Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Spasmorid-M 80mg/250mg Tablets

2. Qualitative and quantitative composition
Each tablet contains 80mg of Drotaverine hydrochloride and 250 mg of Mefenamic acid.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Uncoated tablet
Yellow colour, round, biconvex shape, plain on both sides, uncoated tablets.

4. Clinical particulars

4.1 Therapeutic indications
Spasmorid-M is indicated for the symptomatic relief of:
Dysmenorrhoea
Tension-type headache
Pain associated with smooth muscle spasms associated with biliary and urinary tract disorders.

4.2 Posology and method of administration
For oral administration.

To be taken preferably with or after food.
Undesirable effects may be minimised by using the shortest duration necessary to control symptoms (see section 4.4). The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.

Adults
A single maximum dose is 1 tablet.
The maximum recommended daily dose of drotaverine is 120-240mg in 2 -3 divided doses.

Elderly
The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest dose should be used and for the shortest possible duration. The patient should be monitored for GI bleeding during NSAID therapy.

Children
The use of drotaverine in children has not been established in clinical studies; if drotaverine administration is necessary:
for children above the age of 12 years the maximum daily dose is 160 mg divided in 2 to 4 parts.

No data are available for children below 6 years of age.

Use of mefenamic acid in children under 12 years is not recommended. Use of Spasmorid-M should therefore be avoided in that age group unless the physicians judgement deems it necessary.

4.3 Contraindications

- Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g asthma, bronchospasm, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
- Severe hepatic, renal and cardiac failure and in patients with cardiac insufficiency (See section 4.4)
- During the last trimester of pregnancy (See section 4.6)
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- Patients with inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease)
- 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 symptoms should be regarded as an indication to stop therapy immediately (see section 4.8)

Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (see section 4.5)

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.

Precaution should be taken in patients suffering from dehydration and renal disease, particularly the elderly.

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).

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, renal and hepatic impairment:
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

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).

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

Special caution should be taken when using drotaverine in case of hypotension.

Gastrointestinal bleeding, ulceration and perforation:
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time 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. misoprostal 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 unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).
When GI bleeding or ulceration occurs in patients receiving mefenamic acid, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

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).

Dermatological:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for 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. Mefenamic Acid should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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.

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

Metabolic disorders: Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

4.5 Interaction with other medicinal products and other forms of interaction

Phosphodiesterase inhibitors like papaverine decrease the antiparkinsonian effect of levodopa. When drotaverine is administered concomitantly with levodopa, antiparkinsonian effect decreases and rigidity and tremor may worsen.

Concurrent therapy with other plasma protein binding drugs may necessitate a modification in dosage.

Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients.
Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, 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: Decreased elimination of lithium. 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 Mefenamic acid:
Other analgesics including cyclooxygenase-2-selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

Antidepressants: selective serotonin reuptake inhibitors (SSRIs):
Increased risk of gastrointestinal bleeding (see section 4.4).
Anti-hypertensives and diuretics: Reduced anti-hypertensive effect and reduced diuretic effect. 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 or ulceration (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, reduce GFR and increase plasma glycoside levels.

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

Corticosteroids: Increased risk of gastro-intestinal bleeding or ulceration (see section 4.4).

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

Methotrexate: elimination of the drug can be reduced, resulting in increased plasma levels .

Mifepristone: NSAIDs should not be used for 8 – 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

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

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

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

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

4.6 Fertility, pregnancy, and lactation

Pregnancy

Retrospective human studies and animal studies did not show any direct or indirect harmful effect exerted on pregnancy, embryonal development, delivery or postnatal development by drotaverine. However, Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3 – Contraindications). From the 20th week of pregnancy onward, mefenamic acid 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. Therefore, during the first and second trimester of pregnancy, mefenamic acid should not be given unless clearly necessary. If mefenamic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to mefenamic acid for several days from gestational week 20 onward. Mefenamic acid should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (premature constriction**/**closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, mefenamic acid is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Lactation

The excretion of drotaverine in milk has not been studied in animals. In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. Therefore, Spasmorid-M should not be taken when breastfeeding.

Fertility

No data are available on effects of drotaverine on human fertility. However, mefenamic acid may impair female fertility (see section 4.4).

4.7 Effects on ability to drive and use machines.

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible undesirable effects after taking Spasmorid-M; if affected patients should not drive or operate machinery.

4.8 Undesirable effects

Possible adverse reactions associated with drotaverine and mefenamic acid administration are listed below according to system organ classes: very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000), not known: cannot be estimated from the available data:

Blood and lymphatic system disorders:

Not known: Thrombocytopenia, neutropenia, agranulocytosis, anaemia, haemolytic anaemia and aplastic anaemia have been reported with use of mefenamic acid.

In some cases reversible haemolytic anaemia has occurred. Temporary lowering of the white blood cell count (leukopenia) with a risk of infection which may have been due to mefenamic acid has been reported. Rarely eosinophilia, agranulocytosis and pancytopenia have been reported. Blood studies should therefore be carried out during long term administration and the appearance of any dyscrasia is an indication to discontinue therapy.

Hypoplasia bone marrow, haematocrit deceased, thrombocytopenic purpura, sepsis and disseminated intravascular coagulation has also been reported.

Immune system disorders

Rare to Not known: Allergic reactions (angioedema, urticaria, rash, pruritus) to drotaverine has been observed in rare cases. 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, pruritis, urticaria, purpura, angioedema and less commonly exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme). The occurrence of a rash is a definite indication to withdraw medication.

Nervous system disorders

Rare: headache, dizziness, insomnia.

Not known: Optic neuritis, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing auto-immune 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), and drowsiness, convulsions, and blurred vision.

Cardiac disorders
Rare: palpitation.
Not known: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Hypotension and palpitations have been reported rarely. 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).

Vascular disorders
Rare: hypotension.

Gastrointestinal disorders
Rare: nausea, obstipation.
Not known: The most commonly observed adverse events for mefenamic acid 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 (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

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.

Also reported anorexia, colitis, enterocolitis, gastric ulceration with or without haemorrhage, pancreatitis, and steatorrhea.

Hepato-biliary Disorders
Not known: Borderline elevations of one or more liver function tests may occur in some patients receiving mefenamic acid therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should have their therapy discontinued. Patients on prolonged therapy should be kept under surveillance with particular attention to liver dysfunction. Hepatitis and cholestatic jaundice have been reported with NSAID therapy. Also reported mild hepatoxicity and hepatorenal syndrome.

Psychiatric Disorders
Not known: depression, confusion, hallucinations, nervousness

Eye disorders
Not known: Visual disturbances, eye irritation, reversible loss of colour vision,

Ear and labyrinth disorders
Not known: Tinnitus, vertigo, ear pain

Skin and subcutaneous tissue disorders

Not known: Bullous reactions including Stevens Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome, very rare). Photosensitivity, purpura, angioedema, laryngeal oedema, erythema multiforme, face oedema, perspiration, pruritus, rash and urticaria

Renal and Urinary Disorders
Not known: Nephrotoxicity in various forms, including renal papillary necrosis. As with other prostaglandin inhibitors allergic glomerulonephritis has occurred occasionally. There have also been reports of acute interstitial nephritis with haematuria and proteinuria and occasionally nephrotic syndrome. Dysuria.

Non-oliguric renal failure has been reported on a few occasions in elderly patients with dehydration usually from diarrhoea. Toxicity has been seen in patients with pre-renal condition 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. The drug should not be administered to patients with significantly impaired renal function. It has been suggested that the recovery is more rapid and complete with other forms of analgesic induced renal impairment, with discontinuation of NSAID therapy being typically followed by recovery to the pre-treatment state.

General disorders and administration site conditions
Not known: Malaise, fatigue. Multi-organ failure, pyrexia

Metabolism and Nutritional disorders
Not known: Glucose intolerance in diabetic patients has been reported rarely. Hyponatraemia.

Investigations
Not known: 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 metabolites and not to the presence of bile.

Respiratory, thoracic and mediastinal disorders
Not known: Asthma, dyspnoea

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 the Pharmacy and Poison Board Pharmacovigilance Electronic Reporting System (PvERS) at https://pv.pharmacyboardkenya.org.

4.9 Overdose

It is important that the recommended dose is not exceeded and the regime adhered to since some reports have involved daily dosages of mefenamic acid under 3g.

Symptoms
Symptoms of mefenamic acid overdose include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, and occasionally convulsions. Mefenamic acid may induce tonic-clonic (grand mal) convulsions in overdose. In cases of significant poisoning acute renal failure and liver damage are possible.

Significant overdose of drotaverine has been associated with heart rhythm and conduction disorders including complete bundle branch block and cardiac arrest, which may be fatal.

Therapeutic measure
Patients should be treated symptomatically as required.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition.

Haemodialysis is of little value since mefenamic acid and its metabolites are firmly bound to plasma proteins.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Drotaverine

Pharmacotherapeutic group:
Drugs for functional bowel disorders. ATC: A03A D02.

Mechanism of action

Drotaverine is an isoquinolin derivative, which exerts its spasmolytic effect directly on smooth musculature. The inhibition of the phosphodiesterase enzyme and the consequent increase of cAMP level are determinant in its mechanism of action and lead to the smooth muscle relaxation through the myosin light chain kinase enzyme (MLCK) inactivation.

Drotaverine inhibits phosphodiesterase (PDE) IV enzyme in vitro without inhibiting isoenzymes PDE III and PDE V. Practically, PDE IV appears to be very important in blockage of the contractile activity of smooth muscles; on the basis of what the selective PDE IV blockage might be useful in the treatment of hypermotility disorders and various diseases accompanied with gastrointestinal smooth muscle spasm. PDE III isoenzyme hydrolyses cAMP in myocardium and vascular smooth muscles; it provides explaination, that drotaverine can be an effective spasmolytic agent without significant cardiovascular adverse effects and strong cardiovascular therapeutic activity.

It is effective in all cases of smooth muscle spasms of both neural and muscular origin. Independently from the type of autonomous innervation, drotaverine acts equally on the smooth musculature of gastrointestinal, biliary, urogenital and the vascular system. Due to its vasodilatator effect it increases the blood supply in tissues.

Its effect is stronger than papaverine's, its absorption is more rapid and more complete, and it bonds less to the serum proteins. Its advantage is that the stimulating adverse effect on respiration observed after parenteral administration of papaverine does not occur with drotaverine administration.

Mefenamic acid

Pharmacotherapeutic group:

Anti-inflammatory and antirheumatic products, non-steroids. Fenamates. M01A G01

Mechanism of action

Mefenamic acid is a nonsteroidal 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 (cyclo oxygenase). 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

Drotaverine

Absorption

Drotaverine is rapidly absorbed after both oral and parenteral administration.

Distribution

It is highly bound to plasma albumin (95-98%), alfa and beta globulins. Serum peak concentration is reached within 45-60 min. after oral administration.

Biotransformation

Following the first pass metabolism of drotaverine the 65% of the administered dose reaches the systemic circulation in unchanged form.

It is metabolised in the liver.

Elimination

Biological half-life of drotaverine is 8-10 hours. Practically, it eliminates from the body within 72 hours, in approximately 50% via the urine and about 30 % in the faeces. It is mainly excreted in the form of metabolites; its unchanged form cannot be detected in the urine.

Mefenamic acid

Absorption and distribution

Peak concentrations in plasma are reached in 2 to 4 hours and the half-life of the drug is also 2 to 4 hours.

Metabolism

Mefenamic acid is extensively metabolized 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

In man, approximately 50% of a dose of mefenamic acid is excreted in the urine. Of this, approximately half is the conjugated 3-hydroxymethyl metabolite, a little less than half is the 3-carboxyl metabolite and its conjugates, and the remaining few per cent is mostly conjugated mefenamic acid.

Twenty percent of the drug is recovered in the faeces, mainly as the unconjugated 3-carboxyl metabolite.

5.3 Preclinical safety data

Non-clinical data on drotaverine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Based on the in vitro and in vivo studies, drotaverine did not cause any delay in ventricular repolarisation.

- In vitro in vivo genotoxicity studies (i.e. Ames test, mouse lymphoma test, micronucleus test) drotaverine has not shown any sign suggestive of genotoxicity.
- Drotaverine has no effect on fertility in rats, as well as on embryonic /foetal development in rats and rabbits.

For mefenamic acid, no data of relevance which is additional to that already included in other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients

Magnesium Stearate
Purified Talc
Sodium Starch Glycollate
Croscarmellose Sodium
Polacrilin Potassium (As Kyron-T-314)
Colloidal Anhydrous Silica
Starch Maize
Microcrystalline Cellulose
Povidone (As PVPK-30)
Tartrazine Supra

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months.

6.4 Special precautions for storage:
Store below 30℃ in a cool and dark place, protect from direct sunlight.

6.5 Nature and contents of container
3 x 10 pack: 10 tablets packed in alu-alu blister and such 3 blisters are packed in single carton along with pack insert.

6.6 Special precautions for disposal and other handling:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Galaxy Pharmaceutical Ltd.
1st Floor, Doctors Park, 3rd Parklands Avenue,
P.O.BOX 39107 - 00623, Nairobi, Kenya.

Manufacturing site address:
Saitech Medicare Ltd.
Trilokpur road, Kala-Ambdist. Sirmor,
Himachal Pradesh, India.

8. Marketing authorization number
CTD10090

9. Date of first registration
03/03/2024.

10. Date of revision of the text:
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