1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed.

1. Name of the medicinal product

Tobez Capsules (Ibprofen, Paracetamol & Caffeine Capsules 555 mg)

2. Qualitative and quantitative composition

Each capsule contains

Ibuprofen BP 200 mg

Paracetamol BP 325 mg

Caffeine BP 30 mg

3. Pharmaceutical form

Hard Capsules.

Pink colored capsule

4. Clinical particulars

4.1 Therapeutic indications

Paracetamol is indicated for temporary relief of acute pain associated with: headache (not migraine), backache, dental pain, muscular pain and sore throat. Ibuprofen is indicated for fever. Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

4.2 Posology and method of administration

Adults (18 years and older)

For headache:

The usual recommended dosage is 1 Capsule; an additional Capsule can be taken, with 4 to 6 hours between doses. In case of more intense pain, it is possible to take 2 Capsules. If needed, an additional 2 Capsules can be taken, with 4 to 6 hours between doses.

Tobez is intended for episodic use, up to 4 days for headache.

For migraine:

Take 2 Capsules when symptoms appear. If needed an additional 2 Capsules can be taken, with 4 to 6 hours between doses.

Tobez is intended for episodic use, up to 3 days for migraine.

For both headache and migraine, intake must be limited to 6 Capsules in 24 hours. The medicinal product must not be used for a longer period or at a higher dosage without first consulting a doctor. Drink a full glass of water with each dose.

Children and adolescents (under 18 years of age)

Safety and efficacy of Tobez in children and adolescentshave not been evaluated. Use of Tobez in children and adolescents is therefore not recommended.

Elderly

Based on general medical considerations, caution should be exercised in the elderly,particularly in elderly patients with low body weight.

Hepatic and renal impairment

The effect of hepatic or r enal di sease on thep har m a co kin et ics of Excedri n has not b een eval uated. D ue to the m echanism of ac tion of ac etylsalicylic acid (aspirin) and paracetamol, this could enhance the renal or hepatic impairment. Thus, Tobez is contraindicated in patients with severe hepatic or renal failure, and should be used with caution in patients with mild to moderate hepatic or renal impairment.

4.3 Contraindications

Hypersensitivity to Ibprofen, paracetamol, caffeine or to any of the excipients. Patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory drugs such as diclofenac or ibuprofen.

- Active gastric or intestinal ulcer, gastrointestinal bleeding or perforation and in patients with a history of peptic ulceration.
- Haemophilia or other haemorrhagic disorders
- Severe hepatic or renal failure
- Severe cardiac failure
- Intake of more than 15 mg methotrexate per week (
- Last trimester of pregnancy

4.4 Special warnings and precautions for use

- Tobez should not be taken together with products containing acetylsalicylic acid or paracetamol.
- As with other acute migraine therapies, before treating a suspected migraine in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions.
- Patients who experience vomiting with > 20% of their migraine attacks or who require bedrest with >50% of their migraine attacks should not use Tobez.
- If the patient gets no migraine relief from the first 2-Capsule dose of Tobez, the patient should seek the advice of a physician.
- 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 (MOH) should be suspected in patients who have chronic headaches (15 days or more per month) with concurrent overuse of headache medications for more than 3 months. Therefore, this product should not be used on more than 10 days per month for more than 3 months.
- Caution should be exercised in patients at risk of being dehydrated (e.g. by sickness, diarrhoea, or before or after major surgery).
- Tobez may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Due to the presence of paracetamol:

- Tobez should be given with care to patients with impaired renal or hepatic function or alcohol dependence.
- The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicinal products or medicinal products that induce liver microsomal enzymes (e.g. rifampicin, isoniazide, chloramphenicol, hypnotics and antiepileptics including phenobarbital, phenytoin and carbamazepine). Patients with history of alcohol abuse are at special risk of hepatic damage.
- Patients should be warned not to take other products containing paracetamol concurrently due to the risk of severe liver damage in case of overdose
- Alcoholic beverages should be avoided while taking this medicine because alcohol use in combination with paracetamol may cause liver damage. Paracetamol should be given with caution to patients with alcohol dependence. Due to the presence of caffeine:

- Tobez should be given with care to patients with gout, hyperthyroidism and arrhythmia.

- The patient should limit the use of caffeine containing products when taking Tobez, as excess caffeine may cause nervousness, irritability, sleeplessness and occasionally rapid heartbeat.

4.5 Interaction with other medicinal products and other forms of interaction

This product (like any other paracetamol and/or ibuprofen containing products) should not be taken in combination with other paracetamol and/or ibuprofen products due to increased risk of serious adverse effects.

Ibuprofen:

As with other Ibuprofen containing products, the following combinations hould be avoided:

The dicumarol group:

NSAIDs may increase the effect of anticoagulants such as warfarin Experimental studies show that ibuprofen reinforces the effects of warfarin on bleeding time. NSAIDs and the dicumarol group are metabolised by the same enzyme, CYP2C9.

Anti-platelet agent:

NSAIDs should not be combined with antiplatelet agents such as ticlopidine due to the additive inhibition of the platelet function.

Methotrexate:

NSAIDs inhibit the tubular secretion of methotrexate and some metabolic interaction with reduced clearance of methotrexate may also occur as a result. Accordingly, in high-dose treatment with methotrexate one should always avoid prescribing NSAIDs.

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 cardio-protective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use.

Cardiac glycosides:

NSAIDs can exacerbate heart failure, reduce glomerular filtration and increase plasma cardiac glycoside (e.g. digoxin) levels.

Mifepristone:

A decrease of the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid. Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy

Sulphonylureas:

There are rare reports of hypoglycaemia in patients on sulphonylurea medications receiving ibuprofen.

Zidovudine:

There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen. Quinolone antibiotics: animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have increased risk of developing convulsions.

Cyclosporine:

The concomitant administration of NSAIDs and cyclosporine is thought to be capable of increasing the risk of nephrotoxicity due to decreased synthesis of prostacyclin in the kidney. Accordingly, in the event of combination treatment, renal function must be monitored closely.

Captopril:

Experimental studies indicate that ibuprofen counteracts the effect of captopril on sodium excretion.

Colestyramine:

The concomitant administration of ibuprofen and colestyramine retards and reduces (by 25%) the absorption of ibuprofen. These drugs should be given at an interval of at least 2 hours.

Thiazides, thiazide-related preparations and loop diuretics:

NSAIDs can counteract the diuretic effect of furosemide and bumetanide, possibly through inhibition of prostaglandin synthesis. They can also counteract the antihypertensive effect of thiazides.

Probenecid inhibits the binding of paracetamol to glucuronic acid, thus leading to a reduction in paracetamol clearance by a factor of approximately 2. In patients concurrently taking probenecid, the paracetamol dose

should be reduced. Enzyme-inducing drugs such as certain antiepileptics (phenytoin, phenobarbital, carbamazepine) decreased plasma AUC of paracetamol to approximately 60% in pharmacokinetic studies. Other substances with enzyme-inducing properties (i.e. rifampicin, Hypericum) could also result in decreased concentrations of paracetamol. In addition, the risk of liver damage during treatment with the maximum recommended dose of paracetamol is probably higher in patients who receive enzyme-inducing drugs. Zidovudine may affect paracetamol metabolism and vice versa, which may add to the toxicity of both.

4.6 Fertility, pregnancy and lactation

Pregnancy:

For ibuprofen Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal 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 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-fetal 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 fetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydramnios;

the mother and the neonate, at the end of 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.

Breastfeeding

Paracetamol is excreted in breast milk but not in a clinically significant amount and available published data do not contraindicate breastfeeding. Ibuprofen and its metabolites can pass in very small amounts into breast milk. No harmful effects to infants are known. In light of the above evidences it is not necessary to interrupt breastfeeding, for short-term treatment with the recommended dose of this product.

Fertility

The use of the product may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered.

4.7 Effects on ability to drive and use machines

In general, ibuprofen has no negative impact on the ability to drive or operate machinery. But because at high doses, side effects such as fatigue, vertigo (reported as common) and visual disturbances (reported as uncommon) can occur, the ability to drive and use machines may be impaired in some patients.

4.8 Undesirable effects

Blood and lymphatic system disorders:

Uncommon: Neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia (sometimes Coombs positive), thrombocytopenia with or without purpura, leucopoenia, pancytopenia, eosinophilia and decrease in haemoglobin and haematocrit, epistaxis, menorrhagia.

Immune system disorders:

Uncommon:

Allergic Reactions: Syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis, bronchospasm. Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema.

Very Rare:

Hypersensitivity reactions, skin rash and crosssensitivity with sympathomimetics.

Metabolism and nutrition disorders:

Very Rare:

metabolic acidosis, hypokalemia.

Uncommon:

Gynaecomastia, hypoglycaemic reaction.

Psychiatric disorders:

Very Rare:

Confusion, depression, sleep disturbances, irritability, anxiety, restlessness, excitability.

Nervous system disorders:

Common:

Dizziness, headache, nervousness, vertigo, fatigue, agitation, irritability.

Uncommon:

Depression, insomnia, confusion, emotional lability, somnolence.

Rare:

Paraesthesias, hallucinations, dream abnormalities.

Very Rare:

Paradoxical stimulation, optic neuritis, psychomotor impairment, extrapyramidal effects, tremor and convulsions.

Not known:

aseptic meningitis.

Eye disorders:

Uncommon:

Amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision) usually reversible on cessation of therapy.

Ear and labyrinth disorders:

Common: Tinnitus

Cardiac disorders:

Common: Oedema, fluid retention (usually reversible on discontinuation).

Uncommon: arrhythmias (sinus tachycardia, sinus bradycardia).

Very Rare: Palpitations; tachycardia; arrhythmia and other cardiac dysrhythmias. Hypertension and cardiac failure, hypotension.

Respiratory, thoracic and mediastinal disorders:

Uncommon:

Thickened respiratory tract secretions.

Very Rare:

Asthma, exacerbation of asthma, bronchospasm and dyspnea

Gastrointestinal Disorders:

Common:

Abdominal pain, diarrhea, dyspepsia, nausea, stomach discomfort. Vomiting, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence).

Uncommon:

Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis sometimes fatal, particularly in the elderly. Ulcerative stomatitis and exacerbation of ulcerative colitis and Crohn's disease. Gastritis, pancreatitis.

Skin and subcutaneous tissue disorders:

Common:

Rash (including maculopapular type), pruritus, angioedema and face swelling.

Uncommon:

Vesiculobullous eruptions, urticaria, erythema multiforme, alopecia, photoallergic skin reactions.

Very Rare:

Hyperhidrosis, Exfoliative dermatoses, necrotising fasciitis. Bullous reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Not known:

Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Acute generalised exanthematous pustulosis (AGEP).

Hepatobiliary disorders:

Very Rare:

Abnormal liver function, hepatitis and jaundice. Hepatic failure, hepatic necrosis and liver injury.

Renal and urinary disorders:

Uncommon:

Urinary retention, oedema, nephrotic syndrome, interstitial nephritis.

Very Rare:

Nephrotoxicity, and acute and chronic renal failure. Acute tubular necrosis.

4.9 Overdose

Symptoms

In many cases of paracetamol overdosage there are often no early symptoms. Pallor, nausea, vomiting, anorexia and abdominal pain are early symptoms of paracetamol overdosage. Liver damage may become apparent 12 to 48 hours after ingestion. 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.

Management

Due to differences in the management guidelines of paracetamol overdose in the different member states, as well as the continuous update of treatment recommendations, the national poison centre should be consulted for the most up-to-date treatment recommendations for the treatment of paracetamol overdose. 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Paracetamol, combinations excluding psycholeptics. ATC code: N02BE51

Mechanism of action

Although the exact site and mechanism of analgesic action of paracetamol is not clearly defined, it appears that it induces analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D- aspartate and substance P. Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. The drug's therapeutic effects as an NSAID result from its inhibitory effect on the enzyme cyclo-oxygenase, leading to reduction in prostaglandin synthesis. The exact mechanism of action of ibuprofen is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthesise inhibition.

5.2 Pharmacokinetic properties

Absorption Both paracetamol and ibuprofen are readily absorbed from the gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration. Distribution As for any product containing paracetamol, it is distributed into most body tissues. Biotransformation Paracetamol is metabolised extensively in the liver and excreted in the urine, mainly as inactive glucuronide and sulphate conjugates. Less that 5% is excreted unchanged. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdosage and if left untreated has the potential to cause severe and even irreversible liver damage. Paracetamol is metabolised differently by premature infants, newborns, and young children compared with adults, the sulphate conjugate being most predominant.

5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available. The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments and in humans from extensive clinical experience. There are no new

preclinical data of relevance which are additional to the data already presented in this Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients

Starch, Talc, Magnesium Stearate, Aerosil, Sodium Starch Glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package and keep containers tightly closed.

6.5 Nature and contents of container

2x12 capsules

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

Vadis Pharmaceuticals Limited,

Plot RD 14, Phase 2, Ext. Trans-Ekulu,

Enugu-Nigeria

8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text
