SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of Medicinal Product

ZOF MR (ACECLOFENAC, PARACETAMOL & CHLORZOXAZONE TABLETS)

2. Qualitative and Quantitative Composition

2.1. Qualitative declaration:

Each Film coated tablet contains:

Aceclofenac BP	100 mg.
Paracetamol BP	325 mg.
Chlorzoxazone USP	350 mg.
Excipients	Q.S.

Colour: Tartrazine & Titanium Dioxide BP

2.2. Quantitative declaration:

Batch Size : 1,00,000 Tablets

Sr. No.	Name of Raw Material	Spec	Label claim / tab	Qty per tablet	% Overage	Qty per tablet with Overages	Std. Qty for 1.0 Lac	Reason for inclusion
1.	*Aceclofenac	BP	100 mg	100.0 MG	--	100.0 MG	10.00 KG	Active
2.	*Paracetamol	BP	325 mg	325.0 MG	--	325.0 MG	32.50 KG	Active
3.	*Chlorzoxazone	USP	350 mg	350.0 MG	2%	350.0 MG	35.00 KG	Active
4.	Maize Starch (F/P)	BP		21.00 MG	--	21.00 MG	2.100 KG	Diluents
5.	Povidone K-30 %	BP		11.00 MG	--	11.00 MG	1.100 KG	Binder
6.	Purified Water	BP			--		Q.S.	Solvent
7.	Colloidal Silicon Dioxide	BP		5.00 MG	--	5.00 MG	0.500 KG	Absorbent
8.	Purified Talc	BP		6.00 MG	--	6.00 MG	0.600 KG	Glidant
9.	Magnesium Stearate	BP		5.00 MG	--	5.00 MG	0.500 KG	Lubricant
10.	Kyron T-314	BP		8.00 MG	--	8.00 MG	0.800 KG	Disintegrant
	Avg. wt of tablet		**Total**			**831.0 MG**	**83.10 KG**	

COATING MATERIAL FORMULA:

SR. NO.	NAME OF PACKING MATERIAL.	QTY PER BATCH.	UNIT
1	Iso propyl alcohol BP	16.677	LTR
2	Ready mix of Tartrazine IH	2.2	KG
3	Methylene Chloride BP	25.00	LTR

3. Pharmaceutical Form

TABLETS

Yellow coloured, capsule shaped, biconvex, film coated tablet having break-line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Paracetamol For temporary relief of pain.

Chlorzoxazone For the relief of discomfort associated with acute painful musculoskeletal conditions.

4.2 Posology and method of administration

ZOF MR is supplied for oral administration in adults and should be swallowed whole with a sufficient amount of liquid. It should be taken preferably with or after food.

The maximum recommended dose of ZOF MR is two tablets daily, taken as one tablet in the morning and one in the evening.

4.3 Contraindications

ZOF MR is contraindicated in the following situations:

- Patients sensitive to aceclofenac, paracetamol, Chlorzoxazone or to any of the excipients of the product.
- Patients with a history of or active, recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angio-oedema or urticaria) in response to ibuprofen, aspirin or other NSAIDs.
- Patients with a history of anaphylactic reactions.
- Patients with severe heart failure, hypertension, and hepatic or renal impairment 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.

4.4 Special warnings and precautions for use

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. Concomitant use with NSAIDs, including COX-2 selective inhibitors, should be avoided. It should not be combined with other analgesic medications that contain paracetamol and should be given with care to patients with impaired kidney or liver function.

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

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.

Hepatic Toxicity

Paracetamol may cause liver damage if more than the recommended dose is taken. Allergic reactions like swelling of the face, mouth and throat, difficulty in breathing, itching or rash may occur due to high doses of paracetamol. Severe liver damage may occur if:

- Adult takes more than 4000 mg in 24 hours, which is the maximum daily amount
- Child takes more than 5 doses in 24 hours
- Taken with other drugs containing paracetamol
- Adult has 3 or more alcoholic drinks every day while using this product

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.

Liver diseases

This medicine is not recommended for use in patients with a known history of hepatic impairment due to the increased risk of worsening of the patient's condition. Replacement with a suitable alternative should be done under your doctor's supervision.

Alcohol

Use of alcohol is not recommended during treatment with this medicine due to the increased risk of serious adverse effects.

Abnormal liver enzymes

If the patient develops abnormal liver enzymes during treatment with this medicine, the therapy should be discontinued immediately. Replacement with a suitable alternative should be done under your doctor's supervision.

4.5 Interaction with other medicinal products and other forms of interaction

Aceclofenac

Other Analgesics, Including cox-2 Selective Inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects.

Antihypertensives: Reduced antihypertensive effect.

Diuretics: Reduced diuretic effect. 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: NSAIDs may exacerbate cardiac failure, reduce the glomerular filtration rate (GFR) and increase plasma glycoside levels.

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate. Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase plasma levels, resulting in increased toxicity.

Ciclosporin: Increased risk of nephrotoxicity.

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 GI ulceration or bleeding.

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin. Close monitoring of patients on combined anticoagulants and aceclofenac therapy should be undertaken.

Paracetamol

Drugs that induce hepatic microsomal enzymes, such as alcohol, barbiturates and other anticonvulsants, may increase the hepatotoxicity of paracetamol, particularly after overdosage.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol, with increased risk of bleeding. The effect appears to increase as the dose of paracetamol is increased, but can occur with doses as low as 1.5-2 g paracetamol per day for at least 5-7 days. Occasional doses have no significant effect.

Probenicid inhibits the glucuronidation of paracetamol which can affect the clearance of paracetamol. This should be considered when these medicines are administered concomitantly.

Paracetamol may affect the pharmacokinetics of chloramphenicol. This interaction should be considered when these medications are administered concomitantly, especially in malnourished patients.

Chlorzoxazone:

Interaction with Medicine

Amitriptyline

Tramadol

Codeine

Methadone

Pentazocine

Alprazolam

Disease interactions

Liver Disease

This medicine is not recommended for use in patients with a known history of liver diseases due to the increased risk of serious adverse effects and worsening of the patient's condition. Replacement with a suitable alternative should be done under your doctor's supervision.

4.6 Fertility, pregnancy and lactation

During pregnancy, especially during the last trimester of pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence while taking ACECLOFENAC, PARACETAMOL & CHLORZOXAZONE should refrain from driving or operating machinery.

4.8 Undesirable effects

Aceclofenac

Some common adverse effects include gastro-intestinal disorders (dyspepsia, abdominal pain, nausea), rash, ruber, urticaria, symptoms of enuresis, headache, dizziness, and drowsiness.

Paracetamol

Paracetamol is metabolized primarily in the liver, where most of it is converted to inactive compounds.

Chlorzoxazone: Symptoms of overdose include diarrhea, dizziness, drowsiness, headache, light-headedness, nausea, and vomiting.

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Aceclofenac – Aceclofenac a nonsteroidal anti-inflammatory drug (NSAID) is used to relief pain and inflammation in rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. Aceclofenac should not be given to people with porphyria or breast-feeding mothers and is not recommended for children. It should be avoided near term in a pregnant woman because of the risk of having a patent ductus arteriosus in the neonate.

Paracetamol – Paracetamol is a medication used to treat pain and fever. It is typically used for mild to moderate pain relief. There is mixed evidence for its use to relieve fever in children. It is often sold in combination with other medications, such as in many cold medications. Paracetamol is also used for severe pain, such as cancer pain and pain after surgery, in combination with opioid pain medication. It is typically used either by mouth or rectally but is also available by injection into a vein. Effects last between 2 to 4 hours.

Chlorzoxazone – Chlorzoxazone is a centrally acting muscle relaxant used to treat muscle spasm and the resulting pain or discomfort. It acts on the spinal cord by depressing reflexes. Possible side effects include dizziness, lightheadedness, malaise, nausea, vomiting, and liver dysfunction. Used with acetaminophen it has added risk of hepatoxicity, which is why the combination is not recommended. It can also be administered for acute pain in general and for tension headache (muscle contraction headache).

MECHANISM OF ACTION: ZOF MR tablets, a combination of aceclofenac, paracetamol and chlorzoxazone is an anti-inflammatory painkiller. Aceclofenac works by blocking the action of cyclo-oxygenase, Paracetamol enhances the analgesia of aceclofenac and Chlorzoxazone acts on spinal cord by depressing reflexes. All this relieves pain and inflammation in arthritic conditions.

5.2 Pharmacokinetic properties

Aceclofenac is a phenylacetic acid derivative that inhibits synthesis of the inflammatory cytokines interleukin-1b and tumour necrosis factor, and inhibits prostaglandin E2 production. It increases glycosaminoglycans (GAG) synthesis, the principal macromolecule of the extracellular

matrix, which aids in repair and regeneration of articular cartilage. Thus, aceclofenac has +ve effects on cartilage anabolism combined with modulating effect of matrix catabolism. Paracetamol has analgesic and antipyretic action with weak anti-inflammatory activity. It produces analgesia by increasing pain threshold and antipyresis by acting on the hypothalamic heat-regulating centre.

The clinical result is a reduction of the skeletal muscle spasm with relief of pain and increased mobility of the involved muscles. Blood levels of chlorzoxazone can be detected in people during the first 30 minutes and peak levels may be reached, in the majority of the subjects, in about 1 to 2 hours after oral administration of chlorzoxazone. Chlorzoxazone is rapidly metabolized and is excreted in the urine, primarily in a conjugated form as the glucuronide. Less than one percent of a dose of chlorzoxazone is excreted unchanged in the urine in 24 hours.

Absorption

Aceclofenac: Rapidly absorbed; almost 100% bioavailability; peak plasma levels reached about 1.25-3 hours after oral admin.

Distribution

Aceclofenac: >99.7% bound to plasma proteins; distributes into synovial fluid. Paracetamol: Distributes throughout most fluids of the body.

Metabolism

Aceclofenac: Probably metabolised by CYP2C9; average plasma elimination half-life: 4-4.3 hours. Paracetamol: Mainly metabolised hepatically; plasma elimination half-life: 1-4 hours.

Excretion

Aceclofenac: About two-thirds of the administered dose is removed in the urine, mainly as conjugated hydroxymetabolites. Paracetamol: Most metabolites are removed in the urine within 24 hours.

5.3 Preclinical safety data

No data available,

6. Pharmaceutical Particulars

6.1 List of Excipients:

Sr. No.	Ingredients	Specification
1.	Maize Starch (F/P)	BP
2.	Povidone K-30 %	BP
3.	Purified Water	BP
4.	Colloidal Silicon Dioxide	BP
5.	Purified Talc	BP
6.	Magnesium Stearate	BP
7.	Kyron T-314	BP
8.	Iso propyl alcohol BP	BP
9.	Ready mix of Tartrazine IH	IH
10.	Methylene Chloride BP	BP

6.2 Incompatibilities: Not Applicable

6.3 Shelf-life: 36 Months

6.4 Special precautions for storage:

Store below 30°C, protect from light & moisture.

6.5 Nature and contents of container:

Alu/PVC blister pack of 10 tablets and such 3 blister packed in a carton with package insert.

6.6 Special precautions for disposal

No special requirements

7. Name and Address of the Registrant

WEGA HELTHCARE LTD.

P.O. BOX 7326-01000 THIKA, KENYA.

8. Name and Address of Manufacturer

RELAX BIOTECH PVT.LTD.

862/1, G.I.D.C., MAKARPURA,

BARODA – 390 010 , Gujarat (INDIA)