

SUMMARY OF PRODUCTS CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ALGIC P

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Aceclofenac 100 mg and Paracetamol 500 mg film -coated Tablets

Each film-coated tablet contains Aceclofenac 100 and Paracetamol 500 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Aceclofenac 100 mg and Paracetamol 500 mg film-coated tablets White colored caplet shaped film coated tablets with plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aceclofenac

Aceclofenac is indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Paracetamol

For the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains, aches and pains, symptomatic relief of rheumatic aches and pains and of influenza, feverishness and feverish colds.

4.2 Posology and method of administration

Aceclofenac

1. Aceclofenac film coated tablets are supplied for oral administration and should be swallowed whole with a sufficient quantity of liquid.
2. To be taken preferably with or after food.

3. When Aceclofenac was administered to fasting and fed healthy volunteers only the rate and not the extent of aceclofenac absorption was affected.
4. Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms

Adults

The recommended dose is 200 mg daily, taken as two separate 100 mg doses, one tablet in the morning and one in the evening

Children

There are no clinical data on the use of Aceclofenac in children and therefore it is not recommended for use in children.

Elderly

The elderly, who are more likely to be suffering from impaired renal, cardiovascular or hepatic function and receiving concomitant medication, are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

The pharmacokinetics of Aceclofenac are not altered in elderly patients, therefore it is not considered necessary to modify the dose or dose frequency.

Renal insufficiency

There is no evidence that the dosage of Aceclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDs caution should be exercised

Hepatic insufficiency

There is some evidence that the dose of Aceclofenac should be reduced in patients with hepatic impairment and it is suggested that an initial daily dose of 100 mg be used

Paracetamol

Adults, the elderly and young persons 16 years and over:

2 tablets every 4 hours to a maximum of 8 tablets in 24 hours.

Children 6 – 9 years:

½ tablet every 4 hours to a maximum of 4 doses in 24 hours.

Children 10 – 11 years:

1 tablet every 4 hours to a maximum of 4 doses in 24 hours

Adolescents 12 – 15 years:

1 to 1 ½ tablets every 4 hours to a maximum of 4 doses in 24 hours Do not give to children aged under 6 years of age.

4.3 Contraindications

Aceclofenac

Hypersensitivity to aceclofenac or to any of the excipients listed in section 6.1.

Active, or history of recurrent peptic ulcer/hemorrhage (two or more distinct episodes of proven ulceration or bleeding).

NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.

Hepatic failure and renal failure

Patient's with established congestive heart failure (NYHA IIIV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Active bleeding's or bleeding disorders. Aceclofenac should not be prescribed during pregnancy, especially during the last trimester of pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used (see section 4.6).

4.4 Special warnings and precautions for use

Aceclofenac

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 or recovering from major surgery, and the elderly. The importance of prostaglandins in maintaining renal blood flow should be taken into account in these patients. Renal function should be monitored in these patients (see also section 4.3).

Renal:

Patients with mild to moderate renal impairment should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored regularly. Effects on renal function are usually reversible on withdrawal of Aceclofenac.

Hepatic:

If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Aceclofenac should be discontinued. Close medical surveillance is necessary in patients suffering from mild to moderate impairment of hepatic function. Hepatitis may occur without prodromal symptoms.

Use of Aceclofenac in patients with hepatic porphyria may trigger an attack.

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.

Patients with congestive heart failure (NYHAI) and patients with significant risk factors for cardiovascular events (e.g.hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with aceclofenac after careful consideration. As the cardiovascular risks of aceclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be reevaluated periodically. Aceclofenac should also be administered with caution and under close medical surveillance to patients with a history of cerebrovascular bleeding.

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. Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders involving either the upper or lower gastrointestinal tract, with a

history suggestive of gastro-intestinal ulceration, bleeding or perforation, with ulcerative colitis or with Crohn's disease, or haematological abnormalities, as these conditions may be exacerbated (see section 4.8)

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 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 ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or antiplatelet agents such as aspirin (see section 4.5).

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

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 very rarely 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. Aceclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Exceptionally, varicella can trigger serious cutaneous and soft tissues infections complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of aceclofenac in case of varicella.

Hypersensitivity reactions:

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Haematological:

Aceclofenac may reversibly inhibit platelet aggregation (see section 4.5 anticoagulants under 'Interactions').

Longterm treatment:

All patients who are receiving NSAIDs should be monitored as a precautionary measure e.g. renal, hepatic function (elevation of liver enzymes may occur) and blood counts.

Paracetamol

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with noncirrhotic alcoholic liver disease.

Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor. Contains Paracetamol.

Do not take anything else containing paracetamol while taking this medicine.

Talk to your doctor at once if you take too much of this medicine, even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.

Patients should be advised that paracetamol may cause severe skin reactions. If a skin reaction such as skin reddening, blisters, or rash occurs, they should stop use and seek medical assistance right away.

4.5 Interaction with other medicinal products and other forms of interaction

Aceclofenac

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, including GI bleeding (see section 4.4).

Anti-hypertensives: NSAID's may reduce the effect of antihypertensives. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when ACE- inhibitors or angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Diuretics: Aceclofenac, like other NSAIDs, may inhibit the activity of diuretics. Diuretics can

increase the risk of nephrotoxicity of NSAIDs. Although it was not shown to affect blood pressure control when coadministered with bendroflumazide, interactions with other diuretics cannot be ruled out. When concomitant administration with potassium sparing diuretics is employed, serum potassium should be monitored.

Cardiac glycosides, like digoxin: NSAIDs may exacerbate cardiac failure, reduce GFR (glomerular filtration rate) and inhibit the renal clearance of glycosides, resulting in increased plasma glycoside levels. The combination should be avoided unless frequent monitoring of glycoside levels can be performed.

Lithium: Several NSAID drugs inhibit the renal clearance of lithium, resulting in increased serum concentrations of lithium.

The combination should be avoided unless frequent monitoring of lithium can be performed.

Methotrexate: The possible interaction between NSAIDs and methotrexate should be born in mind also when low doses of methotrexate are used, especially in patients with decreased renal function. When combination therapy has to be used, the renal function should be monitored. Caution should be exercised if both an NSAID and methotrexate are administered within 24 hours of each other, since NSAIDs may increase plasma levels of methotrexate, resulting in increased toxicity.

Mifepristone: NSAIDs should not be used for 812 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone. *Corticosteroids:* Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4). Close monitoring of patients on combined anticoagulants and Aceclofenac therapy should be undertaken.

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.

Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

Ciclosporin, tacrolimus: Administration of NSAID drugs together with cyclosporin or tacrolimus is thought to increase the risk of nephrotoxicity due to decreased synthesis of prostacyclin in the kidney. During combination therapy it is therefore important to carefully monitor renal function.

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

Antidiabetic agents: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents with influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects.

Thus with Aceclofenac, consideration should be given to adjustment of the dosage of hypoglycaemic agents.

Paracetamol

Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, the cholestyramine should not be taken within one hour if maximal analgesia is required.

Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Warfarin: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

4.6 Fertility pregnancy and lactation Aceclofenac

Pregnancy:

There is no information on the use of aceclofenac during pregnancy. Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage, cardiac malformation or gastroschisis after use of prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased preimplantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, aceclofenac should not be given unless clearly

If aceclofenac 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.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to: -cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; 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, aceclofenac is contraindicated during the third trimester of pregnancy (see section 4.3).

Lactation:

There is no information on the secretion of aceclofenac to breast milk; there was however no notable transfer of radio labelled (14C) aceclofenac to the milk of lactating rats..

The use of Aceclofenac should therefore be avoided in pregnancy and lactation unless the potential benefits to the other outweigh the possible risks to the foetus.

Paracetamol

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of the doctor regarding its use. Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

4.7 Effects on ability to drive and use machines

Aceclofenac

Undesirable effects such as dizziness, drowsiness, vertigo, fatigue, visual disturbances or other central nervous system disorders are possible after taking NSAIDs. If affected, patients should not drive or operate machine

Paracetamol

None known.

4.8 Undesirable effects

Aceclofenac

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

(See section 4.4) have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

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, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular and cerebrovascular: 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 stroke) (see section 4.4).

Exceptionally, occurrence of serious cutaneous and soft tissues infections complications during varicella has been reported in association with NSAID treatment.

Other adverse reactions reported less commonly include: Renal: interstitial nephritis.

Neurological and special senses: optic neuritis, reports of aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptom include stiff neck, headache, nausea, vomiting, fever or disorientation (See section 4.4), confusion, hallucinations, malaise and drowsiness.

Haematological: agranulocytosis, aplastic anaemia .

Dermatological: Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity.

If serious adverse reactions occur, Aceclofenac should be withdrawn.

The following is a table of adverse reactions reported during clinical studies and after authorization, grouped by System-Organ Class and estimated frequencies. Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$).

MedDRA SOC	Common 1/100 to <1/10	Uncommon $\geq 1/1,000$ to <1/100	Rare < $\geq 1/10,000$ to <1/1,000	Very rare/ <1/10,000
				Bone Marrow depression

Blood and lymphatic system disorders			Anaemia	Granulocytopenia Thrombocytopenia Neutropenia Haemolytic anaemia
Immune system disorders			Anaphylactic reaction (including shock) Hypersensitivity	
Metabolism and nutrition disorders				Hyperkalemia
Psychiatric disorders				Depression Abnormal dreams Insomnia
Nervous system disorders	Dizziness			Paraesthesia Tremor Somnolence Headache Dysgeusia (abnormal taste)
Eye disorders and labyrinth disorder			Visual disturbance	
Cardiac disorders			Cardiac failure	Palpitations
Vascular disorders			Hypertension	Flushing Hot flush Vasculitis
Respiratory, thoracic				Bronchospasm

and mediastinal disorders			Dyspnoea	Stridor
Gastrointestinal disorders	Dyspepsia Abdominal pain Nausea Diarrhoea	Flatulence Gastritis Constipation Vomiting Mouth ulceration	Melaena Gastrointestinal haemorrhage Gastrointestinal ulceration	Stomatitis Intestinal perforation Exacerbation of Crohn's disease and Colitis Ulcerative Haematemesis Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased			Hepatic injury (including hepatitis) Jaundice Blood alkaline phosphatase increased
Skin and subcutaneous tissue disorders		Pruritus Rash Dermatitis Urticaria	Angioedema	Purpura Severe mucocutaneous skin reaction (including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis
Renal and urinary		Blood urea increased		Renal failure

disorders		Blood creatinine increased		Nephrotic syndrome
General disorders and administration site conditions				Oedema Fatigue Cramps in legs
Investigations				Weight increase

Paracetamol

Adverse effects of paracetamol are rare. Very rare cases of serious skin reactions have been reported.

There have been reports of blood dyscrasias including thrombocytopenia purpura, methaemoglobinaemia and agranulocytosis, but these were not necessarily causality related to paracetamol.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Aceclofenac

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal irritation, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage

b) 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.

Specific therapies such as dialysis or haemoperfusion are probable of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

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. In case of frequent or prolonged convulsions, patients should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

Management of acute poisoning with oral aceclofenac essentially consists of supportive and symptomatic measures for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression.

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk Factors If the patient

a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

b) Regularly consumes ethanol in excess of recommended amounts.

Or

c) Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage.

Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical

attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with Nacetylcysteine may be used up to 24 hours after ingestion of paracetamol however, the maximum protective effect is obtained up to 8 hours post ingestion.

If required the patient should be given intravenous Nacetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

Management of patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the NPIS or a liver unit.

5. PHARMACOLOGICAL PROPERTIES

Aceclofenac

5.1 Pharmacodynamic properties

Mechanisms of Action/Effect

Aceclofenac is a non-steroidal agent with marked anti-inflammatory and analgesic properties. The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

Paracetamol

Mechanisms of Action/Effect

Analgesic – the mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent, through a peripheral action by blocking pain impulse generation.

The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Antipyretic – paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

5.2 Pharmacokinetic properties

After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3.00 hours following ingestion. Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 L.

The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein-bound (>99%). Aceclofenac circulates mainly as unchanged drug. 4'- Hydroxyaceclofenac is the main metabolite

detected in plasma. Approximately two- thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites.

Paracetamol

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1-4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentration.

A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage

5.3 Preclinical safety data

Aceclofenac

The results from preclinical studies conducted with aceclofenac are consistent with those expected for NSAIDs. The principal target organ was the gastro-intestinal tract. No unexpected findings were recorded.

Aceclofenac was not considered to have any mutagenic activity in three *in vitro* studies and an

in vivo study in the mouse. Aceclofenac was not found to be carcinogenic in either the mouse or rat.

Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with aceclofenac (10 mg/kg/day) resulted in a series of morphological changes in some fetuses.

Paracetamol

There is no pre-clinical data of relevance to a prescriber, which is additional to that already included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline cellulose PH 101, Sodium starch glycolate type A, Hydroxypropyl cellulose, Sodium lauryl sulfate, Colloidal silicon dioxide, Magnesium stearate, Instacoat universal white I-CU-1308, Purified water

6.2 Incompatibilities

None stated

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30⁰ C

6.5 Nature and contents of container

10 tablets of Aceclofenac 100 mg and Paracetamol 500 mg Tablets are sealed with PVC/PVdC film on one side and printed Aluminum blister foil on the other side in the form a blister pack and 3 such blister packs are further packed in a printed carton along with instructions for use.

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

MSN Laboratories Private Limited (Formulations division). Plot No.: 42, ANRICH Industrial Estate,

Bollaram, Sangareddy
District, Pin code- 502 325,
India.

8. MARKETING AUTHORIZATION NUMBER

RWANDA FDA-HMP-MA-0029

9. DATE OF FIRST AUTHORIZATION

First Authorization: 15th September,2020

10. DATE OF REVISION OF THE TEXT

May 2017