Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Ibugesic (Ibuprofen 400 mg & Paracetamol 325 mg Tablets)

2. Qualitative and quantitative composition

Each tablet contains Ibuprofen BP 400 mg & Paracetamol BP 325 mg.

3. Pharmaceutical form

White caplet shape uncoated Tablets

4. Clinical particulars

4.1 Therapeutic indications

Ibugesic tablets are indicated in the treatment of minor aches and pains such as headaches, toothaches, muscular aches, backaches and pain due to inflammation and for reduction of fever due to any of the above conditions

4.2 Posology and method of administration

Posology

Adults and Children (12 Years of Age and Over): One tablet thrice daily.

Method of Administration
For oral administration.

4.3 Contraindications

This product is contraindicated:

- In patients with a known hypersensitivity to ibuprofen, paracetamol or any other excipients in the product.
- In concomitant use with other Paracetamol-containing products – increased risk of serious adverse effects.
- In patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, asthma, rhinitis, or urticaria) associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- In patients with active, or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

• In patients with a history of, or an existing gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs.
• Patients with defects in coagulation.
• In patients with severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV).
• In concomitant use with other NSAID containing products, including cyclo-oxygenase-2 (COX-2) specific inhibitors and doses of acetylsalicylic acid above 75 mg daily – increased risk of adverse reactions.
• During the last trimester of pregnancy due to risk of premature closure of the fetal ductus arteriosus with possible pulmonary hypertension.

4.4 Special warnings and precautions for use

Paracetamol

- Keep out of the reach of children.
- Do not take if allergic to paracetamol.
- Patients should contact their healthcare provider if symptoms persist (if the pain lasts for more than 10 days; if there is redness or fever that lasts for more than 3 days).
- Paracetamol should be given with care to patients with impaired kidney or liver function.
- Large doses should be avoided in patients with hepatic impairment. Paracetamol overdose may harm the liver.
- Do not exceed the recommended dose.
- It should be given with care to patients with alcohol dependence.
- Paracetamol provides symptomatic relief only; additional therapy to treat the cause of the pain or fever should be instituted when necessary.

Ibuprofen

- Patients with heart disease and high blood pressure should not take this drug unless directed by a physician.
- Caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.
- Caution in patients prone to GI tract irritation, particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the GI tract such as ulcerative colitis and Crohn's disease.
- The elderly and patients with impaired renal function, heart failure, liver dysfunction, and those taking diuretics are at increased risk for renal toxicity.
- If persistent urinary symptoms (bladder pain, dysuria, urinary frequency), haematuria and cystitis occur, the drug should be stopped immediately.
- Ibuprofen use during nursing should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

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.
This product may interfere with some medicines. These include the following:

- Warfarin, a medicine used to prevent blood clots
- Medicines to treat epilepsy or fits
- Chloramphenicol, an antibiotic used to treat ear and eye infections
- Probenecid, a medicine used to treat gout
- Zidovudine, a medicine used to treat HIV (the virus that causes AIDs)
- Medicines used to treat tuberculosis, such as isoniazid
- ASA, salicylates or other NSAIDs
- Medicines to treat high blood pressure or other heart conditions

Ibuprofen
Serious Drug Interactions

- Use with (ASA) or other NSAIDs, including ibuprofen, may result in possible additive adverse side effects.
- Use with acetaminophen, may increase the risk of adverse renal effect.
- Use with anticoagulants may increase the risk of GI adverse events (e.g. bleeding).
- Use with hypoglycaemic agents (oral agents and insulin) may increase the risk of hypoglycaemia.
- Use with antihypertensives may interfere with circulatory control.
- Use with diuretics may reduce the diuretic effect.
- Use with methotrexate may increase the risk of methotrexate toxicity.
- Use with lithium may increase the risk of lithium toxicity.

4.6 Pregnancy and Lactation

Ibuprofen

No evidence specifically identifies exposure to analgesic doses of ibuprofen as a cause of harm to either the mother or foetus during pregnancy. NSAIDs in general, however, are known to affect the action of prostaglandin synthetase, which could alter a variety of the physiological functions of prostaglandins or platelets during delivery such as facilitating uterine contraction in the mother, closure of the ductus arteriosus in the foetus, and platelet-related haemostasis. Patients should, therefore, be advised not to use ibuprofen during pregnancy without the advice of a physician, particularly during the last trimester. Clinical information is limited on the effects of ibuprofen in pregnancy.

Paracetamol

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 indicates neither malformative nor foeto/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.

Lactating Women

Paracetamol
Paracetamol is excreted in breast milk but not in a clinically significant amount, and available published data do not contraindicate breastfeeding. Therefore, it is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose of this product.

Ibuprofen
Pharmacokinetic studies indicated that following oral administration of ibuprofen 400 mg, the level of drug that appeared in breast milk was below detection levels of 1 µg/ml. The amount of ibuprofen to which an infant would be exposed through this source was considered negligible. However, since the absolute safety of ibuprofen ingested under these circumstances has not been determined, nursing mothers should be advised to consult a physician before using ibuprofen.

4.7 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.

4.8 Undesirable effects

Paracetamol

The following CIOMS frequency rating is used, when applicable: very common: ≥10%; common:
≥1 and <10%; uncommon: ≥0.1 and <1%; rare: ≥0.01 and <0.1%; very rare: <0.01%; not known (cannot be estimated from available data).
Blood and Lymphatic System Disorders
VERY RARE: thrombocytopaenia, neutropaenia, leucopaenia
NOT KNOWN: agranulocytosis, haemolytic anaemia in patients with underlying glucose 6- phosphate-dehydrogenase deficiency.
Immune System Disorders

Ibuprofen

Infections and Infestations
Very rare: Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. This is possibly associated with the mechanism of action of the NSAIDs.
Uncommon: Hypersensitivity reactions with skin rashes and itching, as well as asthma attacks (possibly with drop in blood pressure).

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5 g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:

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

b) Regularly consumes alcohol in excess of recommended amounts.

c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

d) Patients taking isoniazid.

Symptoms

Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function tests become abnormal. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema 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.

In serious poisoning 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 and liver damage may occur.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

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.

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.

Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

Ibuprofen

In children ingestion of more than 400 mg/kg of Ibuprofen 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 and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning 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 and liver damage may occur if there is a co-incident of dehydration. Exacerbation of asthma is possible in asthmatics.

Management

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 if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC Code: M01AE51 – Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations.

The pharmacological actions of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception and antipyresis than the single actives alone.

Ibuprofen is an NSAID that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Prostaglandins sensitise nociceptive afferent nerve terminals to mediators such as bradykinin. Ibuprofen therefore elicits an analgesic effect through peripheral inhibition of the cycloxygenase-2 (COX-2) isoenzyme with a subsequent reduction in sensitisation of nociceptive nerve terminals. Ibuprofen has also been shown to inhibit induced-leucocyte migration into inflamed areas. Ibuprofen has a pronounced action within the spinal cord due, in part, to the inhibition of COX. Ibuprofen's antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swellings and fever.

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 was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), 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 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).

Paracetamol's exact mechanism of action is still not completely defined; however, there is considerable evidence to support the hypothesis of a central antinociceptive effect. Various biochemical studies point to inhibition of central COX-2 activity. Paracetamol may also stimulate the activity of descending 5-hydroxytryptamine (serotonin) pathways that inhibit nociceptive signal transmission in the spinal cord. Evidence has shown that paracetamol is a very weak inhibitor of peripheral COX-1 and 2 isoenzymes.

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

This product is especially suitable for pain which requires stronger pain relief than ibuprofen 400 mg or paracetamol 1000 mg alone, and faster pain relief than ibuprofen.

5.2 Pharmacokinetic properties

Paracetamol:

Absorption: Paracetamol has 88% oral bioavailability and reaches its highest plasma concentration 90 minutes after ingestion. Peak blood levels of free acetaminophen are not reached until 3 hours after rectal administration of the suppository form of acetaminophen and the peak blood concentration is approximately 50% of the observed concentration after the ingestion of an equivalent oral dose (10-20 mcg/mL).
Metabolism: Paracetamol is the major metabolite of phenacetin and acetanilid. Acetaminophen is mainly metabolized in the liver by first-order kinetics and its metabolism of comprised of 3 pathways: conjugation with glucuronide, conjugation with sulfate, and oxidation through the cytochrome P450 enzyme pathway, mainly CYP2E1, to produce a reactive metabolite (N-acetyl- p-benzoquinone imine or NAPQI). At normal therapeutic doses, NAPQI undergoes fast conjugation with glutathione and is subsequently metabolized to produce both cysteine and mercapturic acid conjugates.

Ibuprofen:

Absorption: It is very well absorbed orally and the peak serum concentration can be attained in 1 to 2 hours after extravascular administration. When ibuprofen is administered immediately after a meal there is a slight reduction in the absorption rate but there is no change in the extent of the absorption.

Metabolism: Ibuprofen is rapidly metabolized and biotransformed in the liver to the formation of major metabolites which are the hydroxylated and carboxylated derivatives.10 As soon as it is absorbed, the R-enantiomer undergoes extensive enantiomeric conversion (53-65%) to the more active S-enantiomer in vivo by the activity of alpha-methylacyl-CoA racemase.

5.3 Preclinical safety data

The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments and in humans from extensive clinical experience.

6. Pharmaceutical Particulars

6.1 List of Excipients

Excipients	Specification
Maize Starch	BP
Sodium Starch Glycolate	BP
Providone K 30	BP
Methyl Paraben	BP
Propyl Paraben	BP
Purified Water	BP
Colloidal Anhydrous Silica	BP
Magnesium Stearate	BP
Puridied Talc	BP
Crosscarmellose Sodium	BP
Stearic Acid	BP

6.2 Incompatibilities

None known

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

Store below 30^0C. Protect from light. Keep out of reach of children.

6.5 Nature and Content of container

10 Tablets in one ALU-PVC blister. 1 such blister in one carton with insert.

6.6 Special precautions for disposal and other handling

No special requirements. Any expired or unused drug should be disposed of as per local regulatory requirements.

7. Marketing Authorization Holder

SHALINA HEALTHCARE DMCC

8. Marketing Authorization Number

CTD9472

9. Date of first authorization/renewal of the authorization

1st December 2023

10. Date of revision of the text

11th May 2025