SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ponstan 250 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 250 mg mefenamic acid.

Excipients with known effect
Each capsule contains 77.61 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

No. 1 opaque hard gelatin capsules with ivory body and aqua blue caps containing a white to faintly greyish-white powder and printed 'Ponstan 250'.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. As an anti-inflammatory analgesic for symptomatic relief of mild to moderate pain associated with rheumatic, muscular or arthritic disorders (including rheumatoid arthritis, Still's Disease and osteoarthritis), trauma, headaches, dental pain, post-operative or post-partum states.
2. For control of pyrexia in children.
3. In the management of dysfunctional menorrhagia.
4. Primary dysmenorrhoea.
5. Premenstrual Syndrome.

4.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Do not exceed the stated dose.

Posology

Adults
The usual total daily dose is 1500 mg in divided doses.

Elderly
NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events, especially with long-term use. Therefore, the risks versus the benefits of chronic therapy in the elderly should be carefully considered. The lowest dose compatible with adequate safe clinical control should be employed (see section 4.4).

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Paediatric population
Not recommended for children under 12 years of age.

Method of administration
For oral administration.
Ponstan should be taken preferably with or after food.

4.3 Contraindications

- Hypersensitivity to active substance or any of the excipients listed in section 6.1.
- Use in patients with intestinal ulceration or inflammation and in patients with inflammatory bowel disease.
- Use in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Use in patients with active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Use in patients with renal or hepatic impairment.
- Use in patients with severe heart failure.
- Use in pregnancy or lactation (see section 4.6).
- Use in patients shown to be hypersensitive (e.g. asthma, bronchospasm, rhinitis, angioedema, urticaria) to mefenamic acid, any of the other ingredients of Ponstan capsules, aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs.
- Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (see section 4.5).
- Treatment of pain after coronary artery bypass graft (CABG) surgery.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and GI and cardiovascular risks below).

Patients on prolonged therapy should be kept under regular surveillance with particular attention to liver dysfunction, rash, blood dyscrasias or development of diarrhoea. Appearance of any of these should be regarded as an indication to discontinue therapy immediately.

Precaution should be taken in patients suffering from dehydration and renal disease,

particularly the elderly.

Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained, and treatment should be discontinued. The diagnosis of 'Medication Overuse Headache' should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Skin reactions:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with use of NSAIDs *(*see section 4.8. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Ponstan Capsules should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

SLE and mixed connective tissue disease:
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Respiratory disorders:
Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular and cerebrovascular effects:
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for mefenamic acid.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with mefenamic acid after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
Elderly:
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

Gastrointestinal bleeding, ulceration and perforation:
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events. Smoking and alcohol use are added risk factors.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any abdominal symptoms (especially GI bleeding) particularly in the initial stages.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin re-uptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Ponstan capsules, the treatment should be withdrawn.

As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

Female fertility:
The use of mefenamic acid may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of mefenamic acid should be considered.

In dysmenorrhoea and menorrhagia, lack of response should alert the physician to investigate other causes.

Epilepsy:
Caution should be exercised when treating patients suffering from epilepsy.

In patients who are known or suspected to be poor CYP2C9 metabolisers based on previous history/experience with other CYP2C9 substrates, mefenamic acid should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance (see section 5.2).

<u>Excipients</u>
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is

to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration with other protein bound drugs may require adjustment in their dosage.

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4). Concurrent administration of mefenamic acid with oral anticoagulant drugs requires careful prothrombin time monitoring.

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Lithium: A reduction in renal lithium clearance and an elevation of plasma lithium levels. Patients should be observed carefully for signs of lithium toxicity.

The following interactions have been reported with NSAIDs but have not necessarily been associated with Ponstan:

Other analgesics: Concomitant use of two or more NSAIDs (including aspirin) should be avoided (see section 4.3).

Antidepressants: Selective serotonin re-uptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Antihypertensives and diuretics: A reduction in antihypertensive and diuretic effect has been observed. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

ACE inhibitors and angiotensin-II receptor antagonists: A reduction in antihypertensive effect and an increased risk of renal impairment especially in elderly patients. Patients should be adequately hydrated, and the renal function assessed in the beginning and during concomitant therapy.

Aminoglycosides: Reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Anti-platelet agents: Increased risk of gastrointestinal bleeding (see section 4.4).

Acetylsalicylic Acid: Experimental data implies that mefenamic acid interferes with the anti-platelet effect of low-dose aspirin when given concomitantly, and thus may interfere with aspirin’s prophylactic treatment of cardiovascular disease. However, the limitations of this experimental data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular mefenamic acid use.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure and increases in plasma cardiac glycoside levels may occur when renal function is affected.

Ciclosporin: The risk of nephrotoxicity of ciclosporin may be increased with NSAIDs.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Oral hypoglycaemic agents: Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

Mifepristone: NSAIDs should not be taken for 8-12 days after mifepristone administration, NSAIDs can reduce the effects of mifepristone.

Methotrexate: Elimination can be reduced resulting in increased plasma levels.

Probenecid: Reduction in metabolism and elimination of NSAIDs and metabolites.

Quinolone antibiotics: Animal data indicated that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolone may have an increased risk of developing convulsions.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemaophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Fertility, pregnancy and lactation

Pregnancy
Safety in pregnancy has not been established, and because of the effects of drugs in this class on the foetal cardiovascular system, the use of mefenamic acid in pregnant women is not recommended (see section 4.3).

From the 20th week of pregnancy onward, Ponstan use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

Breast-feeding
Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant. Therefore, mefenamic acid should not be taken by nursing mothers (see section 4.3).

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

a) General description

The most frequently reported side effects associated with mefenamic acid involve the gastrointestinal tract. Diarrhoea appears to be the most common side effect and is usually dose-related. It generally subsides on dosage reduction, and rapidly disappears on termination of therapy. Some patients may not be able to continue therapy.

b) Table of adverse reactions

Frequency of reactions: Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders
Frequency not known: autoimmune haemolytic anaemia *(see section c, Information characterising individual serious and/or frequently occurring adverse reactions)*, anaemia, hypoplasia bone marrow, haematocrit decreased, thrombocytopenic purpura, temporary lowering of the white blood cell count (leukopenia) with a risk of infection, sepsis, and disseminated intravascular coagulation
Rare: agranulocytosis, aplastic anaemia, eosinophilia, neutropenia, pancytopenia

Immune system disorders
Frequency not known: anaphylaxis

Metabolism and nutrition disorders
Frequency not known: glucose intolerance in diabetic patients, hyponatraemia

Psychiatric disorders
Frequency not known: nervousness

Nervous system disorders
Frequency not known: aseptic meningitis, blurred vision, convulsions, dizziness, drowsiness, headache and insomnia

Eye disorders
Frequency not known: eye irritation, reversible loss of colour vision

Ear and labyrinth disorders
Frequency not known: ear pain

Cardiac disorders
Frequency not known: palpitations

Vascular disorders

Frequency not known: hypotension

Respiratory, thoracic and mediastinal disorders
Frequency not known: asthma, dyspnoea

Gastrointestinal disorders
Frequency not known: abdominal pain, diarrhoea *(see section c, Information characterising individual serious and/or frequently occurring adverse reactions)* and nausea with or without vomiting
Less frequent: anorexia, colitis, constipation, dyspepsia, enterocolitis, flatulence, gastric ulceration with or without haemorrhage, pancreatitis, steatorrhoea

Hepatobiliary disorders
Frequency not known: borderline elevations of one or more liver function tests, cholestatic jaundice
Less frequent: mild hepatotoxicity, hepatitis, hepatorenal syndrome

Skin and subcutaneous tissue disorders
Frequency not known: angioedema, laryngeal oedema, erythema multiforme, face oedema, Lyell's syndrome (toxic epidermal necrolysis), perspiration, rash, Stevens-Johnson syndrome, photosensitivity reaction and urticaria

Renal and urinary disorders
Frequency not known: allergic glomerulonephritis, acute interstitial nephritis, dysuria, haematuria, nephrotic syndrome, non-oliguric renal failure (particularly in dehydration), proteinuria, renal failure including renal papillary necrosis

General disorders
Very rare: multi-organ failure, pyrexia

c) Information characterising individual serious and/or frequently occurring adverse reactions

Reversible haemolytic anaemia: Reports are associated with ≥ 12 months of mefenamic acid therapy and the anaemia is reversible with discontinuation of treatment.

Diarrhoea: Although this may occur soon after starting treatment, it may also occur after several months of continuous use.

If diarrhoea persists then inflammatory bowel disease should be excluded; if present mefenamic acid must be stopped.

Note: A positive reaction in certain tests for bile in the urine of patients receiving mefenamic acid has been demonstrated to be due to the presence of the drug and its metabolite and not to the presence of bile.

d) Adverse reactions which may not have been observed but which are generally accepted as being attributable to other NSAIDs

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm, or dyspnoea or (c) assorted skin disorders including rashes of various types, pruritus, urticaria, purpura, angioedema, and more rarely exfoliative or bullous dermatoses, including epidermal necrolysis, toxic epidermal necrolysis (Lyell's syndrome), erythema multiforme and Stevens-Johnson syndrome.

Neurological and special senses: Visual disturbances, optic neuritis, paraesthesia, reports of aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4), depression, confusion, hallucinations, tinnitus, vertigo, malaise, fatigue and drowsiness.

Cardiovascular: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.

Additional information on special populations
Elderly or debilitated patients seem to tolerate gastrointestinal ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

Renal toxicity has been seen in patients with pre-renal conditions leading to a reduction in renal blood flow or blood volume. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Gastric lavage in the conscious patient and intensive supportive therapy where necessary.

Vital functions should be monitored and supported. Activated charcoal has been shown to be a powerful absorbent for mefenamic acid and its metabolites. Studies in experimental animals and humans have shown that a 5 to 1 ratio of charcoal to mefenamic acid results in considerable suppression of absorption of the drug. Haemodialysis is of little value since mefenamic acid and its metabolites are firmly bound to plasma proteins. Overdose has led to fatalities.

Mefenamic acid has a tendency to induce tonic-clonic (grand mal) convulsions in overdose. Acute renal failure and coma have been reported with mefenamic acid overdose. It is important that the recommended dose is not exceeded and the regime adhered to since some reports have involved daily dosage under 3g.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and anti- rheumatic products, non-steroids, fenamates. ATC Code: M01AG01.

Animal models

Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties.

Its anti-inflammatory effect was first established in the UV erythema model of inflammation. Further studies included inhibition of granulation tissue growth into subcutaneous cotton pellets in rats and carrageenin induced rat paw oedema tests.

Antipyretic activity was demonstrated in yeast-induced pyresis in rats. In this model its antipyretic activity was roughly equal to that of phenylbutazone and flufenamic acid, but less than that of indomethacin.

Analgesic activity was demonstrated in tests involving pain sensitivity of rats paws inflamed by brewers yeast. Mefenamic acid was less potent than flufenamic acid in this model.

Prostaglandins are implicated in a number of disease processes including inflammation, modulation of the pain response, dysmenorrhoea, menorrhagia and pyrexia.

In common with most NSAIDs mefenamic acid inhibits the action of prostaglandin synthetase (cyclooxygenase). This results in a reduction in the rate of prostaglandin synthesis and reduced prostaglandin levels.

The anti-inflammatory activity of NSAIDs in the rat paw oedema test has been correlated with their ability to inhibit prostaglandin synthetase. When mefenamic acid is ranked in both these tests it falls between indomethacin and phenylbutazone and it is probable that inhibition of prostaglandin synthesis contributes to the pharmacological activity and clinical efficacy of mefenamic acid.

There is also considerable evidence that the fenamates inhibit the action of prostaglandins after they have been formed. They therefore both inhibit the synthesis and response to prostaglandins. This double blockade may well be important in their mode of action.

5.2 Pharmacokinetic properties

Absorption and distribution
Mefenamic acid is absorbed from the gastrointestinal tract. Peak levels of 10 mg/l occur two hours after the administration of a 1g oral dose to adults.

Biotransformation
Mefenamic acid is predominantly metabolised by cytochrome P450 enzyme CYP2C9 in the liver, first to a 3-hydroxymethyl derivative (metabolite I) and then a 3-carboxyl derivative (metabolite II). Both metabolites undergo secondary conjugation to form glucuronides.

Therefore, in patients who are known or suspected to be poor CYP2C9 metabolisers based on previous history/experience with other CYP2C9 substrates, mefenamic acid should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Elimination
52% of a dose is recovered from the urine, 6% as mefenamic acid, 25% as metabolite I and 21% as metabolite II. Assay stools over a 3-day period accounted for 10-20% of the dose chiefly as unconjugated metabolite II.
The plasma levels of unconjugated mefenamic acid decline with half life of approximately two hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Sodium laurilsulfate
Gelatin
Purified water*
Erythrosine (E127)
Quinoline yellow (E104)
Titanium dioxide (E171)
Patent blue V (E131)
Printing inks containing either shellac, black iron oxide (E172), propylene glycol (E1520) and ammonium hydroxide 28% (E527) or shellac, propylene glycol (E1520), strong ammonia solution, potassium hydroxide (E525) and black iron oxide (E172).

*not detectable

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

HDPE tampertainers of 100 and 500 capsules.

Opaque polypropylene securitainers with a low-density polyethylene wadless closure of 100 and 500 capsules.

PVC/Aluminium blister packs of 10, 12, 42 and 100 capsules (blister strips) and 6 and 30 capsules (blister discs).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Chemidex Pharma Ltd
Vision Exchange Building
Triq it-Territorjals, Zone 1,
Central Business District,
Birkirkara, CBD 1070
Malta.

8. MARKETING AUTHORISATION NUMBER

PA 22643/001/001

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