SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT: PARAFENAC PLUS

Generic Name of Product : Diclofenac Sodium & Paracetamol Capsules

Strength (formula) : Each Hard gelatin capsule contains:
Paracetamol BP.....500 mg
Diclofenac Sodium BP…..25 mg
Excipients…….Q.S.
Approved colour used in empty gelatin capsule shells

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

2.1 Qualitative & Quantitative Composition Declaration:

For 1.00.000 Capsules

Sr. No.	Ingredients	Spec.	Qty. / Cap mg	% OA.	Qty. / Cap mg with % O.A.	Qty. Req. per batch Kg
1.	Paracetamol	BP	500 mg	--	500 mg	50.00
2.	Diclofenac Sodium	BP	25 mg	--	25 mg	2.5
3.	Povidone (K-30)	BP	2.4 mg	--	2.4 mg	0.240
4.	Isopropyl Alcohol	BP	22.6 mg	--	22.6 mg	2.260
5.	Purified Talc	BP	49.5 mg	--	24.5 mg	4.950
6.	Magnesium Stearate	BP	7.6 mg	--	7.6 mg	0.760
7.	Aerosil	BP	15.5 mg	--	15.5 mg	1.550
8.	Size “0” Yellow/Yellow Colour hard Gelatin Capsules	IHS	1.00 LAC Nos	--	1.00 LAC Nos	1.00 LAC Nos

OA: Overage, IHS : - In-House specification, BP: - British Pharmacopoeia

3. PHARMACEUTICAL FORM:

Size “0” Yellow/Yellow Colour hard gelatin Capsules

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

PARAFENAC PLUS is indicated in the treatment of painful rheumatic disorders such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gout. Acute musculoskeletal disorders and soft tissue inflammation such as periarthritis, sprains, strains, tenosynovitis, bursitis, pain in fractures and dislocation. Relief of pain and inflammation associated with orthopaedic, dental, gynaecological and other minor surgical procedures.

4.2 Posology and Method of Administration:

Adults, the elderly and children over 12 years of age:

1 capsule two or three times daily

Not recommended for children under 12 years of age.

Method of Administration:

Oral administration

4.3 Contra – Indications:

PARAFENAC PLUS is contraindicated in:

Hypersensitivity to Paracetamol, diclofenac sodium.
Previous hypersensitivity reactions (eg asthma, urticaria, angioedema or rhinitis) in response to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs.
• Severe hepatic, renal and cardiac failure.
• During the last trimester of pregnancy.
• Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
• History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
• Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4 Special Warning and Precautions for Use:

Paracetamol:

Paediatric population

Not recommended for children under 10 years of age.

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Do not exceed the recommended dose.

Do not take with any other paracetamol-containing products.

If symptoms persist, consult your doctor.

Keep out of the reach of children.

Immediate medical advice should be sought in the event of an overdose even if you feel well, because of the risk of delayed, serious liver damage.

Diclofenac Sodium

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases without previous exposure to the drug. Diclofenac sodium may mask the signs and symptoms of infection due to its pharmacodynamic properties.

The use of Diclofenac Sodium with concomitant NSAIDs including cyclo-oxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

Older people:

Caution is indicated on basic medical grounds. Older people have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). It is recommended that the lowest effective dose be used in frail older people or those with a low body weight.

Respiratory disorders:

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions to NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for a medical emergency). This is also applicable to patients who are known to be allergic to other substances and have previously presented with skin reactions, pruritus or urticaria.

Cardiovascular, Renal and Hepatic Impairment:

Close medical surveillance is required when prescribing diclofenac to patients with impaired hepatic function, as their condition may be exacerbated.

As with other NSAIDs, treatment with diclofenac can be associated with a rise in liver enzymes. During prolonged treatment with diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, or if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), diclofenac should be discontinued. Hepatitis may occur without prodromal symptoms. Caution is called for in patients with hepatic porphyria, since it may trigger an attack.

Fluid retention and oedema have been reported with NSAID therapy, including diclofenac; particular caution is called for in patients with impaired cardiac or renal function, a history of hypertension, older people, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3). Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

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 older people. Renal function should be monitored in these patients.

Cardiovascular and cerebrovascular effects:

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

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Diclofenac treatment for patients with uncontrolled hypertension and/or congestive heart failure (NYHA-I) should be given only after careful consideration.

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with Diclofenac Sodium after careful consideration.

As the cardiovascular risks of diclofenac 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.

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.

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, and in older people. 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.

Patients with a history of GI toxicity, particularly when older, 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 oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin.

When GI bleeding or ulceration occurs in patients receiving Diclofenac Sodium, 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.

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.

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. 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. Diclofenac Sodium should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Female fertility:

The use of Diclofenac Sodium 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 Diclofenac Sodium should be considered.

Haematological Effects:

Diclofenac, in common with other NSAIDs, can reversibly inhibit platelet aggregation and with such patients, careful monitoring is advised.

4.5 Interaction with other medicinal products and other forms of interaction

<u>Diclofenac Sodium</u>

Other analgesics including cyclo-oxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects .

Diuretics and Anti-hypertensives: Reduced diuretic and anti-hypertensive effect may be seen

The combination should be administered with caution, and patients, especially older people, should have their blood pressure monitored. Patients should be adequately hydrated and renal function monitored after initiation of concomitant therapy and periodically thereafter, particularly for those patients on diuretics and ACE inhibitors, due to the increased risk of nephrotoxicity.

Diuretics can increase the risk of nephrotoxicity of NSAIDs. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, hence serum potassium should be monitored.

Digoxin: A rise in plasma concentrations of dixogin may be seen, therefore monitoring of serum digoxin levels recommended.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduced GFR (Glomerular Filtration Rate) and increase plasma glycoside levels.

Lithium: Decreased elimination of lithium, may occur and monitoring of serum lithium levels recommended.

Methotrexate: Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other.

Diclofenac can inhibit the tubular renal clearance of methotrexate thereby increasing methotrexate levels, leading to toxicity.

Ciclosporin: Increased risk of nephrotoxicity, therefore diclofenac should be given at doses lower than those that would be used in patients not receiving ciclosporin.

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.

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical studies do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving concomitant diclofenac and anticoagulants. Close monitoring of such patients is therefore recommended.

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.

Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding

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

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

Phenytoin: Monitoring of phenytoin plasma concentrations recommended due to an expected increase in phenytoin levels.

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption, therefore, it is recommended that diclofenac is administered at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Potent CYP2C9 inhibitors: Caution recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentration and exposure to diclofenac due to inhibition of diclofenac metabolism.

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both

hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. Therefore, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Paracetamol

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

4.6 Pregnancy and lactation

Diclofenac Sodium

Pregnancy:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a 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 death.

In addition, increased incidences of various malformations, including cardiovascular malformations, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, Motifene should not be given unless absolutely necessary. If Motifene is used by a woman when attempting to conceive, or during the first and second trimester of pregnancy, the dose and durations should be kept as low and as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may cause the following in the foetus:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

In the mother and the neonate, at the end of pregnancy:

- an anti-aggregating effect which may occur even at very low doses leading to possible prolongation of bleeding times;

- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Motifene is contraindicated during the third trimester of pregnancy.

Breast-feeding:

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breast-feeding.

Paracetamol

Pregnancy

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 their doctor regarding its use. A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity.

Paracetamol can be used during pregnancy if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breastfeeding

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 machine:

Diclofenac Sodium

Diclofenac Sodium has minor or moderate influence on the ability to drive and use machines. Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances, vertigo, somnolence or other central nervous system disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

Paracetamol

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

4.8 Undesirable effects

Diclofenac sodium

The information below lists reported adverse reactions, ranked using the following frequency classification:

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

Immune system disorders

Hypersensitivity including skin rash may occur.

Not known: anaphylactic shock, angioedema

Blood and lymphatic system disorders

Not known: blood dyscrasias including thrombocytopenia and agranulocytosis

Skin and subcutaneous disorders

Very rare cases of serious skin reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption have been reported.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

Overdose

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:

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

• regularly consumes ethanol in excess of recommended amounts, or

• 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, gastrointestinal bleeding 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 N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, 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 24h from ingestion should be discussed with the NPIS or a liver unit.

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4.9 Overdose

Diclofenac Sodium

Symptoms:

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

Treatment:

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures.

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 closely monitored 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. Specific therapies such as forced diureses, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.
Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Paracetamol

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Risk factors

If the patient:

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5. Pharmacological properties

5.1 Pharmacodynamic properties

Diclofenac Sodium

Pharmacotherapeutic group: Acetic acid derivatives and related substances
ATC code: M01AB05
Diclofenac Sodium is a non-steroidal agent with marked analgesic/anti-inflammatory properties.
It is an inhibitor of prostaglandin synthetase (cyclo-oxygenase)

Paracetamol

Pharmacotherapeutic group: ATC code: N02B E01, Other analgesics and antipyretics.
Paracetamol is an antipyretic analgesic. The mechanism of action is probably similar to that of aspirin and dependent on the inhibition of prostaglandin synthesis. The inhibition appears, however, to be on a selective basis.

5.2 Pharmacokinetic properties

Diclofenac Sodium

Diclofenac sodium is rapidly absorbed from the gut and is subject to first-pass metabolism. Therapeutic plasma concentrations occur about ½ hour after administration of Diclofenac sodium. The active substance is 99.7% protein bound and the plasma half-life for the terminal elimination phase is 1-2 hours. Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in unchanged form. The remainder of the dose is excreted via the bile in metabolised form.
Following rapid gastric passage, the gastro-resistant pellet component of Diclofenac sodium ensures quick availability of the active component in the blood stream. The prolonged release pellets cause a delayed release of the active component, which means one single daily dose is usually sufficient.

Paracetamol

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes and the half life in plasma is 1 to 4 hours after therapeutic doses. Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; 20 to 50% may be bound at the concentrations encountered during acute intoxication. Following therapeutic doses 90 to 100% of the drug may be recovered in the urine within the first day. However, practically no paracetamol is excreted unchanged, and the bulk is excreted after hepatic conjugation.

5.3 Preclinical safety data

No Clinical data.

6. Pharmaceutical particulars

6.1 List of excipients

Povidone, Isopropyl Alcohol, Purified Talc, Magnesium Stearate, Aerosil.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in dry place, below 30°C. Protect from light, heat and moisture.

6.5 Nature and contents of container

10 x 1 x 10 Capsules Alu-PVC blister

6.6 Special precautions for disposal and other handling

No special instructions needed.

7. Marketing authorisation holder

(Company) Name: RONAK EXIM PRIVATE LIMITED
Address: Sant Kabir Road, Behind Gendi Gate,
Police Station, Baroda – 390 001, GUJARAT
Country: INDIA
E-mail: ahmedi@ronakoverseas.com

8. Marketing authorization number(s)

Not applicable.

9. Date of first authorization/renewal of the authorization

Not applicable.

10. Date of revision of the text

Not applicable.

RONAK EXIM PVT. LTD. INDIA