SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINALPRODUCT

ALGIC-P (Aceclofenac 100 mg and Paracetamol 500 mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Aceclofenac 100 mg and Paracetamol 500 mg Tablets

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

Symptomatic treatment of mild to moderate pain and fever.

Adults and children from 27 kg (approximately 8 years old).

4.2 Posology and method of administration

Aceclofenac

Posology

When Aceclofenac was administered to fasting and fed healthy volunteers only the rate and not the extent of Aceclofenac absorption was affected.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).

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.

Paediatric population

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 (see also Precautions).

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.

Method of administration

To be taken preferably with or after food. The tablets should be swallowed whole with a sufficient quantity of liquid.

Paracetamol

Dosage

Use the lowest effective dose, for the shortest possible duration: Use the 1000 mg dose if pain and/or fever is not relieved by a 500 mg dose of paracetamol.

Recommended dosage: approximately 60 mg/kg/day to be divided into several doses without exceeding the maximum doses indicated in the table below. In children, the dosage should be adjusted according to weight.

Approximate ages based on weight are given for information purposes only.

Weight (approximate age)	**Maximum dose by administration**	**Administration interval**	**Maximum daily dose**
Child 27 kg – 40 kg (approximately 8 to 12 years)	500 mg (1 tablet)	6 hours minimum	2000 mg per day or 2 g (4 tablets)
Child 41 kg – 49 kg	500 mg (1 tablet)	4 hours minimum	3000 mg per day

(approximately 13 to 15 years)			or 3 g (6 tablets)
Adults and children from 50 kg (about 15 years)	500 mg to 1000 mg or 500 mg to 1 g (1 to 2 tablet(s))	4 hours minimum	3000 mg per day or 3 g (6 tablets)

Warning: Take into account all medicines containing paracetamol to avoid an overdose, including those obtained without a prescription .

Only on medical advice and in the absence of concomitant risk factors, the dosage may be increased up to 4000 mg (4 g) per day, or 8 tablets per day, in patients weighing at least 50 kg (from approximately 15 years of age).

Special populations

The maximum daily dose should not exceed 60 mg/kg/day nor exceed 3000 mg per day (3 g/day) in the following situations:

- Adults weighing less than 50 kg,
- In case of low reserves or hepatic glutathione deficiency (e.g.: chronic malnutrition, fasting, recent weight loss, anorexia, cachexia),
- Dehydration.

Liver failure (mild to moderate), chronic alcoholism and Gilbert's syndrome (familial non-hemolytic jaundice)

It is recommended to reduce the dose and increase the minimum interval between two doses. The daily dose of paracetamol should not exceed 2000 mg/day (2 g/day).

Renal failure

In case of renal insufficiency and unless advised otherwise by a doctor, it is recommended to reduce the maximum daily dose and increase the minimum interval between 2 doses according to the table below.

Adults:

Creatinine clearance	**Administration interval**	**Maximum daily dose**
10-50 mL/min	6 hours minimum	3000 mg/day (3 g/day)
<10 mL/min	8 hours minimum	2000 mg/day (3 g/day)

Elderly people

Clinical experience indicates that the recommended dosage in adults is generally adequate. However, concomitant risk factors, some of which occur more frequently in the elderly, should be taken into account and may require dosage adjustment.

Mode of administration

Oral route.

The tablets should be swallowed as they are with a glass of water.

Processing time

Frequent or prolonged use without medical supervision is not recommended.

If symptoms persist beyond 5 days in the case of pain or 3 days in the case of fever, if symptoms worsen or if new symptoms appear, treatment should be reassessed.

4.3 Contraindications

Aceclofenac

Hypersensitivity to the active substance 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 (see section 4.4).

Patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

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

Active bleedings 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).

Paracetamol

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

Severe liver failure.

4.4 Special warnings and precautions for use

Aceclofenac

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below). The use of Aceclofenac with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see

section 4.5).

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 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 (NYHA-I) and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, 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 re-evaluated 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 gastro intestinal 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 hemorrhage 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').

Long-term 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.

<u>Paracetamol</u>

Patients should be advised not to take any other medicines containing paracetamol. Taking multiple doses at once may cause serious liver damage; in this case, the patient should seek medical advice immediately.

In a child treated with 60 mg/kg/day of paracetamol, the association of another antipyretic is only justified in case of ineffectiveness.

In case of acute viral hepatitis, treatment should be stopped.

Precautions for use

Paracetamol should be administered with caution in the following situations (see section 4.2) :

- Adult weighing less than 50 kg
- Mild to moderate hepatic impairment
- Chronic alcoholism and recent withdrawal
- Renal failure
- Gilbert's syndrome
- Concomitant treatment with drugs affecting liver function (e.g. potentially hepatotoxic drugs or drugs that induce cytochrome P450 enzymes such as phenobarbital, phenytoin, carbamazepine, topiramate, rifampicin)
- Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency (can lead to hemolytic anemia)
- Dehydration
- In case of low reserves or hepatic glutathione deficiency (e.g.: chronic malnutrition, fasting,

recent weight loss, anorexia, cachexia)

- Elderly people

The consumption of alcoholic beverages during treatment is not recommended.

In case of long-term use, high doses, or incorrect use of analgesics in patients with chronic headaches, headaches may appear or worsen; they should not be treated with higher doses of this medicine. In such cases, the use of analgesics should be discontinued on medical advice. Caution is advised when co-administering paracetamol and flucloxacillin due to an increased risk of high anion gap metabolic acidosis (HAMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as in those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Excipient with known effect

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-hypertensive: 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 co-administered with bendrofluazide, 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 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

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

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Close monitoring of patients on combined anti-coagulants 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.

Anti-platelet 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

Associations requiring precautions for use

+ Antivitamins K

Risk of increased effect of antivitamin K and risk of bleeding when taking paracetamol at

maximum doses (4 g/day) for at least 4 days.

More frequent monitoring of INR. Possible adaptation of the dosage of antivitamin K during treatment with paracetamol and after its discontinuation.

+ Flucloxacillin

Caution should be exercised when using paracetamol concomitantly with flucloxacillin, as concomitant use has been associated with high anion gap metabolic acidosis, particularly in patients with risk factors (see section 4.4).

Interactions with paraclinical examinations

Taking paracetamol can distort the measurement of blood sugar by the glucose oxidase-peroxidase method in the event of abnormally high concentrations.

Taking paracetamol can distort the blood uric acid measurement using the phosphotungstic acid method.

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 pre- and post-implantation 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. From the 20th week of pregnancy onward, Aceclofenac 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, Aceclofenac should not be given unless clearly necessary. 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Aceclofenac for several days from gestational week 20

onward. Aceclofenac 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, Aceclofenac is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast feeding:

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.

Fertility:

The use of Aceclofenac 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 Aceclofenac should be considered.

Paracetamol

Pregnancy

Animal studies have not shown any teratogenic or fetotoxic effects of paracetamol.

A large body of data from pregnant women demonstrates the absence of any malformation or foetal/neonatal toxicity.

Epidemiological studies of the neurodevelopment of children exposed to paracetamol in utero have produced inconclusive results. If clinically necessary, paracetamol may be used during pregnancy; however, it should be used at the lowest effective dose, for the shortest possible duration and with the lowest possible frequency.

Breastfeeding

After administration, paracetamol is excreted in small amounts in breast milk. At therapeutic doses, administration of this drug is possible during breastfeeding.

Fertility

Due to the potential mechanism of action on cyclooxygenases and prostaglandin synthesis, paracetamol could impair fertility in women, through an effect on ovulation reversible upon stopping treatment.

Effects on male fertility have been observed in one animal study. The relevance of these effects to humans is unknown.

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 machinery.

Paracetamol

Paracetamol has no or negligible influence on the ability to drive and use machines.

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.

Aceclofenac is both structurally related and metabolised to diclofenac for which a greater amount of clinical and epidemiological data consistently point towards an increased risk of

general arterial thrombotic events (for example myocardial infarction or stroke, particularly at high doses or in long treatment). Epidemiological data has also found an increased risk of acute coronary syndrome and myocardial infarction associated with the use of Aceclofenac (see section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use). 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 such as 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 (≥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).

MedDRA SOC	**Common 1/100 to<1/10**	**Uncommon ≥1/1,000 to**	**Rare < ≥1/10,000 to**	**Very rare/ <1/10,000**
Blood and lymphati system disorders			Anaemia	Bone Marrow depression Granulocytopenia Thrombocytopenia
Immune system disorders			Anaphylactic reaction (includin shock)	
Metabolism and nutrition disorders				Hyperkalemia

Psychiatric disorder				Depression Abnormal dreams Insomnia
Nervous system disorders	Dizziness			Paraesthesia Tremor Somnolence Headache Dysgeusia
Eye disorders			Visual disturbance	
Ear and labyrinth disorder				Vertigo Tinnitus
Cardiac disorders			Cardiac failure	Palpitations
Vascular disorders			Hypertension	Flushing Hot flush Vasculitis
Respiratory, thoraci and mediastinal			Dyspnoea	Bronchospasm 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
Hepatobiliary disorders	Hepatic enzyme increased			Hepatic injury (including hepatitis Jaundice Blood alkaline
Skin and subcutaneous tissue disorders		Pruritus Rash Dermatitis Urticaria	Angioedema	Purpura Severe mucocutaneous skin reaction (including Stevens Johnson Syndrome and Toxic Epiderma

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

Paracetamol

Adverse reactions are classified by system organ class. Their frequencies are defined as follows:

- Very common (≥1/10)
- Common (≥1/100 to < 1/10)
- Uncommon (≥1/1000 to < 1/100)
- Rare (≥1/10,000 to < 1/1000)
- Very rare (< 1/10,000)
- Frequency not known (cannot be estimated from the available data)

Blood and lymphatic system disorders

- Very rare: thrombocytopenia, leukopenia and neutropenia.

Immune system disorders

- Rare: hypersensitivity reactions.
- Frequency not known: anaphylactic reaction (including hypotension), anaphylactic shock, angioedema (Quincke's edema).

  Their occurrence requires the immediate and definitive discontinuation of this medication and related medications.

Respiratory, thoracic and mediastinal disorders

- Frequency not known: bronchospasm (cases of bronchospasm have been identified with paracetamol, mainly in asthmatic patients sensitive to aspirin or other non-steroidal anti-inflammatory drugs).

Metabolism and nutrition disorders

- Frequency not known: pyroglutamic acidosis, in patients with factors predisposing to glutathione depletion.

Gastrointestinal disorders

- Frequency not known: diarrhea, abdominal pain.

Hepatobiliary disorders

- Frequency not known: increased liver enzymes.

Skin and subcutaneous tissue disorders

- Rare: erythema, urticaria, skin rash. Their occurrence requires immediate and permanent discontinuation of this medicine and related medicines.
- Rare: purpura. If this effect occurs, this medication must be stopped immediately. The medication may be reintroduced only on medical advice.
- Very rare: serious skin reactions. If these occur, immediate and permanent discontinuation of this medicine and related medicines is required.
- Frequency not known: fixed pigmented erythema.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions to the National Regulatory Agents.

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 are possible.

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

The risk of serious poisoning (therapeutic overdose or accidental poisoning) may be particularly

high in the elderly, in young children, in patients with liver disease, in chronic alcoholism, in patients suffering from chronic malnutrition (see section 4.2), fasting, recent weight loss, familial cholemia (Gilbert's syndrome) as well as in patients receiving enzyme-inducing drugs. In these cases, poisoning may be fatal.

Symptoms

Nausea, vomiting, anorexia, pallor, malaise, sweating, abdominal pain usually appear within the first 24 hours.

Overdose may cause hepatic cytolysis leading to hepatocellular failure requiring liver transplantation, gastrointestinal bleeding, metabolic acidosis, encephalopathy leading to coma and death.

Cases of disseminated intravascular coagulation have been observed in the context of paracetamol overdose.

Simultaneously, there is an increase in hepatic transaminases, lactic dehydrogenase, bilirubin and a decrease in the prothrombin rate that can appear 12 to 48 hours after ingestion. Clinical symptoms of liver damage are usually observed after 1 to 2 days, and reach a maximum after 3 to 4 days.

Overdose may also result in acute pancreatitis, hyperamylasemia, acute renal failure, and pancytopenia.

Emergency driving

- Stopping treatment
- Immediate transfer to hospital for emergency medical care, despite the absence of significant early symptoms.
- Rapid evacuation of the ingested product, by aspiration and gastric lavage preferably within 4 hours following ingestion.
- Blood sample to perform the initial plasma paracetamol assay. The plasma paracetamol concentration should be measured at least 4 hours after ingestion (an earlier assay is not reliable)
- Treatment of overdose typically involves administering the antidote N-acetylcysteine as early as possible by IV or oral route if possible before the tenth hour. Although less effective, a protective effect of the antidote can be obtained up to 48 hours post ingestion. In this case the antidote should be administered for a longer period.
- Symptomatic treatment.
- Liver tests should be performed at the start of treatment and repeated every 24 hours. In most cases, liver transaminases return to normal within 1 to 2 weeks with full recovery of liver function. However, in very severe cases, liver transplantation may be necessary.

- Further measures will depend on the severity, nature and progression of clinical symptoms of paracetamol poisoning and should follow standard intensive care protocols.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Aceclofenac

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

Pharmacotherapeutic group: OTHER ANALGESICS and ANTIPYRETICS-ANILIDES.
ATC code: N02BE01
Paracetamol has a central and peripheral mechanism of action.

5.2 Pharmacokinetic properties

Aceclofenac

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.
No changes in the pharmacokinetics of Aceclofenac have been detected in the elderly.

Paracetamol

Absorption

Absorption of oral paracetamol is complete and rapid. Peak plasma concentrations are reached 30 to 60 minutes after ingestion.

Distribution

Paracetamol is rapidly distributed to all tissues. Concentrations are comparable in blood, saliva and plasma. Plasma protein binding is low.

Biotransformation

Paracetamol is metabolized mainly in the liver. The two major metabolic pathways are glucuronidation and sulfoconjugation. The latter pathway is rapidly saturable at doses higher than therapeutic doses. A minor pathway, catalyzed by cytochrome P 450, is the formation of a reactive intermediate (N-acetyl benzoquinone imine), which under normal conditions of use is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercaptopuric acid. On the other hand, during massive poisoning, the quantity of this toxic metabolite is increased.

Elimination

Elimination is mainly urinary. 90% of the ingested dose is eliminated by the kidney in 24 hours, mainly in glucuroconjugate (60 to 80%) and sulfoconjugate (20 to 30%) form.

Less than 5% is eliminated unchanged.

The elimination half-life is approximately 2 hours.

Pathophysiological variations

Renal impairment: In case of renal impairment (see section 4.2), the elimination of paracetamol and its metabolites is delayed.

Hepatic impairment: The metabolism of paracetamol is impaired in patients with chronic hepatic impairment, as evidenced by increased plasma paracetamol concentrations and a longer elimination half-life (see section 4.2).

Elderly subject: the conjugation capacity is not modified (see section 4.2).

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

No conventional studies based on currently accepted standards for assessing reproductive and developmental toxicity are available.

6. Pharmaceutical particulars

6.1 List of Excipients

Core Tablet:

Microcrystalline cellulose (PH 101)

Sodium starch Glycolate Type A,

Hydroxy Propyl cellulose-LF Pharma,

Sodium Lauryl sulphate,

Colloidal silicon dioxide,

Magnesium stearate.

Coated Tablets:

Instacoat universal white I-CU- 1308 (Hypromellose, Polyethylene Glycol, Talc, Titanium Dioxide) and Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.

Protect from light and moisture

Keep out of reach of children.

6.5 Nature and contents of container

Pack type: 10's Alu-PVC/PVdc blister pack

Pak size: 1x10, 3x10 and 10x10.

Note: Not all pack sizes may be marketed.

POM	PP	Schedule 2	NS2

Pharmacological Classification:
3.1 Nonsteroidal anti-inflammatory medicines

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 authorisation holder

MSN Laboratories Private Limited.
MSN House, Plot No: C-24,
Sanathnagar Industrial Estate,
Hyderabad-500018,
Telangana, India

Manufacture By

MSN Laboratories Private Limited
(Formulations division).
Plot No.: 42, Anrich Industrial Estate,
Bollaram, Sangareddy District,
Pin Code. 502325
Telangana, India.

8. Marketing Authorisation Number(S)

CTD13593

9. Date of First Authorisation/Renewal of the Authorisation

17/06 2026

10. Date of Revision of the Text

17/06 2026