCI
Tablets
250 mg

Caution: Federal law prohibits dispensing without prescription

GENPHARM INC.

NDC 55567-054-07  98 Tablets Unit Dose

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.
TICLOPIDINE HCl

Tablets

250 mg

Caution: Federal law prohibits dispensing without prescription

GENPHARM INC.

NDC 55567-054-07

98 Tablets
Unit Dose

7 Blister Strips
of 14 Tablets

TICLOPIDINE HCl

Tablets

250 mg

Caution: Federal law prohibits dispensing without prescription

Manufactured by:
GENPHARM INC.
Toronto, Canada M8Z 2M6
1-800-661-7134

NDC 55567-054-07

98 Tablets
Unit Dose

7 Blister Strips
of 14 Tablets