LIFEFLU (Paracetamol BP 500mg; Menthol BP0.75mg; Phenylephrine HCl BP 5mg; Chlorpheniramine Maleate BP 2mg Tablets)

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

LIFEFLU (Paracetamol BP 500mg; Menthol BP 0.75mg; Phenylephrine HCl BP5mg; Chlorpheniramine BP 2mg Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Paracetamol BP	500mg
Menthol BP	0.75mg
Phenylephrine HCl BP	5mg
Chlorpheniramine Maleate	2mg
Excipients BP	q.s.

3 PHARMACEUTICAL FORMS

Oral Tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indication.

LIFEFLU is indicated in the relief of nasal congestion caused by colds, allergies, and hay fever. It relieves red, itchy, watery eyes; sneezing; itchy nose or throat; and runny nose caused by allergies. It also has analgesic and antipyretic properties and weak anti-inflammatory activity. It is used in the management of mild to moderate pain and may also be used as an adjunct to opioids in the management of severe pain such as cancer pain. It's the preferred choice for pain in children because of its association of aspirin with Reye's syndrome in this age-group.

4.2 Posology and method of administration.

Method of administration

Adults: 1 tablet three to four times daily.

Children: (6-12years): ½ tablet three to four times daily; (2-6years): ¼ tablet three to four times daily.

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients.
- Active, gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy.

• Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

• Hepatic failure.

• Renal failure.

• Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

• Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.

4.4 Special warnings and precaution for use.

- A frequent or time extended use is unadvised. A time extended use, unless controlled by a medical professional, can harm the health.
- The maximal dose should not be exceeded. In order to prevent the risk of overdose, no other medical product containing paracetamol should be taken simultaneously.
- Taking at once a dose corresponding to several times the daily dose can seriously damage the liver; there might not be any conscious loss. Despite, it is recommended to call a doctor in regard to the risk of irreversible liver damage.
- Caution should be given if the following risk factors, lowering the liver toxicity threshold, are present: liver failure (including Gilbert's syndrome), acute hepatitis, kidney failure, chronic alcoholism and very meagre adults (< 50 kg). In those cases, the posology should be adapted.
- A concomitant treatment with drugs influencing the liver function, dehydration, chronic malnutrition (low glutathione liver stock) are as well regarded as risk factors for the emergence of liver toxicity and that can lower the liver toxicity threshold. The maximal daily dose should certainly not be exceeded in these patients.
- Caution should be given in case of paracetamol administration to patients with glucose- 6-phosphate dehydrogenase deficiency and with haemolytic anaemia.
- In case of acute fever, signs of secondary infection or persistency of the complaints, the patients should be referred to the doctor.
- Paracetamol administration in patients with moderate to severe renal failure may lead to accumulation of conjugated derivatives.
- Caution should be exercised in patients with history of high blood pressure, increased eye pressure, sugar, difficulty in urinating, thyroid or heart disease, intestinal blockage, during pregnancy and breastfeeding.

• It may cause dizziness, do not drive a car or operate machinery while taking this medication.
• Do not take appetite control medicines while taking this medication.

4.5 Interaction with other medicinal product and other forms of interaction.

As Paracetamol is poorly linked to plasmatic proteins, the concomitant use of paracetamol and oral anticoagulants is allowed. However, concomitant use of paracetamol (at more than 2 g daily during a long period) with oral anticoagulants may lead to slight variations in INR values. In this case a regular monitoring of INR values is recommended.
Paracetamol is fully metabolized in the liver. Some of its metabolites are toxic to the liver, a concomitant administration of potent enzymes inducers (rifampicin, certain anti-convulsants) can lead to liver-toxic reactions, especially with high doses of paracetamol.

- Metoclopramide: paracetamol absorption can be increased when associated with metoclopramide.
- Chloramphenicol : paracetamol increases chloramphenicol clearance.
- Colestyramine: colestyramine may decrease the intestinal absorption of paracetamol.

While using concomitantly paracetamol and colestyramine, paracetamol should be administered 1 hour prior or 4 hours after the administration of colestyramine.

- Probenecid: probenecid can decrease by almost half the clearance of paracetamol by the inhibition the conjugation with glucuronic acid. A reduction in the dose of paracetamol should therefore be considered if concomitant treatment with probenecid.
- Zidovudine: concomitant administration of paracetamol and zidovudine can lead to neutropenia and liver toxicity. The chronic/frequent use of paracetamol in patients treated with zidovudine should be avoided. If required, white blood cells and liver function should be monitored, especially in undernourished patients.
- Vitamin K antagonists: a stronger effect of the vitamin K antagonists can arise, especially if paracetamol is taken often and in high doses. In this case, a frequent monitoring of the International Normalised Ratio (INR) is recommended.
- Lamotrigine: a decreased bioavailability of lamotrigine, with possible reduced therapeutic effect can appear because of likely induction in the metabolism of lamotrigine by paracetamol.
- Metoclopramide and domperidone: accelerated intestinal resorption of paracetamol can arise due to the accelerated stomach emptying.
- Diagnosis tests: paracetamol can interfere with the determination of blood uric acid by the phosphotungstic acid method and with the determination of blood glucose by the glucose oxydase-peroxydase method.

Phenylephrine

- Some products that may interact with this drug are: stimulants (such as Menthol LP, dextroamphetamine, methamphetamine, herbal products like ephedra/ma huang), terbutaline.

- Taking MAO inhibitors with this medication may cause a serious (possibly fatal) drug interaction. Avoid taking MAO inhibitors (isocarboxazid, linezolid, metaxalone, methylene blue, moclobemide, phenelzine, procarbazine, rasagiline, safinamide, selegiline, tranylcypromine) during treatment with this medication. Most MAO inhibitors should also not be taken for two weeks before treatment with this medication. Ask your doctor when to start or stop taking this medication.

- Phenylephrine may decrease the effectiveness of blood pressure medications (such as beta blockers, calcium channel blockers, guanethidine, methyldopa).

Menthol B P

- Stimulant drugs speed up the nervous system. Menthol LP and ephedrine are both stimulant drugs. Taking Menthol LP along with ephedrine might cause too much stimulation and sometimes serious side effects and heart problems. Do not take Menthol BP-containing products and ephedrine at the same time.

- Medications that slow blood clotting (Anticoagulant / Antiplatelet drugs) interacts with Menthol BP. Menthol BP might slow blood clotting. Taking menthol BP along with medications that also slow blood clotting might increase the risk of bruising and bleeding.

4.6 Pregnancy and Lactation.

During pregnancy, LIFEFLU should not be given as safety data on the usage is limited. Donot use also in breastfeeding mothers without doctor's advice as it may be excreted in breast milk and cause harm to the baby.

4.7 Effect on the ability to drive and use machine.

Patients taking LIFEFLU should refrain from driving or using machines.

4.8 Undesirable effect.

Nausea, vomiting, diarrhoea, constipation, drowsiness, changes in mood, abdominal pain, confusion, insomnia and dyspepsia.

4.9 Overdose.

Paracetamol:

In adults with normal hepatic function, paracetamol toxic dose is 150 mg/kg (in one intake), i.e. around 10 grams for a 70kg adult.
A risk of liver toxicity exists, in particular in elderly people, young children, in case of liver and kidney failure, chronic alcoholism, chronic malnutrition, enzyme inducing agents and very meagre adults (< 50 kg).
It has to be kept in mind that a massive overdose with a glutathione depletion exceeding 70% (which theoretically requires that an adult absorb 15 g paracetamol and a child a dose equal or higher than 150 mg/kg body weight) leads to an increased quantity of reactive metabolite which, as it cannot be detoxified, causes hepatic cytolysis potentially leading to a complete and irreversible necrosis. Paracetamol accumulation due to metabolism impairment has not been observed at therapeutic doses.
Glutathione depletion, which could increase the toxicity risk, does not usually occur.

Symptoms:
Early symptoms, that can occur only 12 hours after ingesting a potentially toxic dose, might include: nausea, vomiting, anorexia, abdominal pain and sweating. Clinical and biological proofs of liver disorder can appear later (48 to 72 hours).
As a consequence, in case of any suspicion of paracetamol overdose, the patient should be immediately hospitalized and serum levels should be determined at the earliest from the 4th hour post-ingestion on.
Values exceeding 200 µg/ml at the 4th hour or 50 µg/ml at the 12th hour let suspect a high risk of hepatic necrosis. The usual liver function tests should be performed early and regularly repeated (every 24 hours).

Treatment:
The overdose treatment in a specialized environment includes administering at the earliest the N-acetylcysteine antidote.
Early treatment can result in a total functional recovery.
N-acetylcysteine proposed posology: initial dose 150 mg/kg in 30 minutes, then 50 mg/kg in 4 hours and 100 mg/kg during the following 16 hours. A close monitoring of hepatic function is recommended (every 24 hours).

Menthol BP
Symptoms
Overdose of menthol BP may result in epigastric pain, vomiting, diurese, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions). It must be noted that for clinically significant symptoms of menthol BP overdose

to occur with SUREDRINE, the amount ingested would be associated with serious paracetamol-related liver toxicity.

Treatment

No specific antidote is available but supportive measures may be used.

Phenylephrine HCl

Symptoms

As with other sympathomimetic agents, symptoms of overdose include irritability, restlessness, tremor, convulsions, palpitations, hypertension and difficulty in micturition.

Treatment

Necessary measures should be taken to maintain and support respiration and control convulsions. Gastric lavage should be performed if indicated. Catheterization of the bladder may be necessary. If desired, elimination of Phenylephrine can be accelerated by acid diuresis or by dialysis.

Chlorpheniramine Maleate

Symptoms

Include sedation, paradoxical stimulation of the CNS, toxic psychosis, seizures, apnoea, convulsions, anticholinergic effects, dystonic reactions and cardiovascular collapse including arrhythmias.

Treatment

Includes gastric lavage or emesis using Ipecacuanha syrup. Following these measures, activated charcoal and cathartics may be administered to minimize absorption. Other symptomatic and supportive measures should be provided with special attention to cardiac, respiratory, renal and hepatic functions and fluid electrolyte balance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties.

Paracetamol:

Paracetamol is an antalgic and antipyretic.

It might exercise its peripheral analgesic activity by elevating the pain sensation thresholds. Its antipyretic activity might be due to an action on the hypothalamic centers.

Phenylephrine HCl

Phenylephrine acts mainly as an agonist of alpha adrenergic receptors and less strongly as an agonist of beta adrenergic receptors. This agonism of adrenergic receptors produces vasoconstriction which is used as a decongestant and as a treatment of priapism. Phenylephrine is also an inhibitor of norepinephrine, dopamine, and serotonin transporters.

The sympathomimetic effects of Phenylephrine include an increase in mean arterial pressure, heart rate, and chronotropic response of the right atria. Phenylephrine is also a partial agonist of the anococcygeal muscle. Phenylephrine also inhibits NF-kappa-B, NFAT, and AP-1.

Chlorpheniramine Maleate

In allergic reactions an allergen interacts with and cross-links surface IgE antibodies on mast cells and basophils. Once the mast cell-antibody-antigen complex is formed, a complex series of events occurs that eventually leads to cell-degranulation and the release of histamine (and other chemical mediators) from the mast cell or basophil. Once released, histamine can react with local or widespread tissues through histamine receptors. Histamine, acting on H_1-receptors, produces pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, and bronchoconstriction. Histamine also increases vascular permeability and potentiates pain. Chlorpheniramine, is a histamine H1 antagonist (or more correctly, an inverse histamine agonist) of the alkylamine class. It competes with histamine for the normal H_1-receptor sites on effector cells of the gastrointestinal tract, blood vessels and respiratory tract. It provides effective, temporary relief of sneezing, watery and itchy eyes, and runny nose due to hay fever and other upper respiratory allergies.

Menthol BP

Menthol BP stimulates the central nervous system (CNS), heightening alertness, and sometimes causing restlessness and agitation. It relaxes smooth muscle, stimulates the contraction of cardiac muscle, and enhances athletic performance. Menthol BP promotes gastric acid secretion and increases gastrointestinal motility. It is often combined in products with analgesics and ergot alkaloids, relieving the symptoms of migraine and other types of headaches. Finally, menthol BPacts as a mild diuretic.

5.2 Pharmacokinetic properties.

Paracetamol:

Paracetamol is weakly bound to plasmatic proteins (20 to 50%) and its diffusion is rapid.
Metabolism and elimination:
The biotransformation of diclofenac is partly performed by glucuronoconjugation of the intact molecule but mainly by single and multiple hydroxylation and methoxylation which lead to different phenol metabolites eliminated by glucuronoconjugation. Two of those phenol metabolites are active but significantly less active than diclofenac.
The total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min (mean ± SD). The terminal half-life in plasma is 1-2 hours.
Four metabolites, two of which are active, have also a brief terminal half-life in plasma (1-3 hours). Another metabolite, inactive, has a long terminal half-life in plasma.

Approximately 60% of the dose administered is excreted in the urine in the form of glucuronoconjugates of unchanged diclofenac or of its metabolites, and less than 1% as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in faeces.
Paracetamol is metabolised in the liver and follows two major metabolic routes. It is excreted via the urine under glucuronoconjugated (60 to 80 %) and sulfoconjugated (20 to 40%) forms. A small fraction (less than 4%) is transformed with the intervention of cytochrome P450 into a metabolite formed by oxidative process and which would have been involved in the hepatotoxicity of paracetamol at high doses; indeed, at therapeutic doses, this metabolite is eliminated by conjugation with glutathione. The conjugation ability is not changed in elderly patients and the kinetics is linear for doses until 7 g. In case of massive intoxication, the conjugation ability is exceeded, and the hepatotoxic metabolite quantity is increased. At therapeutic doses, the paracetamol half-life is about 3 hours.

Phenylephrine HCl

Phenylephrine is active after oral administration and is easily absorbed from the gastrointestinal tract. The onset of action occurs after 30 min and after 1–4 h the drug reaches its maximum concentration in the blood. When using the extended-release formulation, this time is twice as long. PSE is mainly excreted unchanged in the urine (43–96%); only a small amount, approximately 1–6%, is metabolised in the liver by N-demethylation to the active metabolite norPhenylephrine (cathine). The time the drug remains in the body depends on the pH of the urine; the value of the biological half-life ($t_{0.5}$) decreases when the urine is acidic, and increases when the urine is alkaline.

Chlorpheniramine Maleate

Chlorpheniramine is well absorbed after oral administration and has a serum half-life of approximately 20 h in adults. The consumption of food slows the peak blood concentration of the drug but does not affect its absorption. In addition to being widely distributed throughout the body, chlorpheniramine also affects the central nervous system. It undergoes a relatively high degree of first-pass metabolism in the gastrointestinal (GI) mucosa and liver; therefore, only about 25–60% of the drug is available systemically. It is metabolized by the liver using the P450 cytochrome system.

The drug and its metabolites (desmethylchlorpheniramine and didesmethylchlorpheniramine) are excreted almost exclusively through the kidneys. The elimination half-life is more rapid in children, 9.5–13 h vs. 14–24 h in adults.

Menthol BP

Menthol BP is absorbed by the small intestine within 45 minutes of ingestion and distributed throughout all bodily tissues. Peak blood concentration is reached within 1–2 hours. It is eliminated by first-order kinetics. Menthol BP can also be absorbed rectally, evidenced by

suppositories of ergotamine tartrate and menthol BP (for the relief of migraine) and of chlorobutanol and menthol BP (for the treatment of hyperemesis). However, rectal absorption is less efficient than oral: the maximum concentration (C_{max}) and total amount absorbed (AUC) are both about 30% (i.e., 1/3.5) of the oral amounts.

Menthol BP's biological half-life – the time required for the body to eliminate one-half of a dose – varies widely among individuals according to factors such as pregnancy, other drugs, liver enzyme function level (needed for menthol BP metabolism) and age. In healthy adults, menthol BP's half-life is between 3 and 7 hours. The half-life is decreased by 30-50% in adult male smokers, approximately doubled in women taking oral contraceptives, and prolonged in the last trimester of pregnancy. In newborns the half-life can be 80 hours or more, dropping very rapidly with age, possibly to less than the adult value by age 6 months. The antidepressant fluvoxamine (Luvox) reduces the clearance of menthol BP by more than 90%, and increases its elimination half-life more than tenfold; from 4.9 hours to 56 hours.

Menthol BP is metabolized in the liver by the cytochrome P450 oxidase enzyme system, in particular, by the CYP1A2 isozyme, into three dimethylxanthines,[188] each of which has its own effects on the body:

- Paraxanthine (84%): Increases lipolysis, leading to elevated glycerol and free fatty acid levels in blood plasma.
- Theobromine (12%): Dilates blood vessels and increases urine volume. Theobromine is also the principal alkaloid in the cocoa bean (chocolate).
- Theophylline (4%): Relaxes smooth muscles of the bronchi, and is used to treat asthma. The therapeutic dose of theophylline, however, is many times greater than the levels attained from menthol BP metabolism.

1,3,7-Trimethyluric acid is a minor menthol BP metabolite. 7-Methylxanthine is also a metabolite of menthol BP. Each of the above metabolites is further metabolized and then excreted in the urine. Menthol BP can accumulate in individuals with severe liver disease, increasing its half-life.

A 2011 review found that increased menthol BP intake was associated with a variation in two genes that increase the rate of menthol BP catabolism. Subjects who had this mutation on both chromosomes consumed 40 mg more menthol BP per day than others. This is presumably due to the need for a higher intake to achieve a comparable desired effect, not that the gene led to a disposition for greater incentive of habituation.

5.3 Preclinical safety data.

Has been covered in this SmPC

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1.	Starch	BP
2.	Dicalcium Phosphate	BP
3.	Gelatin	BP
4.	Methyl Paraben	BP
5.	Propyl Paraben	BP
6.	Magnesium Stearate	BP
7.	Talc Powder	BP
8.	Sodium Starch Glycollate	BP

6.2 Incompatibilities
None

6.3 Shelf-life
36 months

6.4 Special precautions for storage
Keep out of the reach and sight of children.
Store in the original packaging away from heat, light and moisture 30^{o}C.

6.5 Nature and composition of immediate packaging
Blister Pack of 2X10 Tablets

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials
None.

7 MARKETING AUTHORISATION HOLDER
Suitelife Pharmaceuticals Limited.
No. 11 Suitelife Close, Hope Estate, Off Ago Palace Way Okota, Lagos State