Provas® Duo

(Paracetamol + Ibuprofen)

1. NAME OF THE PRODUCT

Provas® Duo (Paracetamol + Ibuprofen) Tablet 500mg/200mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Provas® Duo Tablet 500mg/200mg

Each film coated tablet contains:

Paracetamol BP……..... 500mg

Ibuprofen BP……..... 200mg

3. PHARMACEUTICAL FORM

Tablet

Appearance:

White to off white color, pearlescent, film coated oval shaped tablets, having both sides plain.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

For the temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever.

Provas® Duo is especially suitable for pain which requires stronger analgesia than ibuprofen or paracetamol alone.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology: For short term-use only. Lowest effective dose should be used for the shortest duration necessary to relieve symptoms. Patient should consult a doctor if the symptoms persist or worsen or required for more than 3 days.

Adults: One tablet up to three times per day with water; leave at least six hours between doses. If one tablet does not control symptoms, a maximum of two tablets may be taken up to three times a day; leave at least six hours between doses.

Do not take more than six tablets (3000mg paracetamol, 1200mg ibuprofen) in any 24 hours period. To minimize side effects, it is recommended that patients take with food.

Elderly: No special dosage modifications are required. The elderly is at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, lowest effective dose should be used for the shortest

possible duration; patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy. Not for use by children under 18 years.

Method of Administration:

For oral administration.

4.3. CONTRAINDICATIONS:

- In patients with a known hypersensitivity to active substances or to any of the excipients.
- 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.
- In 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 75mg 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:

Do not exceed the recommended dose.

Paracetamol: Greater overdose hazards in non-cirrhotic alcoholic liver disease. Even if the patient feels well, because of the risk of delayed, serious liver damage.

Ibuprofen: Undesirable effects may be minimized by using the lowest effective dose for the shortest duration with food.

Elderly: Increased frequency of adverse reactions especially GI bleeding and perforation which may be fatal.

Caution is required in patients with certain conditions:

Respiratory disorders: History of bronchial asthma or allergic disease, NSAIDs have been reported to precipitate bronchospasm.

SLE and mixed connective tissue disease: There may be an increased risk of aseptic meningitis.

Cardiovascular and cerebrovascular effects: Appropriate monitoring required for patients with a history of hypertension and/or mild to moderate

congestive heart failure as fluid retention, hypertension and edema is known to occur in association with NSAID therapy.

Cardiovascular, renal and hepatic impairment: Patients at 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.

Gastrointestinal effects: NSAIDS should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for patients with GI bleeding and perforation, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk. Caution should be advised and discontinue 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 antiplatelet agents such as acetylsalicylic acid.

Severe skin reactions: Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, are known to occur rarely in association with the use of NSAIDs. Acute generalized exanthematous pustulosis (AGEP) is known to occur in relation to ibuprofen-containing products. Use of this product should be discontinued at the first appearance of signs and symptoms such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Masking of symptoms of underlying infections: This product can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome. When this medicine is administered for fever or pain relief, monitoring is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Impaired female fertility: In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Paracetamol/ibuprofen is contraindicated in combination with other paracetamol containing products.

Paracetamol/Ibuprofen is contraindicated in combination with:

- ***Acetylsalicylic acid:*** Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects, unless low-dose acetylsalicylic acid (not above 75mg daily) has been advised by a doctor.

Paracetamol/ibuprofen should be used with caution in combination with:

- ***Cholestyramine:*** The speed of absorption of paracetamol is reduced. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.
- ***Metoclopramide and Domperidone:*** The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.
- ***Warfarin:*** The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Paracetamol/ibuprofen should be used with caution in combination with:

- ***Anticoagulants:*** NSAIDs may enhance the effects of anticoagulants i.e. warfarin.
- ***Antihypertensives (ACE inhibitors and angiotensin II antagonists) and diuretics:*** In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. 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 may increase the risk of nephrotoxicity of NSAIDs.
- ***Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs):*** Increased risk of gastrointestinal bleeding.
- ***Cardiac glycosides:*** NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
- ***Cyclosporine:*** Increased risk of nephrotoxicity.
- ***Corticosteroids:*** Increased risk of gastrointestinal ulceration or bleeding.
- ***Lithium & methotrexate:*** Decreased elimination of lithium and methotrexate.
- ***Mifepristone:*** NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
- ***Quinolone antibiotics:*** Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
- ***Tacrolimus:*** Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- ***Zidovudine:*** Increased risk of haematological toxicity with NSAIDS are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
- ***Chloramphenicol:*** An antibiotic used to treat ear and eye infections.
- ***Probenecid:*** A medicine used to treat gout.

4.6. PREGNANCY AND LACTATION:

Pregnancy: There is no experience of use of this product in humans during pregnancy. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency. In view of the known effects of NSAIDs on the fetal cardiovascular system (risk of closure of ductus arteriosus), use in the last trimester is contraindicated. The onset of labor may be delayed, and duration increased with an increased bleeding tendency in both mother and child. NSAIDs should not be used during the first two trimesters of pregnancy or labor unless the potential benefit to the patient outweighs the potential risk to the fetus. Therefore, if possible, the use of this product should be avoided in the first six months of pregnancy and contraindicated in the last three months of pregnancy.

Lactation: Ibuprofen and its metabolites can pass in very small amounts into the breast milk. No harmful effects to infants are known. Paracetamol is excreted in breast milk but not in a clinically significant amount. Therefore, it is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose.

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:

Common: Abdominal pain, vomiting, diarrhoea, nausea, dyspepsia and abdominal discomfort, alanine aminotransferase increased, gamma-glutamyltransferase increased and liver function tests abnormal with paracetamol, blood creatinine increased, blood urea increased.

Uncommon: Hypersensitivity with urticaria and pruritus, headache and dizziness, peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melena, haematemesis, mouth ulceration, exacerbation of colitis and crohn's disease, gastritis, pancreatitis, flatulence and constipation, various skin rashes, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine phosphokinase increased, haemoglobin decreased and platelet count increased.

Very rare: Severe hypersensitivity reactions. Symptoms can include facial, tongue and throat swelling, dyspnea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock), confusion, depression and hallucinations, aseptic meningitis, paresthesia, optic neuritis and somnolence, visual disturbance, tinnitus, vertigo, cardiac failure and edema, hypertension, respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm

and dyspnea, abnormal liver function, hepatitis and jaundice, nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, acute and chronic renal failure, fatigue and malaise.

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalized exanthematous pustulosis (AGEP), photosensitivity reactions.

4.9. OVERDOSE:

Paracetamol: Liver damage is possible in adults who have taken 10g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage.

Management: Immediate 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-acetyl cysteine may be used up to 24 hours after ingestion of paracetamol. 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 immediately in hospital.

Ibuprofen: In children ingestion of more than 400mg/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.

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:

Therapeutic Classification: Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations.

ATC Code: M01AE51.

Mechanism of action: The pharmacological actions of paracetamol and ibuprofen 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.

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. Ibuprofen is an NSAID known to elicit an analgesic effect through peripheral inhibition of the cycloxygenase-2 (COX-2) isoenzyme with a

subsequent reduction in sensitization of nociceptive nerve terminals; 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. Its 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.

5.2. PHARMACOKINETIC PROPERTIES:

Paracetamol: Readily absorbed from the gastrointestinal tract. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent. Plasma levels of paracetamol from this product are detected from 5 minutes with peak plasma concentrations occurring at 0.5-0.67 hours after ingestion on an empty stomach. When this product was taken with food peak paracetamol plasma levels were lower and delayed by a median of 55 minutes, but overall extent of absorption was equivalent. Paracetamol is metabolized in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life is approximately 3 hours. No significant differences in the paracetamol pharmacokinetic profile are observed in the elderly.

Ibuprofen: Well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Plasma levels of ibuprofen from this product are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty stomach.

Ibuprofen is metabolized 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. The elimination half-life is approximately 2 hours.

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

The bioavailability and pharmacokinetic profiles of paracetamol and ibuprofen taken are not altered when taken in combination as a single or repeat dose.

5.3. PRECLINICAL SAFETY DATA:

The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments. There are no new preclinical data of relevance which are additional to the data already presented in this Summary of Product Characteristics. Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Microcrystalline cellulose
- Croscarmellose sodium
- Silicon dioxide fumed
- Stearic acid
- Magnesium stearate
- Opadry silver
- Purified Water

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Keep out of the reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Alu/PVC blister, pack size is 30's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

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

6.7. DRUG PRODUCT SPECIFICATIONS:

Innovator's Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

108579

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

11th June, 2021

10. DATE OF REVISION OF THE TEXT

پرووَاس® ڈیو ٹیبلٹ

(پیراسیٹامول + آئبوپروفِن)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری

سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔