1.6.1.1 Name of the medicinal Product

Prolonged-Release Diclofenac Tablets BP

1.6.1.1.1 strength

100 mg/tablet

1.6.1.1.2 Pharmaceutical Form

Oral tablet

1.6.1.2 Qualitative and Quantitative Composition

1.6.1.2.1 Qualitative declaration

Diclofenac Sodium BP

1.6.1.2.2 Quantitative declaration

Sr. No.	Ingredients Chemical Name	Specification	Quantity/ dosage unit (mg)	Reason for Inclusion
01	Diclofenac Sodium (A)	BP	100.0	Non-steroidal Anti-inflammatory Agent
02	Dextrose Anhydrous (C)	BP	118.0	Diluent
03	Xanthan Gum	BP	20.00	Release retarding agent
04	Hypromellose (Metolose K-100 M)	BP	10.00	Release retarding agent
05	P.V.P.K. 30 (Povidone)	BP	15.00	Binder
06	Isopropyl Alcohol #	BP	150.0	Solvent
07	Purified Talc	BP	3.330	Lubricant
08	Microcrystalline Cellulose (pH 102)	BP	28.33	Antiadherent
09	Magnesium Stearate	BP	5.340	Lubricant
10	Colour Iron Oxide Red Spraycel SC-SP 2099	In-House	9.000	Coating agent
11	Isopropyl Alcohol #	BP	72.00	Solvent
12	Dichloromethane #	BP	108.0	Solvent

Note: (A)= Quantity of active ingredient is to be calculated on the basis of 100% potency and on anhydrous basis.
(C) = Quantity of Dextrose anhydrous BP to be reduced against incremental Increase in quantity of Diclofenac Sodium due to Assay compensation.

(#) = This will not remain in the final product.

1.6.1.2.3 Pharmaceutical Form

Oral, Coated Tablet

Brick red coloured, round shaped, biconvex, prolonged release film coated tablets, plain on both side.

1.6.1.3 Clinical Particulars

1.6.1.3.1 Therapeutic Indications

Arthritic conditions: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gout. Acute musculo-skeletal disorders such as periarthritis (for example frozen shoulder), tendinitis, tenosynovitis and bursitis. Other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery.

1.6.1.3.2 Posology and Method of Administration

Adults: Prolonged-release Diclofenac Tablets BP 100 mg once daily.

Children and adolescents: Prolonged-release Diclofenac Tablets BP 100 mg is not suitable for children and adolescents.

1.6.1.3.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, angioedema, urticaria or acute rhinitis) to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs. Patients with a history of, or active, gastro-intestinal ulcers, bleeding or perforation (two or more distinct episodes of proven ulceration or bleeding). Severe hepatic, renal and heart failure. During the last trimester of pregnancy. Diclofenac sodium is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

1.6.1.3.4 Special Warnings and Special Precautions for Use

Gastro-intestinal: Patients with symptoms indicative of gastro-intestinal disorders, with a history suggestive of gastro-intestinal ulceration or perforation, with ulcerative colitis or with Crohn's disease as these conditions may be exacerbated.

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

Caution should be advised in patients with severe renal, cardiac or hepatic impairment. A history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema, defects of haemostasis, bleeding diathesis or haematological abnormalities, previous history of bronchial asthma.

Diclofenac sodium may mask the signs and symptoms of infection due to its pharmacodynamics properties.

Female fertility: Diclofenac may impair female fertility and is not recommended in women attempting to conceive.

Use in pregnancy: Diclofenac Sodium should not be used during the first two trimesters of pregnancy or labour unless the potential benefit outweighs the potential risk to foetus.

Use in lactation: Diclofenac Sodium passes into the breast milk in small amounts. Diclofenac should not be administered during breast feeding in order to avoid adverse effects in the infant.

Paediatric Use: Diclofenac is not recommended for use in children as safety and efficacy in this age group have not been established.

1.6.1.3.5 Interaction with other medicinal products and other forms of interaction

Lithium: Diclofenac sodium may increase plasma concentrations of lithium.

Anticoagulants: Diclofenac may enhance the effects of anti-coagulants like Warfarin.

Cyclosporin: Possible increased risk of nephrotoxicity.

Methotrexate: Decrease elimination of Methotrexate.

Other NSAIDs including cyclo-oxygenase-2 selective inhibitors and corticosteroids:

Coadministration of diclofenac sodium with these agents may increase the risk of gastro-intestinal

bleeding or ulceration.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

Diuretics: Diclofenac Sodium may inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels.

Antihypertensive: Concomitant use of NSAIDs with antihypertensive drugs (i.e. beta-blockers,angiotensin converting enzyme (ACE) inhibitors, diuretics) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

Zidovudine: Increased risk of haematological toxicity when NSAIDs given with zidovudine.

1.6.1.3.6 Fertility, Pregnancy and Lactation

Pregnancy: Diclofenac Sodium should not be used during the first two trimesters of pregnancy or labour unless the potential benefit outweighs the potential risk to foetus.

Breast-feeding: Diclofenac Sodium passes into the breast milk in small amounts. Diclofenac should not be administered during breast feeding in order to avoid adverse effects in the infant.

1.6.1.3.7 Effects on ability To Drive and use Machines

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

1.6.1.3.8 Undesirable Effects

Common adverse effects of Diclofenac sodium: Abdominal pain or cramps, constipation, diarrhoea, flatulence, GI bleeding, GI perforation, peptic ulcer, vomiting, dyspepsia, nausea,dizziness, headache, liver function test abnormalities, renal function abnormalities, anemia, prolonged bleeding time, pruritus, rash, tinnitus, edema.

1.6.1.3.9 Overdose

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

Management: 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 potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

1.6.1.4 Pharmacological Properties

1.6.1.4.1 Pharmacodynamics Properties

Diclofenac sodium is a non-steroidal agent with analgesic, antipyretic and anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase (cyclooxygenase).

1.6.1.4.2 Pharmacokinetic Properties

Absorption: Diclofenac is absorbed from the gastro-intestinal tract and is subject to first-pass metabolism. Mean peak concentrations of 0.5 µg/mL is reached on average 4 hours after ingestion of 100 mg sustained release tablet. Mean plasma concentrations of 13 ng/mL can be recorded at 24 hours (16 hours) after administration of RELAXO-SR-100.

Distribution: The apparent volume of distribution (V/F) of Diclofenac sodium is 1.4 L/kg. More than 99% of Diclofenac is bound to plasma proteins, primarily to albumin. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma values, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours.

Metabolism: Diclofenac Sodium is metabolized in the liver via hydroxylation and conjugation. Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-,4'-hydroxy-,5-hydroxy-,4',5-dihydroxy- and 3'-hydroxy-4'-methoxy- diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much smaller extent than diclofenac.

Elimination: It is excreted in urine (65%) and in feces via biliary elimination (35%) as metabolites. The terminal elimination phase half-life is about 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac has a much longer plasma half-life.

1.6.1.4.3 Preclinical Safety Data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. In standard preclinical animal studies, there was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac has no influence on the fertility of parent animals in rats. Except for minimal fetal effects at maternally toxic doses the prenatal, perinatal and postnatal development of the offspring was not affected.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus

in the pregnant rat. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats.

1.6.1.5 Pharmaceutical Particulars

1.6.1.5.1 List of Excipients

Dextrose Anhydrous BP

Xanthan Gum BP

Hypromellose (Metolose K-100 M) BP

P.V.P.K. 30 (Povidone) BP

Isopropyl Alcohol BP

Purified Talc BP

Microcrystalline Cellulose (pH 102) BP

Magnesium Stearate BP

Colour Iron Oxide Red Spraycel SC-SP 2099

Dichloromethane BP

1.6.1.5.2 Incompatibilities

Not applicable.

1.6.1.5.3 Shelf Life

24 months

1.6.1.5.4 Special Precautions for Storage

Store below 30°C. Protect from light & moisture.

1.6.1.5.5 Nature and Contents of Container

10 Tablets are in Strip Pack. Such 10 Strips are packed in Printed Carton with Packing Insert.

1.6.1.5.6 Special precaution for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

1.6.1.6 Marketing Authorization Holder And Manufacturing Site Addresses

1.6.1.6.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

1.6.1.6.2 Name and Address of manufacturing site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

1.6.1.7 Marketing Authorization Number

To be included after obtaining first registration.

1.6.1.8 Date of First <Registration> / Renewal of The <Registration>

It will be applicable after registration of this product.

1.6.1.9 Date of Revision of the Text

1.6.1.10 Dosimetry (If Applicable)

Not Applicable

1.6.1.11 Instructions for preparation of radiopharmaceuticals (if Applicable)

Not Applicable