

Ticlopidine

Core Safety Profile

Formulation: 250 mg film-coated tablet

4.2 Posology and method of administration

Paediatric Population

The use in children and adolescents is not recommended due to lack of experience in clinical trials.

4.3 Contraindications

Haemorrhagic diathesis

Organic lesions which are liable to bleed i.e. active gastroduodenal ulcer or haemorrhagic cerebrovascular accident in the acute phase

Blood disease involving prolonged bleeding time

History of hypersensitivity to ticlopidine or any of the product components

History of leucopenia, thrombocytopenia or agranulocytosis

4.4 Special warnings and precautions for use

Haematological and haemorrhagic adverse effects can occur. Agranulocytosis, pancytopenia and rare cases of leukaemia have been reported in postmarketing experience

Serious sometimes fatal haematological and haemorrhagic adverse effects (see section 4.8 Undesirable effects) may occur, especially associated with:

- Inadequate monitoring, late diagnosis and inappropriate therapeutic measures for adverse effects

- Concomitant administration of anticoagulants or antiplatelet agents such as aspirin and nonsteroidal anti-inflammatory medicinal products. However, in case of STENT implantation, ticlopidine should be combined with aspirin (100 to 325 mg per day) for about one month following implantation.

Haematological monitoring

Blood cell counts (BCCs) with differential and platelet counts should be performed at the start of treatment and then every two weeks for the first three months of therapy and within 15 days after discontinuation of ticlopidine, should the treatment be stopped within the first three months of therapy.

When the neutrophil numbers have fallen below $1500/\text{mm}^3$, the values should be confirmed. If the presence of neutropenia (neutrophils $<1,500/\text{mm}^3$) or

thrombocytopenia (platelets $<100,000/\text{mm}^3$), are confirmed, the drug should be discontinued.

Because of the long plasma half-life of ticlopidine hydrochloride, it is recommended that any patient who discontinues Ticlopidine for any reason within the first 90 days have an additional CBC with white cell differential count obtained two weeks after discontinuation of therapy. Blood count parameters, including the differential leukocyte count and the platelet count, should be monitored until they return to normal values.

Clinical Monitoring

It is necessary for the patient to be informed about signs and symptoms that are possibly connected to neutropenia (fever, sore throat, ulcers in the oral cavity), thrombocytopenia, and/or haemostasis problems (prolonged or unexpected haemorrhage, ecchymosis, purpura, dark faeces) or a TTP (see below).

It is necessary to advise the patients to suspend medication and to immediately consult their physician in the event that one of the above signs or symptoms appears. The decision to resume the treatment can only be taken after taking into consideration clinical and laboratory records.

The patient should also be informed about symptoms of hepatitis (e.g. jaundice, pale stools, dark urine) and should be encouraged to report these symptoms to the doctor.

The clinical diagnosis of a rare, potentially fatal thrombotic thrombocytopenic purpura (TTP) is characterised by the presence of thrombocytopenia, haemolytic anemia, neurological symptoms similar to those of a TIA or a stroke or renal dysfunction and fever.

The onset may be sudden. Most cases have been reported in the first 8 weeks of initiating therapy.

Due to the risk of fatal outcome, in the event of suspected thrombotic thrombocytopenic purpura, a specialist team should be contacted.

Treatment with plasmapheresis has been reported to improve the prognosis. Since the administration of platelets may lead to increased thrombosis, it should be avoided if possible".

- Haemostasis :

Ticlopidine must be used with caution in patients who are at increased risk of bleeding.

The medicinal product should not be given in combination with heparins, oral anticoagulants and antiplatelet medicinal products (see section 4.4 Special warnings and precautions for use and section 4.5 Interaction with other medicinal products and other forms of interaction); however, in exceptional cases of concomitant treatment, close clinical and laboratory monitoring is required (see section 4.5 Interaction with other medicinal products and other forms of interaction).

In the event of even minor surgical procedures (e.g. dental extraction) prolonged bleeding time has to be expected. If the patient is to undergo elective surgery, treatment should wherever possible be stopped at least ten days before surgery (except in cases in which anti-thrombotic activity is explicitly required) in consideration of the haemorrhagic risk induced by the medicinal product".

In the event of emergency surgery, 3 means may be used alone or in combination to limit the risk of haemorrhage and prolonged bleeding time: administration of 0.5 to 1 mg/kg of methylprednisolone i.v., to be renewed; desmopressin at a dosage of 0.2 to 0.4 µg/kg; platelet transfusions.

- As ticlopidine is extensively metabolised by the liver:

The medicinal product should be used with caution in patients with impaired liver function. In case of suspected liver dysfunction, liver function tests should be carried out, especially during the first months of treatment, and treatment should be discontinued and liver function test should be performed if hepatitis or jaundice develops.

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, in renally impaired patients, it may be necessary to reduce the dosage of ticlopidine or discontinue it altogether if hemorrhagic or hematopoietic problems are encountered.

All patients should be carefully monitored for clinical signs and symptoms of adverse reactions especially during the first three months of therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations with increased haemorrhagic risk:

NSAIDs:

Increase of haemorrhagic risk (increase of platelet antiaggregant activity and NSAIDs effect on the gastro-duodenal mucous membrane). If such medicinal products are necessary, close clinical monitoring is required.

Antiplatelet medicinal products:

Increase of haemorrhagic risk (increase of platelet antiaggregant activity). If such medicinal products are necessary, close clinical monitoring is required.

Salicylic derivatives (by extrapolation from acetylsalicylic acid):

Increase of haemorrhagic risk (increase of platelet antiaggregant activity and salicylic derivatives effect on the gastro-duodenal mucous membrane). If such medicinal products are necessary, close clinical monitoring is required. In case of STENT(s) implantation see section 4.4 Special warnings and precautions for use.

Oral anticoagulant:

Increase of haemorrhagic risk (combination of anticoagulant activity and platelet antiaggregant activity). If such medicinal products are necessary, close clinical and biological monitoring (INR) is required.

Heparins:

Increase of haemorrhagic risk (combination of anticoagulant activity and platelet antiaggregant activity). If such medicinal products are necessary, close clinical and biological monitoring (APTT) is required.

Combinations requiring special precautions:

Theophylline

Increase of plasma theophylline levels with risk of overdosage (decrease in total plasma theophylline clearance). Clinical monitoring, and if necessary plasma theophylline levels are required. Theophylline dosage must be adjusted during and after treatment with ticlopidine.

Digoxin

Co-administration of ticlopidine and digoxin leads to a slight decrease (approximately 15%) in plasma digoxin levels. This should not affect the therapeutic efficacy of digoxin.

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. There have been rare reports of increased phenytoin levels and phenytoin toxicity when ticlopidine is co-prescribed. Caution should be exercised in coadministering this medicinal product with ticlopidine and it may be useful to remeasure phenytoin blood concentrations.

Other concomitant therapies:

In clinical studies, ticlopidine was given concomitantly with beta-blockers, calcium channel blockers and diuretics: no clinically significant adverse interactions were reported.

In-vitro studies demonstrate that ticlopidine does not interact with plasma protein binding of propranolol.

The biological half-life of Antipyrine which is metabolized via the Cytochrome P 450 system is prolonged by 25% during coadministration with ticlopidine. This is also expected for substances with similar hepatic metabolism. Especially for substances with a narrow therapeutic index, dose adjustment is necessary at the beginning and after discontinuation of coadministration.

The coadministration of ticlopidine and antacids leads to a 20-30% lower ticlopidine plasma level.

Chronic therapy with cimetidine increases the ticlopidine plasma level significantly.

In very rare instances, lowering of cyclosporine blood level has been reported. Therefore, cyclosporine blood level should be monitored in case of coadministration.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of ticlopidine in pregnant women has not been established. Unless absolutely necessary, ticlopidine should not be used during pregnancy.

Lactation

Studies in rats have shown that ticlopidine is excreted in the milk.

The safety of ticlopidine in nursing women has not been established. Unless absolutely necessary, ticlopidine should not be used during breast feeding.

4.7 Effects on ability to drive and use machines

The side-effects of ticlopidine, such as dizziness, may adversely affect the ability to drive or use machines.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

Very common $\geq 10\%$; Common ≥ 1 and $< 10\%$; Uncommon ≥ 0.1 and $< 1\%$; Rare ≥ 0.01 and $< 0.1\%$; Very rare $< 0.01\%$, Unknown (cannot be estimated from available data).

System Organ Class	Common	Uncommon	Rare	Very rare	Unknown
Blood and lymphatic system disorders ¹	Neutropenia including severe neutropenia (see section 4.4), agranulocytosis.	Isolated thrombocytopenia or exceptionally accompanied by haemolytic anemia. <u>Sepsis and septic shock may be fatal complications of agranulocytosis.</u>	Pancytopenia, bone marrow aplasia, thrombotic thrombocytopenic purpura, <u>leukemia</u> , <u>thrombocytosis</u> (see section 4.4).		
Immune system disorders				Immunological reactions with different manifestations such as allergic reactions, eosinophilia, anaphylaxis, Quincke edema, arthralgia, vasculitis, lupus syndrome, allergic pneumopathy, <u>hypersensitivity nephropathy</u> sometimes resulting in	

System Organ Class	Common	Uncommon	Rare	Very rare	Unknown
				<i>renal failure</i>	
Nervous system disorders	<u>Headache, dizziness</u>	<u>Sensory disturbances (peripheral neuropathy)</u>	<u>Tinnitus</u>		
Vascular disorders		Bruising, ecchymosis, epistaxis, <u>haematuria, conjunctival haemorrhage</u> , peri- and postoperative bleedings, hemorrhage that may be severe and sometimes fatal consequences have been observed	Intracerebral bleeding		
Gastrointestinal disorders	Diarrhoea, nausea	<u>Gastroduodenal ulcer</u>		Severe diarrhoea with colitis (including lymphocytic colitis)	
Hepatobiliary disorders	Increase in hepatic enzymes, increase of alkaline phosphatases and transaminases. (See section 4.4).	Elevation of bilirubin	Hepatitis (cytolytic and /or cholestatic)	Cases of hepatitis reported with fatal outcome, fulminant hepatitis	
Skin and subcutaneous tissue disorders	Skin rashes, particularly maculopapular or urticarial, often accompanied by pruritus, these skin rashes may be generalized	<u>Exfoliative dermatitis</u>		Erythema multiforme, Stevens Johnson syndrome, Lyell syndrome	
General disorders and administration				Fever	

System Organ Class	Common	Uncommon	Rare	Very rare	Unknown
site conditions					
Investigations	Increased serum cholesterol and triglyceride levels				

¹Blood cell counts (BCCs) were closely monitored in two large clinical studies conducted in 2,048 TIA/stroke patients treated with ticlopidine (multicentre controlled clinical trials CATS and TASS) (see section 4.4).

4.9 Overdose

Based on its pharmacodynamic properties, a risk of bleeding can be expected.

Following overdosage, gastric lavage and other general supportive measures are recommended.

If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of ticlopidine.(SEE SECTION 4.4 Special warnings and precautions for use)

It is not possible to dialyse ticlopidine.