



RICHYGOLD INTERNATIONAL LIMITED

COMMON TECHICAL DOCUMENTS

Product Name= RGI IBUPROFEN CAPLET

Generic Name= IBUPROFEN BP 400MG

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

RGI IBUPROFEN CAPLET

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet containsIbuprofen BP 400mg

Excipients with known effect:

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Caplet.

A white oblong caplet with 3 breaklines on the upper punch.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an anti-inflammatory, analgesic and antipyretic for short-term management of mild to moderate pain such as is associated with headache, dental pain, fever, period pain, muscular strain, backache, and for the management of the symptoms of head colds and influenza.

4.2 Posology and method of administration

For oral administration and short term use only.

Adults and children over 12 years: Initial dose is one tablet and subsequently if necessary, one every four hours with a maximum of 3 tablets in a 24 hour period i.e. a maximum dose of 1200mg in a 24 hour period.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).



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If the medicinal product is required for more than 3 days or if the symptoms worsen, the patient should consult a doctor.

If in adolescents this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Not suitable for children under 12 years of age without medical advice NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed please refer to section 4.4. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

4.3 Contraindications

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

Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding) or other gastrointestinal disorder.

Patients with a known history of hypersensitivity reactions (e.g. asthma, bronchospasm, rhinitis, angioedema or urticaria) in response to ibuprofen (the active substance) or any of the excipients in Nurofen Express, acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs).

Use in children under 12 years of age.

Patients with severe hepatic failure or severe renal failure (See Section 4.4).

Severe heart failure (NYHA Class IV).

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. During the last trimester of pregnancy (See Section 4.6).

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 relieve symptoms.

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)

Prolonged use of NSAIDs in the elderly is not recommended.



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Other NSAIDs: Use with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided (see section4.5).

SLE and mixed connective tissue disease: Systemic lupus erythematosus and mixed connective tissue disease, due to increased risk of aseptic meningitis (see section 4.8).

Gastrointestinal bleeding, ulceration and perforation: NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see Section 4.8 –Undesirable effects).

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without any 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 (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 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.

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

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 (see Section 4.5).

Cardiovascular and cerebrovascular effects:

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. < 1200 mg/day) is associated with an increased risk of arterial thrombotic events. Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.



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Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen(2400 mg/day) are required.

Severe Skin Reactions: Serious skin reactions, some of them fatal, including Exfoliative Dermatitis, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis, have been reported rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of 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. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen containing products. Ibuprofen should be discontinued at the first appearance of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Masking of symptoms of underlying infections:

Rgi Ibuprofen caplet can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Rgi Ibuprofen caplet are administered for fever or pain relieve in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. It is advisable to avoid use of ibuprofen in cases of varicella.

Renal: Renal impairment as renal function may deteriorate (see section 4.3 and 4.8).

Hepatic: Hepatic dysfunction (see section 4.3 and 4.8).

Respiratory: Patients with bronchospasm or SLE should consult their doctor before taking this medicine. Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease. Impaired female fertility: There is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Other Warnings: As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis. If you are pregnant, elderly or have asthma or are receiving regular medical treatment please consult your doctor before taking this medication. Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of 'Medication Overuse Headache' should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.



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Advice for patients on a controlled sodium diet: This medicinal product contains 55.89mg sodium per tablet, equivalent to 2.79% of the WHO recommended maximum daily intake of 2g of sodium for an adult. This should be considered in patients whose overall intake of sodium must be markedly restricted.

Sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. There is a risk of renal impairment in dehydrated adolescents.

4.5 Interaction with other medicinal products and other forms of interactions

Ibuprofen should be avoided in combination with:

Acetylsalicylic acid: Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Other NSAIDs including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4).

Ibuprofen should be used with caution in combination with:

- Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see Section 4.4).
- Anti-coagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see Section 4.4). It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).
- Antihypertensives (ACE inhibitors and Angiotensin II Antagonists) and Diuretics: NSAIDs may diminish the effects of these drugs. In some patients with compromised renal function (e.g., dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist agents that inhibit cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or



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angiotensin II antagonists. 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 can increase the risk of nephrotoxicity of NSAIDs.

- Cardiac glycosides:** NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.
- Lithium:** decreased elimination of lithium.
- Methotrexate:** decreased elimination of methotrexate.
- Ciclosporin:** increased risk of nephrotoxicity with NSAIDs.
- Other NSAIDs:** avoid concomitant use of two or more NSAIDs.
- Aminoglycosides:** reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.
- Probenecid:** reduction in metabolism and elimination of NSAID and metabolites.
- Oral hypoglycaemic agents:** inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased hypoglycaemia.
- Zidovudine:** There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
- Mifepristone:** NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
- Tacrolimus:** Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- 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.

4.6 Fertility, pregnancy and lactation

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



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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.

During the first and second trimester of pregnancy, ibuprofen should not be given, unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction, which may progress to renal failure with oligo-hydroaminosis;

The mother and the neonate, at the end of the 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, in the last trimester of pregnancy use of ibuprofen is contraindicated.

Lactation/Breastfeeding:

In limited studies, ibuprofen and its metabolites appears in the breast milk in very low concentration (0.0008% of the maternal dose) and is unlikely to affect the breast-fed infant adversely.

Fertility:

There is some evidence that medicinal products which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment (see Section 4.4 regarding femalefertility).

4.7 Effects on ability to drive and use machines

None expected at recommended doses and duration of therapy.



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4.8 Undesirable effects

The list of the following adverse effects relates to those experienced with ibuprofen at OTC doses (maximum 1200mg per day), for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Adverse events which have been associated with ibuprofen are given below, listed by system organ class and frequency.

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

The adverse events observed most often are gastrointestinal in nature. Adverse events are mostly dose-dependent, in particular the risk of occurrence of gastrointestinal bleeding which is dependent on the dosage range and duration of treatment. The undesirable effects are less frequent when the maximum daily dose is 1200mg.

Clinical studies suggest that the use of ibuprofen particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see Section 4.4).

System Organ Class	Frequency	Adverse Event
Blood and lymphatic System disorders	Very rare	Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding, and bruising.
Immune System disorders	Uncommon	Hypersensitivity reactions consisting of 1: Urticaria and pruritus
	Very rare	Severe hypersensitivity reactions. Symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock). Aggravated asthma, bronchospasm
	Not known	Respiratory tract reactivity comprising asthma or dyspnoea.
Nervous System disorders	Uncommon	Headache, dizziness.



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	Very rare	Aseptic meningitis 2
Ear and labyrinth disorders	Uncommon	Hearing impaired
Cardiac disorders	Very rare	Cardiac failure and oedema
Vascular disorders	Very rare	Hypertension
Gastrointestinal disorders	Uncommon	Abdominal pain, dyspepsia and nausea.
	Rare	Diarrhoea, flatulence, constipation and vomiting.
	Very rare	Peptic ulcers, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly (see Section 4.4). Ulcerative stomatitis, gastritis. Exacerbation of colitis and Crohn's disease (see Section 4.4).
Hepatobiliary disorders	Very rare	Liver disorders, especially in long-term treatment.
Skin and Subcutaneous Tissue disorders	Uncommon	Various skin rashes
	Very rare	Severe forms of skin reactions such as bullous reactions including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis can occur.
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Acute generalised exanthematous pustulosis (AGEP) Photosensitivity reactions
Renal and Urinary disorders	Very rare	Acute renal failure, papillary necrosis, especially in long-term use associated with increased serum urea and oedema
Investigations	Very rare	Decreased haemoglobin levels and urea renal clearance decreased.
Infections and infestations	Very rare	Exacerbation of infections related inflammation (e.g. development of necrotizing fasciitis), in exceptional cases, severe skin infections



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		and soft-tissue complications may occur during a varicella infection.
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Description of Selected Adverse Reactions

1. Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely, exfoliative and bullous dermatoses (including toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme).
2. The pathogenic mechanism of drug-induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

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.

4.9 Overdose

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms: Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache, dizziness, nystagmus, blurred vision, loss of consciousness and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as vertigo, drowsiness, occasionally excitation and disorientation or coma.



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Occasionally patients develop convulsions. In serious poisoning hyperkalaemia and metabolic acidosis may occur and the prothrombin time/INR may be

prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Management: No specific actions antidote is available. Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal or gastric emptying if the patient presents within one hour of ingestion of a potentially toxic amount. If ibuprofen has already been absorbed, alkaline substances may be administered to promote the excretion of acid ibuprofen in the urine. If

frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: propionic acid derivative

ATC Code: M01A E01

Ibuprofen is an NSAID that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

The clinical efficacy of ibuprofen has been demonstrated in pain associated with headache, toothache and dysmenorrhoea and fever; furthermore in patients with pain and fever associated with cold and flu and in pain models such as sore throat, muscular pain or soft tissue injury and backache.

A study in dental pain has shown that patients experienced statistically significant pain relief in 15 minutes after the administration of Rgi Ibuprofen 400mg Caplet, compared with placebo. In this study, significantly more patients achieved meaningful pain relief after administration of Rgi Ibuprofen 400mg Caplet than after administration of paracetamol tablets (96.3% vs 67.9%). These patients also achieved significantly greater reduction in pain intensity and greater pain relief over 6hours compared with patients receiving paracetamol. Using measures of distractibility, patients receiving sodium ibuprofen experienced significantly greater benefit than those receiving placebo.



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Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of Health Products Regulatory Authority, ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Ibuprofen is rapidly absorbed from the gastrointestinal tract. Ibuprofen is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid.

Peak plasma concentration of ibuprofen occurs 1 - 2 hours after administration of ibuprofen acid. The median peak plasma concentration after administration of Rgi Ibuprofen caplet containing 512 mg of sodium ibuprofen is achieved in approximately 35 minutes.

Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete.

Elimination half-life is approximately 2 hours.

No significant differences in pharmacokinetic profile are observed in the elderly.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

Product specific pharmacokinetic properties:

A comparison of 2 x Rgi Ibuprofen caplet (sodium ibuprofen 256mg) with 2 x Rgi Ibuprofen caplet (ibuprofen acid 200mg) showed that the median peak plasma concentration was achieved more than twice as fast for the sodium ibuprofen (35 min) compared to the standard Rgi Ibuprofen caplet (90 min).

5.3 Preclinical safety data

The toxicity of ibuprofen in animal experiments was observed as lesions and ulcerations in the gastrointestinal tract. Ibuprofen did not show a mutagenic potential in vitro and was not carcinogenic in rats and mice. Experimental studies have demonstrated that ibuprofen crosses the placenta but there is no evidence of any teratogenic action.



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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin

Starch (for paste)

Dibasic calcium phosphate

Methyl Paraben

Propyl Paraben

Sodium Starch Glycollate

Pvpk-30

Talcum

Magesium Stearate

Colloidal Anhy. Silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a cool dry place not above 30 decree centigrade

6.5 Nature and contents of container

500 Caplets packed in a jar

6.6 Special precautions for disposal and other handling

Not applicable.



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7 MANUFACTURER/MARKETING AUTHORISATION HOLDER

Richygold International limited(Pharmaceutical formulaions) / Plot 103C Amuwo Odofin Industrial Estate off Oshodi Apapa Express way Sanya Lagos.

8 MARKETING AUTHORISATION NUMBER