P O N T A C I D

DESCRIPTION:

PONTACID CAPSULE 250 MG : A size 1, light blue / ivory capsule with marking 'DUO 861'.
PONTACID FORTE TABLET 500 MG : A blue, oblong, 17mm tablet with marking 'dp 500' on one side.

COMPOSITION:

PONTACID CAPSULE 250 MG: Each capsule contains Mefenamic Acid 250 mg.
PONTACID FORTE TABLET 500 MG: Each tablet contains Mefenamic Acid 500 mg.

Gelatin for Hard Capsule: Bovine source certified with Malaysia's Halal certification.

PHARMACODYNAMICS:

Mefenamic Acid has analgesic, anti-inflammatory and anti-pyretic action. It inhibits the enzymes of prostaglandin synthetase and also antagonizes the actions of prostaglandin at the receptor sites. These effects may also be responsible for its effectiveness in the treatment of primary dysmenorrhoea. The pain of primary dysmenorrhoea is thought to be due to increased abnormal uterine activity and uterine ischaemia, probably induced by release of $PGF_{2\alpha}$ or due to increase in the ratio of $PGF_{2\alpha}$: PGE_2. Prostaglandins are also believed to be responsible, at least in some part, for the symptoms of menorrhagia.

PHARMACOKINETICS:

Single and multiple studies have shown that mefenamic acid usually reaches peak plasma levels 2 to 4 hours after oral administration with a half life of 2 hours. Mefenamic acid and its metabolites are firmly bound to plasma proteins. Two distinct metabolic products, one a hydroxymethyl derivative and the other a carboxy derivative, have been identified in both plasma and urine. Mefenamic acid and its two metabolic derivatives become conjugated with glucuronic acid through an ester linkage which is alkali labile and are excreted principally in the urine, but also to some extent in the bile and faeces. Following a single dose, 67% of the total dose is excreted in the urine as unchanged drug or as one of two metabolites. 20% to 25% of the dose is excreted in the faeces during the first three days.

INDICATIONS:

For treatment of primary dysmenorrhoea and primary menorrhagia. Short term relief of mild to moderate pain such as dental pain and soft tissue pain.

RECOMMENDED DOSAGE:

Adults: Initially 500 mg followed by 250 mg 6 hourly as required.

(i) ***Dysmenorrhoea.*** 500 mg three times daily with meals from the onset of pain and continued for the usual duration of pain.

(ii) ***Menorrhagia.*** 500 mg three times daily with meals from the onset of menses and continued according to the judgement of the physician. Therapy should not be continued for more than 7 days except on the advise of a physician.

(iii) ***Other indications.*** Short term relief of mild to moderate pain such as dental pain and soft tissue pain – 500 mg three times daily. After assessing the risk/ benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.

ROUTE OF ADMINISTRATION: Oral

CONTRAINDICATIONS:

1. In patients with ulceration or inflammation of gastrointestinal tract or known to be hypersensitive to mefenamic acid.
2. Patients in whom aspirin and / or other NSAIDs have induced symptoms of bronchospasm, allergic rhinitis or urticaria because the potential exists for cross sensitivity.
3. Patients with impaired renal function.
4. Patients previously experiencing diarrhoea on taking this drug.
5. Patients who have previously exhibited hypersensitivity to mefenamic acid,
6. Children under 14 years of age.
7. Preoperatively, in patients who have undergone coronary artery bypass graft (CABG) surgery and revascularization procedures.
8. Patients with severe uncontrolled heart failure.
9. Patients with cerebrovascular bleeding or other bleeding disorders.
10. Patients with severe liver impairment or active liver disease.
11. Patients with known hyperkalemia

WARNING & PRECAUTIONS:

WARNINGS:

RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (eg. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious adverse events and other risk factors associated with peptic ulcer disease (eg. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctor should warn patient about signs and symptoms of serious gastrointestinal toxicity. The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Certain patients who develop diarrhoea may be unable to tolerate the drug because of recurrence of the symptoms on subsequent exposure. In these subjects, the drug should be promptly discontinued. Mefenamic acid should be used with caution in known asthmatics. If rash occurs, the drug should be promptly discontinued.

Mefenamic acid may cause an exacerbation of chronic urticaria in patients with this disease. Mefenamic acid may prolong aspirin induced gastrointestinal bleeding. However, mefenamic acid itself appears to be less liable than aspirin to cause gastrointestinal bleeding. Diarrhoea has occurred rarely following recommended dosage. If diarrhoea occurs, the drug should be promptly discontinued. The patient so affected is usually henceforth unable to tolerate the drug. Caution should be exercised in administering mefenamic acid to patients on anticoagulant therapy and should not be given when prothrombin concentrations is in the range of 10 to 20% of normal. Careful monitoring of blood coagulation factors is recommended (see ***Drug Interactions***).

It is recommended that estimations of haemoglobin and blood counts be carried out at regular intervals. A false positive reaction for urinary bile, using the diazo tablet test, may result after mefenamic acid administration. If biliuria is suspected, other diagnostic procedures, such as the Harrison test, should be performed.

Renal effects: Acute interstitial nephritis with haematuria, proteinuria and occasionally nephrotic syndrome may result from long-term administration of NSAIDs. A second form of renal toxicity with pre-renal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. Administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state. Since mefenamic acid is eliminated primarily by the kidneys the drug should not be administered to patients with significantly impaired renal functions.

Hepatic effects: Mefenamic acid should be used with caution in patients with hepatic impairment.

As with other NSAIDs borderline elevations of liver function tests may occur. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg. eosinophilia, rash, etc.) mefenamic acid should be discontinued.

CardiovascularThrombotic Events: Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular event, principally myocardial infarction, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk of an adverse cardiovascular event in patient taking NSAID,

especially in those wit cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration. There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension: NSAIDs may lead to the onset of new hypertension or worsening the pre-existing hypertension and patients taking antihypertensive with NSAIDs may have an impaired antihypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart Failure: Fluid retention and oedema have been observed in some patients taking NSAIDs, there caution is advised in patients with fluid retention or heart failure.

Severe Skin Reactions: NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Paediatric use: Safety and effectiveness in children below the age of 14 have not been established.

INTERACTION WITH OTHER MEDICATIONS:

A number of compounds are inhibitors of CYP2C9. Drug interactions studies of mefenamic acid and these compounds have not been conducted. The possibility of altered safety and efficacy should be considered when mefenamic acid is used concomitantly with these drugs.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Aspirin: When mefenamic acid is administered with aspirin, its protein binding is reduced, although the clearance of free mefenamic acid is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of MEFENAMIC ACID and aspirin is not generally recommended because of the potential of increased adverse effects.

Diuretics: Clinical studies, as well as post marketing observations, have shown that mefenamic acid can reduce the natriuretic effect-of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy of NSAIDs, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. The concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal haemorrhage. Mefenamic acid like other nonsteroidal anti-inflammatory agents can inhibit platelet aggregation and may prolong prothrombin time in patients on warfarin therapy. Mefenamic acid has been shown to displace warfarin from protein binding sites and may enhance the response to oral anticoagulants. NSAIDs, such as mefenamic acid should be used in combination with warfarin, only if absolutely necessary. Concurrent administration of mefenamic acid with oral anticoagulant drugs requires frequent prothrombin time monitoring.

Antacids: In a single dose study (n=6), ingestion of an antacid containing 1.7-gram of magnesium hydroxide with 500-mg of mefenamic acid increased the Cmax and AUC of mefenamic acid by 125% and 36%, respectively.

USE IN PREGNANCY & LACTATION:

Use in pregnancy: Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryofoetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. Caution should be exercised in prescribing mefenamic acid during the first and second trimesters of pregnancy. Mefenamic acid is contraindicated for use during the last trimester of pregnancy because of the risk of premature closure of the ductus arteriosus and the potential to prolong labour and delay birth. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

Use of NSAIDs at about 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation

Use in lactation: Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant. Thus mefenamic acid should not be taken by the nursing mother because of the effects of this class of drug on the infant cardiovascular system.

SIDE EFFECTS:

Gastrointestinal: *Frequently,* gastrointestinal tract; diarrhoea, nausea with or without vomiting, other gastrointestinal symptoms, and abdominal pain. Diarrhoea was of sufficient severity to require discontinuation of the medication. The occurrence of diarrhoea is usually dose related, generally subsides on reduction of dosage and rapidly disappears on termination of therapy. *Less frequently,* anorexia, pyrosis, flatulence and constipation. Gastrointestinal ulceration with or without haemorhage.

Haematopoietic: Auto-immune haemolytic anaemia associated with a continuous administration of mefenamic acid for 12 months or longer. In such cases the Coombs test results are positive with evidence of both accelerated RBC production and RBC destruction. The process is reversible upon termination of mefenamic acid administration. Decreases in haematocrit and primarily in those who have received prolonged therapy. Leukopenia, eosinophilia, thrombocytopenia purpura, agranulocytosis, pancytopenia, and bone marrow hypoplasia have also been reported on occasion.

Nervous system: Drowsiness, dizziness, nervousness, headache, blurred vision, and insomnia have occurred.

Integumentary: Urticaria, rash, and facial oedema have been reported.

Renal: As with othere NSAIDs, renal failure including papillary necrosis has been reported. In elderly patients renal failure has occurred after taking mefenamic acid for 2 to 6 weeks. The renal damage may not be completely reversible. Haematuria and dysuria have also been reported with mefenamic acid.

Others: Mild hepatic toxicity and increased need for insulin in a diabetic have been reported. There have been rare reports of palpitation, dyspnoea and reversible loss of colour vision.

SYMPTOMS AND TREATMENT OF OVERDOSE:

No specific information is available on the management of acute massive overdosage.

Symptoms: Symptoms of overdosage are related to the amount of drug ingested and range from gastrointestinal discomfort and diarrhoea to muscle twitching, convulsions and coma.

Treatment: Treatment is by gastric lavage in the conscious patient and intensive supportive therapy where necessary. Activated charcoal has been shown to be a powerful adsorbent of mefenamic acid and its metabolites.

Because mefenamic acid and its metabolites are firmly bound to plasma proteins, haemodialysis and peritoneal dialysis may of little value.

STORAGE CONDITIONS:

Store below 25ºC. Protect from light. Keep out of reach of children. Jauhkan daripada kanak-kanak.

PACK SIZE:

Blister pack: 5x10's, 10x10's, 50x10's, 100 x 10's. *Not all pack sizes may be available.*

SHELF LIFE:

Please refer to outer package.

PRODUCT REGISTRATION HOLDER & MANUFACTURER:

DUOPHARMA (M) SDN BHD

Lot 2599 Jalan Seruling 59 Kaw 3, Taman Klang Jaya, 41200 Klang, Selangor, MALAYSIA