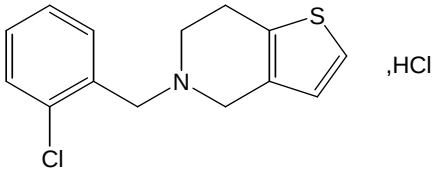
Tilodene

Ticlopidine hydrochloride

PRODUCT INFORMATION

Name of the Medicine

Active ingredient: Ticlopidine hydrochloride
Chemical name: 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno-(3,2-c) pyridine hydrochloride (IU PAC)
The structural formula for ticlopidine hydrochloride is:



Molecular formula: $C_{14}H_{14}ClNS.HCl$ Molecular weight: 300.2
CAS Registry No.: 53885-35-1

Description

Ticlopidine hydrochloride is a white crystalline solid, which is slightly soluble in acetone and sparingly soluble in water, ethanol, methylene chloride, and buffer solutions above pH 6.0. An aqueous solution of ticlopidine has a pH of 3.6. Each Tilodene tablet contains 250 mg of ticlopidine hydrochloride. The tablets also contain cellulose - microcrystalline, povidone, starch - maize, ammonium chloride, stearic acid, magnesium stearate and Opadry II White Y-30-18037.

Pharmacology

Mechanism of action. Ticlopidine is an inhibitor of platelet aggregation. When taken orally 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 characterised, but does not involve inhibition of the prostacyclin/thromboxane pathways. Platelet cyclic AMP (adenosine monophosphate) does not see m to play a role in the mechanism of action of ticlopidine. Ticlopidine interferes with platelet membrane function by inhibiting ADP (adenosine diphosphate) induced platelet-fibrinogen binding and subsequent platelet-platelet interactions.

The effect of ticlopidine 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. Although it is unclear how ticlopidine brings about these changes, a suggested mechanism is that it inhibits ADP induced exposure of the fibrinogen binding site of the glycoprotein IIb-IIIa complex.

Pharmacodynamics

Inhibition of platelet aggregation is detected within four days of administration of a dosage regimen of 250 mg twice daily. Maximum platelet aggregation inhibition (60 to 70%) is achieved 8 to 11 days following dosing with 250 mg twice daily. At the therapeutic dose, ADP induced platelet aggregation is inhibited by 50 to 70%. Lower total daily doses of 375 and 250 mg result in 30 to 60% and 25 to 50% inhibition of platelet aggregation, respectively. Template bleeding time is usually prolonged by two- to fivefold of baseline values with the therapeutic dose of ticlopidine. Upon discontinuation of ticlopidine dosing, bleeding time and other platelet function tests return to normal within two weeks in the majority of patients. At the recommended therapeutic dose, ticlopidine has no known significant pharmacological actions in humans other than inhibition of platelet function.

Pharmacokinetics

After oral administration of the therapeutic dose of ticlopidine, rapid absorption occurs, with peak plasma levels occurring approximately two hours after dosing. Absorption is at least 80% complete. Administration of ticlopidine after meals results in an increased (20%) level of ticlopidine in plasma.

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 repeat dosing at 250 mg twice daily, the terminal elimination half-life rises to four to five days and steady state levels of ticlopidine hydrochloride in plasma are obtained after approximately 14 to 21 days.

Ticlopidine 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 in a saturable manner to alpha1-acid glycoprotein. At concentrations attained with the recommended dose, only 15% or less ticlopidine in plasma is bound to this protein.

Ticlopidine is metabolised extensively by the liver; no intact ticlopidine is detected in the urine. Following an oral dose of radioactive ticlopidine hydrochloride administered in solution, 60% of the radioactivity was recovered in the urine and 23% in the faeces. Unmetabolised ticlopidine is a minor component in plasma after a single dose, but at steady state, ticlopidine is the major component. Approximately 40 to 50% of the radioactive metabolites circulating in plasma are covalently bound to plasma proteins.

Clearance of ticlopidine decreases with age. Steady state trough values in elderly patients (mean age 70 years) are about twice those in young volunteer populations.

Impaired hepatic function. Ticlopidine has been studied in patients with varying degrees of hepatic function abnormalities. Impaired hepatic function resulted in higher than normal levels of unchanged ticlopidine following single or multiple doses.

Impaired renal function. Patients with mildly (creatinine clearance 50 to 80 mL/minute) or moderately (creatinine clearance 20 to 50 mL/minute) impaired renal function were compared to normal subjects (creatinine clearance 80 to 150 mL/minute) in a study of the pharmacokinetic and platelet pharmacodynamic effects of ticlopidine (250 mg twice daily) for eleven days. Concentrations of unchanged ticlopidine were measured after a single 250 mg dose and after the final 250 mg dose on day 11. Area under the curve (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.

Clinical Trials

Secondary Prevention of Stroke

In a randomised, stratified, triple-blind multicentre trial comparing ticlopidine 250 mg BD (n=532) and placebo (n=541: the "Canadian American Ticlopidine Study", or CATS), 1073 male and female patients who had experienced a previous atherothrombotic stroke between one week and four months previously, and were at risk of recurrent stroke, were treated for up to 3 years. The primary endpoint was non-fatal (non-haemorrhagic) stroke, non-fatal myocardial infarction or vascular death. Ticlopidine significantly reduced the overall risk of stroke by 24% (p=0.017) compared to placebo. During the first year, the reduction in risk of fatal and non-fatal stroke over placebo was 33%. A risk-reduction for the primary composite endpoint, compared to placebo, was maintained to the three year conclusion (see Table 1).

Table 1 Percentage Risk Reduction and Yearly Cumulative Event Rates of Ticlopidine over Placebo for Secondary Prevention in the CATS Study

	Analysis	1 year	2 years	3 years	Significance
Primary Endpoint (composite)	Intention to treat	32% (11.2, 16.4%)*	19% (20.0, 24.7)*	14% (27.7, 32.2)*	P=0.049
	Efficacy	37% (10.4, 16.5)*	23% (19.3, 25.1)*	24% (24.4, 32.3)*	P=0.014

* Yearly cumulative event rate per 100 (Ticlopidine, placebo)

Primary Prevention of Stroke

In a randomised, stratified, triple-blind multicentre trial comparing ticlopidine 250 mg BD and aspirin 650mg BD (the "Ticlopidine Aspirin Stroke Study", or TASS), 3069 patients (1987 men, 1082 women) aged forty or more who had experienced transient ischaemic attack (TIA) and/or transient monocular blindness (amaurosis fugax), reversible ischaemic neurological deficit (RIND) or minor stroke (including symptomatic lacunar infarct) within the previous 3 months and not eligible for surgery and likely to survive for at least 2 years, were included and followed for at least 2 and up to 5 years. The primary endpoint was a composite of non-fatal stroke or all death. Secondary endpoints included all stroke, all mortality and vascular mortality and non-fatal stroke or non-fatal myocardial infarction. Over the duration of the study, ticlopidine significantly reduced the risk of fatal or non-fatal stroke by 27% (p=0.011) compared to aspirin. During the first year, when the risk of stroke is greatest, the reduction in risk of stroke (fatal and non-fatal) compared to aspirin was 48% (see Table 2). The risk-reduction was demonstrated in men and women.

Table 2 Percentage Risk Reduction and Yearly Cumulative Event Rates of Ticlopidine over Aspirin for Primary Prevention in the TASS Study

	Analysis	1 year	2 years	3 years	Significance
Primary Endpoint (composite)	Intention to treat	41% (5.2, 8.8)*	20% (11.6, 14.6)*	12% (17.0, 19.4)*	P=0.048
	Efficacy	42% (4.6, 7.9)*	18% (10.3, 12.6)*	13% (14.5, 16.6)*	P=0.048
Secondary Endpoint (composite)	Intention to treat	46% (3.4, 6.2)*	26% (7.4, 9.9)*	21% (10.0, 12.7)	P=0.024
	Efficacy	48% (3.4, 6.4)*	22% (7.6, 9.8)*	21* (10.3, 13.0)*	P=0.011

* Yearly cumulative event rate per 100 (Ticlopidine, aspirin)

Indications

Patients with high risk of thromboembolic stroke following ischaemic cerebrovascular disturbance (transient ischaemic attack, transient monocular blindness, reversible ischaemic neurological deficit and previous stroke) who are intolerant of, or unresponsive to, aspirin.

Tilodene is not indicated for other types of stroke, e.g. haemorrhagic, embolic, postangiographic, and following carotid thromboendarterectomy.

Contraindications

1. Hypersensitivity to the drug or its excipients.

2. Haematopoietic disorders such as neutropenia, agranulocytosis and thrombocytopenia.

3. A haemostatic disorder or active pathological bleeding (e.g. bleeding peptic ulcer or intracranial bleeding).

4. Severe hepatic impairment or cholestatic jaundice.

5. Elderly patients (over 65 years) with renal and/or hepatic impairment.

6. Patients with renal disease on haemodialysis.

7. Severe heart failure with hepatic congestion.

Precautions

Neutropenia, thrombocytopenia and Thrombotic Thrombocytopenia Purpura (TTP)
Neutropenia/ myelosuppression have resulted from the use of ticlopidine. The bone marrow typically shows a reduction in myeloid precursors. Recovery usually occurs within one to three weeks of drug withdrawal. In rare instances, fatalities have occurred.

In two large clinical trials, 17 out of 2,048 patients (about 1%) progressed to severe neutropenia and/or agranulocytosis (absolute neutrophil count < 450 cells/mm^3) and only recovered when therapy was discontinued. A larger group of 33 patients experienced transient neutropenia, seven patients discontinued treatment and 26 continued on therapy. All patients recovered.

The onset of neutropenia may occur suddenly. The period of maximal risk is from three weeks to three months after starting therapy, peaking at approximately four to six weeks after initiation. (See Precautions, Laboratory monitoring, for haematological testing regimen.)

In rare instances, thrombocytopenia may occur in isolation or together with neutropenia, and cases of pancytopenia, aplastic anaemia immune thrombocytopenia and thrombocytopenic thrombotic purpura have also been reported, some of which have been fatal. The incidence of TTP peaks at approximately four to six weeks and declines thereafter.

TTP is characterised by thrombocytopenia, microangiographic haemolytic anaemia (schistocytes [fragmented red blood cells] see 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.

Important. If clinical evaluation and repeat laboratory testing confirm the presence of neutropenia (absolute neutrophil count < 1,200 cells/mm^3) or thrombocytopenia (< 80,000 cells/mm^3) the drug should be discontinued and whole blood counts with differentials should be monitored until they return to normal. In clinical trials, when therapy was discontinued immediately on detection of neutropenia, reversal was the usual outcome within 1-3 weeks of drug withdrawal.

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

Laboratory monitoring
Important. All patients should have a baseline whole blood count with white cell differential and platelet counts performed prior to the start of treatment and then every two weeks during the first four months of therapy (more frequent monitoring is necessary for patients whose absolute neutrophil counts have been consistently declining or are 30% less than the baseline count). Thereafter, whole blood count (including platelet count) and white cell differential count need only be repeated for symptoms or signs suggestive of neutropenia or thrombocytopenia.

Since ticlopidine has a long plasma half-life, it is recommended that patients discontinuing therapy for any reason during the first four months should have a whole blood count with white cell differential and platelet counts performed for at least two weeks after cessation of therapy.

Periodic liver function tests and measurement of cholesterol levels should also be conducted during therapy with Tilodene. (See **Adverse Effects, Altered laboratory findings**.)

Clinical monitoring
All patients have to be carefully monitored for clinical signs and symptoms of adverse drug effects (see Adverse Effects). The signs and symptoms possibly related to neutropenia (fever, chills, sore throat, ulcerations in oral cavity), thrombocytopenia and/or abnormal haemostasis (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 doctor immediately if any of the above occur. The decision to restart treatment should only be taken according to clinical and laboratory findings. In the case of suspected thrombotic thrombocytopenia purpura (TTP, characterised by thrombocytopenia, haemolytic anaemia, neurological symptoms, renal dysfunction and fever), treatment should be ceased immediately and the patient referred for specialist care. The onset of TTP may occur suddenly with most cases being reported within the first eight weeks of initiation of therapy.

Haemorrhagic complications
Ticlopidine prolongs template bleeding time, therefore, it should be used with caution in patients who have lesions with a propensity to bleed (e.g. ulcers, see Contraindications), or who are taking drugs (e.g. NSAIDs) that might induce such lesions. Tilodene should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or pathological conditions.

On the basis of physiological principles and findings in the pharmacology studies, fresh platelet transfusions and corticosteroids may ameliorate haemorrhagic complications due to ticlopidine, but this effect has not been verified in clinical trials. Platelet transfusions are not indicated in patients with TTP on ticlopidine.

In the case of excessive bleeding after injury or surgery, standard supportive measures should be carried out if indicated, including gastric lavage (when the gag reflex is not impaired), platelet transfusion and use of corticosteroids (see **Emergency Surgery below**).

Elective surgery
Tilodene 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 haemostasis 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 normalise bleeding time in ticlopidine treated subjects, but there is no experience with ticlopidine treated surgical patients to show that such treatment improves haemostasis.

Impaired renal function
There is limited experience in patients with renal impairment. 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 haemorrhagic or haematopoietic problems are encountered.

Ticlopidine is contraindicated in patients with renal disease on haemodialysis.

Impaired hepatic function
Ticlopidine is contraindicated in patients with severe hepatic dysfunction or cholestatic jaundice, and should be used with caution in patients with less severe hepatic dysfunction.

Mild increases in alkaline phosphatase and transaminases may be seen in patients during Tilodene treatment, but are inconsequential in the majority of patients. (See **Adverse Effects, Altered laboratory findings**.)

Use in the elderly

The major clinical trials with ticlopidine were conducted in an elderly population with an average age of 64 years. No significant differences in responses to ticlopidine have been observed between elderly and young patients who participated in clinical studies.

Ticlopidine is contraindicated in elderly patients (over 65 years) with renal and/or hepatic impairment.

Carcinogenesis, mutagenesis, impairment of fertility

Reproductive studies have been performed in mice and rabbits (oral doses up to 200 mg/kg/day) and rats (oral doses up to 400 mg/kg/day) and have revealed no evidence of impaired fertility or teratogenic effects. At the highest doses tested there were increased incidences of resorptions and reduced litter sizes, but this is thought to be due to maternal toxicity rather than a direct effect on the foetus.

Use in pregnancy (Category B1)

Tilodene is not recommended for use in pregnancy. (See Carcinogenesis, mutagenesis and impairment of fertility.)

Use in lactation

Tilodene is not recommended for use in breastfeeding mothers.

Ticlopidine administration to rats during the lactation period prejudiced the survival of pups of mothers receiving the 400 mg/kg/day dose. However, the reproductive performance, postnatal differentiation and functional behavioural tests did not show any changes attributable to ticlopidine. Consistent with the reduced survival of rat pups from mothers receiving ticlopidine during the lactation period was the finding that ticlopidine is excreted into milk. Six hours after a 25 mg/kg oral dose of ^{14}C-ticlopidine, the milk concentration to maternal blood plasma concentration ratio was 8.0 and this ratio was maintained for eight hours, indicating that accumulation occurs in milk.

Use in children

The safety and efficacy of ticlopidine in children under the age of 18 years have not been studied, therefore, Tilodene is not recommended in this population.

Interactions with Other Medicines

Oral anticoagulants and heparins
The tolerance and safety of coadministration of Tilodene with heparin, oral anticoagulants or fibrinolytic agents have not been established when used in patients with a high risk of thromboembolic stroke following ischaemic cerebrovascular disturbance. If it is desired to switch a patient from an anticoagulant drug to Tilodene, the former drug should be discontinued and its haemostatic effects fully subsided prior to initiation of Tilodene therapy.

Aspirin
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. The tolerance and safety of this combination have not been established in patients with a high risk of thromboembolic stroke following ischaemic cerebrovascular disturbance.

Antiplatelet drugs
Concomitant use with other antiplatelet agents including aspirin carries an increased risk of haemorrhage and requires very close monitoring.

Antipyrine
Antipyrine is a model for drugs metabolised by the microsomal hepatic enzyme system (cytochrome p-450 system). Therapeutic doses of ticlopidine caused a 30% increase in the plasma half-life of antipyrine and may cause analogous effects on similarly metabolised drugs. Therefore, dosage of drugs metabolised by hepatic microsomal enzymes with low therapeutic ratios or in patients with hepatic impairment may require adjustment to maintain optimal therapeutic blood levels when starting or stopping concomitant therapy with ticlopidine.

Carbamazepine
Increased carbamazepine levels and consequent neurological symptoms (dizziness, drowsiness and ataxia) with concomitant administration of ticlopidine have been reported. Patients should be monitored for signs of carbamazepine toxicity when these drugs are taken in combination. Plasma carbamazepine levels should be monitored and carbamazepine dosage adjusted when ticlopidine is added or withdrawn.

Theophylline
In healthy volunteers, concomitant administration of ticlopidine 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. Theophylline dosage must be adjusted during and after treatment with ticlopidine.

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

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

Antacids
Administration of ticlopidine after antacids resulted in a 20% decrease in plasma levels of ticlopidine.

Phenobarbital
In a small number of healthy volunteers, the inhibitory effects of ticlopidine on platelet aggregation were not altered by chronic administration of phenobarbital.

Phenytoin
Cases of elevated phenytoin plasma levels and/or somnolence and lethargy have been reported during coadministration with ticlopidine. Caution should be exercised in coadministering this drug with Tilodene and it is advised to remeasure phenytoin blood concentrations.

NSAIDs
There is an increased risk of haemorrhage with the concurrent use of NSAIDs. If such drugs are necessary clinical and laboratory monitoring (including skin bleeding time) is required.

Plasma protein binding
In vitro studies demonstrate that ticlopidine does not interact with propranolol or phenytoin, basic drugs which are also highly protein bound, with respect to plasma protein binding.

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

Adverse Effects

Adverse effects were relatively frequent, with over 50% of patients reporting at least one. Most (30 to 40%) involved the gastrointestinal tract. Most adverse effects were mild, but 21% of patients discontinued therapy because of an adverse event, principally diarrhoea, rash, nausea, vomiting, gastrointestinal 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 the multicentre, controlled clinical trials comparing ticlopidine, 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 are shown in Table 1.

Table 1: Percent of patients with adverse events in controlled studies

Adverse Event	Ticlopidine (n= 2048)	Aspirin (n = 1527)	Placebo (n = 536)
Any event	60.0 (20.9)	53.2 (14.5)	34.3 (6.1)
Diarrhoea	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)
Gastrointestinal 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)

Note: incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Gastrointestinal
Ticlopidine therapy has been associated with a variety of gastrointestinal complaints including diarrhoea and nausea. The majority of cases are mild, but about 13% of patients discontinued therapy because of these. They usually occur within three months of initiation of therapy and typically are resolved within one to two weeks without discontinuation of therapy. Very rare cases of severe diarrhoea with colitis (including lymphocytic colitis) have been reported. If the effect is severe or persistent, therapy should be discontinued.

Haemorrhagic
Ticlopidine has been associated with a number of bleeding complications, mainly bruising or ecchymosis and epistaxis. Haematuria, conjunctival haemorrhage, gastrointestinal bleeding and peri-operative bleeding and spontaneous post-traumatic bleeding have been reported.

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

Rash
Ticlopidine has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within three months of initiation of therapy, with a mean onset time of eleven days. If the drug is discontinued, recovery should occur within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of severe rashes including Stevens-Johnson syndrome, erythema multiforme and exfoliative dermatitis.

Less frequent adverse effects (Probably related.)
Clinical adverse experiences occurring in 0.5 to 1.0% of patients in the controlled trials include the following:

Gastrointestinal. Hepatitis (cytolytic and cholestatic) during the first months of treatment, gastrointestinal fullness.

Dermatological. Urticaria.

Nervous system. Headache.

Body as a whole. Asthenia, pain.

Haemostatic. Epistaxis.

Special senses. Tinnitus.

In addition, rare or very rare, relatively serious events have also been reported, mainly from overseas postmarketing experience: aplastic anaemia, haemolytic anaemia with reticulocytosis, allergic reactions, anaphylaxis, Quincke edema, arthralgia, hypersensitivity nephropathy, allergic pneumopathy, allergic pneumonitis, systemic lupus (positive antinuclear antibody (ANA)), peripheral neuropathy, vasculitis, serum sickness, arthropathy, hepatitis, cholestatic jaundice, angioedema, fever, nephrotic syndrome, myositis, hyponatraemia, immune thrombocytopenia, thrombocytopenic thrombotic purpura (TTP), isolated thrombocytopenia, renal failure, hepatic necrosis, sepsis, hepatocellular jaundice, myalgia, cramps and interstitial nephritis.

Altered laboratory findings

Haematological
Neutropenia, thrombocytopenia, agranulocytosis, eosinophilia, pancytopenia, thrombocytosis and bone marrow depression have been reported. (see Precautions).

Hepatic
Ticlopidine therapy has been associated with mild elevations of alkaline phosphatase and transaminases, which generally occur within one to four months of therapy initiation. No progressive increases were seen in closely monitored clinical trials, but most patients with these abnormalities had therapy discontinued. Occasionally, patients had developed minor deviations in bilirubin.

Cholesterol
Ticlopidine therapy has been associated with increased serum cholesterol and triglycerides. Serum levels of high density lipoprotein C, low density lipoprotein C, very low density lipoprotein C and triglycerides are increased 8 to 10% within one month of therapy and persist at those levels. The ratios of the lipoprotein subfractions are unchanged. The effect is not correlated with age, sex, alcohol use or diabetes.

Dosage and Administration

The recommended dose is 250 mg twice daily with food. Tilodene should be taken with meals to minimise gastrointestinal intolerance.

Overdosage

Based on animal studies, overdosage may cause severe gastrointestinal intolerance.

Two cases of deliberate overdosage with ticlopidine have been reported in postmarketing surveillance. A 38 year old male took a single 6,000 mg dose of ticlopidine (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. A 64 year old female took a single 7500 mg dose of ticlopidine (30 tablets), which led to disorientation, somnolence, urinary and faecal incontinence and anorexia, which resolved within a week.

Following overdosage, gastric lavage and other general supportive measures are recommended. Coagulation parameters should be checked; the patient should be monitored closely for evidence of bleeding (including intracranial and other occult bleeding); full blood count (including platelet count) should be monitored for up to two weeks after the overdose.

Contact the Poison Information Centre on 131126 (Australia) for advice on the management of overdosage.

Presentation and Storage Conditions

Tilodene, Ticlopidine hydrochloride tablets, 250 mg (white to off-white, oval, film coated, marked T250 on one side and G on reverse): 60's.

Store below 25°C.

Poison Schedule of the Medicine

S4 (Prescription Only Medicine)

Name and Address of the Sponsor

Alphapharm Pty Limited
Chase Building 2
Wentworth Park Road
Glebe NSW 2037

ABN 93 002 359 739

www.alphapharm.com.au

Date of Approval

Approved by the Therapeutic Goods Administration on 18 April 2007.