

PRODUCT INFORMATION

ANAGRAINE

COMPOSITION

Each ANAGRAINE tablet contains 5 mg metoclopramide and 500 mg paracetamol.

ACTIONS

Metoclopramide stimulates gastrointestinal tract motility and accelerates gastric emptying and intestinal transit and has been shown to increase the speed of absorption of paracetamol. Metoclopramide also possesses dopamine antagonist activity. It is useful in the symptomatic relief of nausea and vomiting.

Paracetamol is an analgesic useful in the relief of pain associated with migraine.

INDICATIONS

For the symptomatic relief of headache, nausea and vomiting associated with migraine.

CONTRAINDICATIONS

Hypersensitivity to paracetamol or metoclopramide, phaeochromocytoma and in cases wherever stimulation of the gastrointestinal tract may be dangerous, eg. in the presence of gastrointestinal haemorrhage, mechanical obstruction or perforation.

Insufficient safety data exists to support the use of ANAGRAINE (metoclopramide/paracetamol combination) in pregnancy or during lactation (see PRECAUTIONS).

Children under 12 years of age (see PRECAUTIONS).

PRECAUTIONS

Metoclopramide

Dystonic reactions occur in approximately 1% of patients given metoclopramide. These occur more frequently in children and young adults and may occur after a single dose.

Tardive dyskinesia may occur in some patients following long term therapy or may appear after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movement of the tongue, face, mouth or jaw (eg. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of

the extremities. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. If these symptoms appear, it is suggested that the dosage of all antipsychotic or other antidopaminergic agents be progressively reduced with a view to discontinuation if possible. Should it be necessary to reinstitute treatment, increase the dosage of the agent, or switch to a different antidopaminergic agent, the syndrome may be masked. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop.

Care should be exercised in patients being treated with other centrally active drugs.

Since extrapyramidal symptoms may occur with both metoclopramide and neuroleptics such as phenothiazines, care should be exercised in the event of both drugs being prescribed concurrently.

Neuroleptic malignant syndrome has been reported with metoclopramide in combination with neuroleptics as well as with metoclopramide monotherapy.

Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately 1/3 of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported with prolactin elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin stimulating neuroleptic drugs. However, neither clinical nor epidemiological studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

The frequency and severity of seizures or extrapyramidal reactions may be increased in epileptic patients given metoclopramide. Following operations such as pyloroplasty or gut anastomosis, metoclopramide therapy should be withheld for 3 or 4 days as vigorous muscular contractions may not help healing.

The symptomatic relief provided by metoclopramide may delay recognition of serious disease. It should not be given until diagnosis has been established, and should not be substituted for appropriate investigation of the patient's symptoms.

If vomiting persists in a patient receiving metoclopramide, the patient should be reassessed to exclude the possibility of an underlying disorder, eg. cerebral irritation

Impaired renal function

ANAGRAINE should be administered with caution to patients with renal dysfunction and severe renal insufficiency.

Impaired hepatic function

ANAGRAINE should be administered with caution to patients with hepatic dysfunction.

Use in pregnancy

Insufficient safety data exists on ANAGRAINE (metoclopramide/paracetamol combination) (see CONTRAINDICATIONS)

Metoclopramide (Category A)

Adequate human data on use during pregnancy are not available for metoclopramide.

Paracetamol (Category A)

Use in lactation

Adequate human data on use during lactation and adequate animal reproduction studies are not available for metoclopramide.

Paracetamol is excreted in breast milk. The amount available for ingestion by the infant has been reported variously as less than 0.1% of a single dose of paracetamol 500mg, and as 0.04 to 0.23% of a single 650mg dose. Maternal ingestion of paracetamol in usual analgesic doses does not appear to present a risk to the breastfed infant.

Insufficient safety data exists on the paracetamol/metoclopramide combination (see CONTRAINDICATIONS)

Use in children

The safety and efficacy of ANAGRAINE has not been established in children (see CONTRAINDICATIONS).

There is a higher incidence of adverse reactions from metoclopramide in this age group.

Effect on ability to drive or operate machinery

Patients should be cautioned about engaging in activities requiring mental alertness for a few hours after taking ANAGRAINE.

Interactions

The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics or tranquilisers.

Since metoclopramide accelerates abnormally slow gastric and small bowel peristaltic activity, it may change absorption of orally administered drugs. The absorption of drugs from the small bowel may be accelerated (eg. paracetamol, tetracycline, l-dopa), whereas absorption of drugs from the stomach may be diminished (eg. digoxin).

Anticoagulant dosage may require reduction if paracetamol medication is prolonged.

Paracetamol absorption is increased by drugs which increase gastric emptying, eg. metoclopramide, and decreased by drugs which decrease gastric emptying, eg. propantheline, antidepressants with anticholinergic properties, narcotic analgesics. Paracetamol may increase chloramphenicol concentrations. The likelihood of paracetamol toxicity may be increased by the concomitant use of enzyme inducing agents such as alcohol or anticonvulsant drugs.

ADVERSE REACTIONS

Metoclopramide

The most frequent adverse reactions to metoclopramide are restlessness, drowsiness, fatigue and lassitude, which occur in approximately 10% of patients.

Less frequently, insomnia, headache, dizziness, nausea, or bowel disturbances may occur. Rare (<1 in 1000) cases of acute depression have been reported. Anxiety or agitation may occur.

Raised serum prolactin levels have been observed during metoclopramide therapy; this effect is similar to that noted with many other compounds.

Although uncommon at normal dosage, various extrapyramidal reactions to metoclopramide, usually of the dystonic type, have been reported. Reactions include spasm of the facial muscles, trismus, rhythmic protrusion of the tongue, a bulbar type of speech, spasm of the extraocular muscles including oculogyric crises, unnatural positioning of the head and shoulders and opisthotonos. There may be a generalized increase in muscle tone. The majority of reactions occur within 36 hours of starting treatment and the effects usually disappear within 24 hours of withdrawal of the drug, however, close observation is required and in cases of more severe reactions, an antiparkinson drug (eg. benzotropine) or an anticholinergic antihistamine (eg. diphenhydramine) should be given.

Tardive dyskinesia which may be persistent, has been reported, particularly in elderly patients undergoing longterm therapy with metoclopramide.

Very rare (<1 in 10,000) occurrences of the neuroleptic malignant syndrome have been reported. This syndrome is potentially fatal and comprises hyperpyrexia, altered consciousness, muscle rigidity, autonomic instability and elevated levels of creatine phosphokinase (CPK) and must be treated urgently (recognized treatments include dantrolene and bromocriptine). ANAGRAINE must be stopped immediately if this syndrome occurs.

Methaemoglobinaemia has also been reported.

Paracetamol

Reports of adverse reactions are rare. Although the following reactions have been reported, a causal relationship to the administration of paracetamol has been neither confirmed or refuted: dyspepsia, nausea, allergic and haematological reactions.

DOSAGE AND ADMINISTRATION

ANAGRAINE should be taken at the first warning of a migraine attack. If symptoms persist, further doses may be taken at four-hourly intervals. Total dosage in any 24 hour period should not exceed the quantity stated.

The dosage recommendations given below should be strictly adhered to if side effects of the dystonic type are to be avoided. It should be noted that a total daily dosage of metoclopramide, especially for adolescents and young adults, should not normally exceed 0.5mg/kg body weight.

Adults: The recommended dose is one or two tablets initially, and then one or two tablets every 4 hours (maximum dose of 6 tablets in 24 hours)

Adolescents (12-17 years): The recommended dose is one tablet initially, and then one tablet every 4 hours (maximum dose of 3 tablets in 24 hours)

OVERDOSAGE

Symptoms. In the case of paracetamol, toxic symptoms including vomiting, abdominal pain, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis and coma. In adults, hepatotoxicity may occur after ingestion of a single dose of paracetamol 10 to 15g; a dose of 25g or more is potentially fatal. Symptoms during the first two days of acute poisoning by paracetamol do not reflect the potential seriousness of the intoxication. Major manifestations of liver failure such as jaundice, hypoglycaemia and metabolic acidosis may take at least three days to develop. Liver damage and death may occur.

Extrapyramidal side effects are more frequently reported adverse reactions to metoclopramide overdosage. Very rarely AV block has been observed.

Treatment. In cases of overdosage, management should consist of reducing the absorption of ingested drug, close observation and supportive therapy. Prompt administration of activated charcoal may reduce absorption. Methionine and acetylcysteine may be used as antidotes if given within a few hours of paracetamol overdose. Antiparkinson and antihistamine/anticholinergic drugs such as diphenhydramine hydrochloride have effectively controlled extrapyramidal reactions.

Haemodialysis appears ineffective in removing metoclopramide. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of metoclopramide.

PRESENTATION

ANAGRAINE tablets contain 5 mg metoclopramide and 500 mg paracetamol. Packed in blister packs of 8 tablets. .

POISONS SCHEDULE

S3 – 8 tablets

SPONSOR

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos St
St Leonards NSW 2065
Australia

[Grandfathered by the TGA]

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