SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Combogesic 500 mg/150 mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg and Ibuprofen 150 mg.

Excipient with known effect:

Lactose monohydrate 3.81 mg

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

White coloured, capsule shaped tablets 19 mm in length with breakline on one side and plain on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For temporary relief of pain associated with: headache, migraine, backache, period pain, dental pain, muscular pain, cold and flu symptoms, sore throat and fever.

4.2 Posology and method of administration

Posology

For oral administration and short term use only (not more than 3 days).

The patient should consult a doctor if the symptoms persist or worsen or if the product is required for more than 3 days. This medicine is for short-term use and is not recommended for use beyond 3 days.

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

Adults

The usual dosage is one to two tablets taken every six hours, as required, up to a maximum of six tablets in 24 hours.

Children under18 years

This product is not recommended for children under 18 years.

Elderly

No special dosage modifications are required (see section 4.4). The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.

Patients with renal/hepatic impairment

No special dosage adjustments are required (see section 4.4)

Method of administration

This product is recommended to be taken with a full glass of water.

4.3 Contraindications

This product is contraindicated for use:

- in patients with known hypersensitivity reaction to paracetamol, ibuprofen, other NSAIDs or to any of the excipients listed in section 6.1.
- in patients with active alcoholism as chronic excessive alcohol ingestion may predispose patients to hepatotoxicity (due to the paracetamol component).
- in patients who have experienced asthma, urticaria, or allergic-type reactions after taking acetylsalicylic acid or other NSAIDs.
- in patients with active or history of gastrointestinal bleeding or peptic ulceration.
- In patients with severe heart failure (NYHA Class IV), hepatic failure or renal failure (see section 4.4.)
- in patients with cerebrovascular or other active bleeding
- in patients with blood-formation disturbances

- during the third trimester of pregnancy (see section 4.6).

This product should not be taken with other medicinal products containing paracetamol, ibuprofen, acetylsalicylic acid, salicylates or with any other anti-inflammatory drugs (NSAIDs) unless under a doctor's instruction (see section 4.5).

4.4 Special warnings and precautions for use

This medicine is for short-term use and is not recommended for use beyond 3 days.

Hepatic Impairment

The use of paracetamol at higher than recommended doses can lead to hepatotoxicity and even hepatic failure and death. Also, patients with impaired liver function or a history of liver disease, or who are on long term ibuprofen therapy or paracetamol treatment should have hepatic function monitored at regular intervals, as ibuprofen has been reported to have a minor and transient effect on liver enzymes.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though rare, have been reported with ibuprofen as with other NSAIDs. If abnormal liver tests persist or worsen, or if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), ibuprofen should be discontinued. Both active drugs have been reported to cause hepatotoxicity and even hepatic failure, especially paracetamol.

Patients who regularly consume alcohol in excess of recommended amounts should not take this medicine.

Dose reduction is recommended in patients showing signs of worsening hepatic function. Treatment should be stopped in those patients who develop severe liver failure (see section 4.3).

Renal Impairment

Paracetamol can be used in patients with chronic renal disease without dosage adjustment. There is minimal risk of paracetamol toxicity in patients with moderate to severe renal failure. However, for the ibuprofen component of this product - caution should be used when initiating treatment with ibuprofen in patients with dehydration. The two major metabolites of ibuprofen are excreted mainly in the urine and impairment of renal function may result in their accumulation. The significance of this is unknown. NSAIDs have been reported to cause nephrotoxicity in various forms: interstitial nephritis, nephritic syndrome and renal failure. Renal impairment from ibuprofen use is

usually reversible. In patients with renal, cardiac or hepatic impairment, those taking diuretics and ACE Inhibitors, and the elderly, caution is required since the use of nonsteroidal anti-inflammatory drugs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored in these patients.

Treatment should be stopped in those patients who develop severe renal failure (see section 4.3).

Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Elderly

No adjustment in labelled dosage is necessary for older patients who require paracetamol therapy. Those who require therapy for longer than 10 days should consult their physician for condition monitoring; however, no reduction in recommended dosage is necessary. However, caution should be taken with regard to the use of ibuprofen as it should not be taken by adults over the age of 65 without consideration of co-morbidities and co-medications because of an increased risk of adverse effects, in particular heart failure, gastrointestinal ulceration and renal impairment.

Haematological Effects

Blood dyscrasias have been rarely reported. Patients on long-term therapy with ibuprofen should have regular haematological monitoring.

Coagulation Defects

Like other NSAIDs, ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, products containing ibuprofen

should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy.

Gastrointestinal Events

Upper gastro-intestinal ulcers, gross bleeding or perforation have been described with NSAIDs. The risks increase with dose and duration of treatment, and are more common in patients over the age of 65 years. Some patients will experience dyspepsia, heartburn, nausea, stomach pain or diarrhoea. These risks are minimal when this product is used at the prescribed dose for a few days.

Products containing ibuprofen should be used with caution, and at the lowest effective dose for the shortest duration, in patients with a history of gastrointestinal haemorrhage or ulcer since their condition may be exacerbated.

Due to the ibuprofen component should be given with care to patients with a history of GI disease (ulcerative colitis, Chrohn's disease) as well as in patients with porphyria and varicella.

This product should be discontinued if there is any evidence of gastrointestinal bleeding.

The concurrent use of acetylsalicylic acid and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Cardiovascular Thrombotic Events

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. $\leq$ 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.

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.

Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration.

There is no consistent evidence that the concurrent use of acetylsalicylic acid mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAIDs use.

Hypertension*:*

NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensive medicines with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore caution is advised in patients with fluid retention or heart failure.

Severe Skin Reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Pre-existing asthma

Products containing ibuprofen should not be administered to patients with acetylsalicylic acid sensitive asthma and should be used with caution in patients with pre-existing asthma.

Ophthalmological effects

Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who develop visual disturbances during treatment with products containing ibuprofen should have an ophthalmological examination.

Aseptic Meningitis

For products containing ibuprofen aseptic meningitis has been reported only rarely, usually but not always in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

Potential Laboratory Test Interferences

Using current analytical systems, paracetamol does not cause interference with laboratory assays. However, there are certain methods with which the possibility of laboratory interference exists, as described below:

Urine Tests:

Paracetamol in therapeutic doses may interfere with the determination of 5-hydroxyindoleacetic acid (5HIAA), causing false-positive results. False determinations may be eliminated by avoiding paracetamol ingestion several hours before and during the collection of the urine specimen.

Masking of symptoms of underlying infections

{Combogesic} 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 {Combogesic}are administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Flucloxacillin

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillian. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Special Precautions

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when products containing ibuprofen are added to the treatment program.

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 stopping the medicine.

One film-coated tablet contains 3.81 mg of lactose, resulting in 22.86 mg of lactose per maximum recommended daily dose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions of paracetamol with other medicines have been noted:

- anticoagulant drugs (warfarin) - dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time.
- paracetamol absorption is increased by substances that increase gastric emptying, e.g. metoclopramide.
- paracetamol absorption is decreased by substances that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, and narcotic analgesics.
- paracetamol may increase chloramphenicol plasma concentrations.
- the risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents.
- paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.
- cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.
- Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid alone or with other drugs for tuberculosis.
- Severe hepatotoxicity has occurred after use of paracetamol in a patient taking zidovudine and co-trimoxazole.
- Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4)

The following interactions of ibuprofen with other medicines have been noted:

- anticoagulants, including warfarin – ibuprofen interferes with the stability of INR and may increase risk of severe bleeding and sometimes fatal haemorrhage, especially from the gastrointestinal tract. Ibuprofen should only be used in patients taking warfarin if absolutely necessary and they must be closely monitored.
- Ibuprofen may decrease renal clearance and increase plasma concentration of lithium.
- Ibuprofen may reduce the anti-hypertensive effect of ACE inhibitors, beta-blockers and diuretics and may cause natriuresis and hyperkalemia in patients under these treatments.
- Ibuprofen reduces methotrexate clearance.
- Ibuprofen may increase plasma levels of cardiac glycosides.

- Ibuprofen may increase the risk of gastrointestinal bleeding especially if taken with corticosteroids.
- Ibuprofen may prolong bleeding time in patients treated with zidovudine.
- Ibuprofen may also interact with probenecid, antidiabetic medicines and phenytoin.
- Ibuprofen may also interact with tacrolimus, ciclosporin, sulphonylureas and quinolone antibiotics.

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).

This product may interfere with some medicines. These include:

- 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
- acetylsalicylic acid, salicylates or other NSAID medicines
- medicines to treat high blood pressure or other heart conditions
- diuretics, also called fluid tablets
- lithium, a medicine used to treat some types of depression
- methotrexate, a medicine used to treat arthritis and some types of cancer
- corticosteroids, such as prednisone, cortisone

The above medicines may be affected by this product or may affect how well this product works.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no experience of use of this product in humans during pregnancy. Congenital abnormalities have been reported in association with NSAID administration in humans, although evidence of adverse effects during pregnancy following paracetamol treatment is lacking.

For ibuprofen

From the 20th week of pregnancy onward, Combogesic use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Combogesic should not be given unless clearly necessary. If Combogesic 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Combogesic for several days from gestational week 20 onward. Combogesic should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

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.

Consequently, Combogesic is contraindicated during the third trimester of pregnancy (see section 4.3).

For paracetamol

A large amount of data on pregnant women using paracetamol indicate neither malformative, nor feto/neonatal toxicity. 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.

Breast-feeding

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

This product has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Clinical trials with this product have not indicated any other undesirable effects other than those for paracetamol alone or ibuprofen alone.
Adverse reactions have been ranked under headings of frequency using the following convention:

1. Very common (≥ 1/10);
2. Common (≥ 1/100, < 1/10);
3. Uncommon (≥ 1/1000, < 1/100);
4. Rare (≥ 1/10000, < 1/1000);
5. Very rare (< 1/10000)
6. Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	**Uncommon**: Decrease in haemoglobin and haematocrit. Although a causal relationship has not been established, bleeding episodes (e.g. epistaxis, menorrhagia) have been reported in during therapy with the drug. **Very Rare**: Haematopoietic disorders (agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia leucopenia, neutropenia, pancytopenia and thrombocytopenia with or without purpura) have been reported following paracetamol use, but were not necessarily causally related to the drug.
Cardiac disorders	**Common**: Oedema, fluid retention; fluid retention generally responds promptly to discontinuation of the drug. **Very Rare**: Palpitations; tachycardia; arrhythmia and other cardiac dysrhythmias have been reported. Hypertension and cardiac failure have been reported in association with NSAID treatment.[1]
Ear and labyrinth disorders	**Very Rare**: Vertigo. **Common**: Tinnitus (for medicines containing ibuprofen)
Eye disorders	**Uncommon**: Amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision) have occurred but

	is usually reversed after cessation of therapy. Any patient with eye complaints should have an ophthalmological examination which includes central vision fields.
Gastrointestinal Disorders	**Common**: Abdominal pain, diarrhea, dyspepsia, nausea, stomach discomfort and vomiting **Uncommon**: Flatulence and constipation, peptic ulcer, perforation or gastrointestinal haemorrhage, with symptoms of melaena haematemesis sometimes fatal, particularly in the elderly. Ulcerative stomatitis and exacerbation of ulcerative colitis and Crohn's disease have been reported following administration. Less frequently gastritis has been observed and pancreatitis reported.
General disorders and administration site conditions	**Very Rare**: Fatigue and malaise.
Hepatobiliary disorders	**Very Rare**: Abnormal liver function, hepatitis and jaundice. In overdose paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury.
Immune system disorders	**Very Rare**: Hypersensitivity reactions including skin rash and cross-sensitivity with sympathomimetics have been reported. **Uncommon**: Other allergic reactions have been reported but a causal relationship has not been established: Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema.
Investigations	**Common**: Alanine aminotransferase increased, gamma-glutamyltransferase increased and liver function tests abnormal with paracetamol. Blood creatinine increased and blood urea increased. **Uncommon**: Aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinease increased. haemoglobin decreased and platelet count increased.
Metabolic and nutrition disorders	**Very Rare**: In the case of metabolic acidosis, causality is uncertain as more than one drug was ingested. The case of metabolic acidosis followed the ingestion of 75 grams of paracetamol, 1.95 grams of acetylsalicylic acid, and a small amount of a liquid household cleaner. The patient also had a history of seizures which the authors reported may have contributed to an increased lactate level indicative of metabolic acidosis. Metabolic side effects have included hypokalemia. Metabolic side effects including metabolic acidosis have been reported following a massive overdose of acetaminophen. **Uncommon**: Gynaecomastia, hypoglycaemic reaction. **Not Known:** Hypokalaemia[2]. High anion gap metabolic acidosis[3].
Nervous system disorders	**Common**: Dizziness, headache, nervousness **Uncommon**: Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma **Rare**: Paraesthesias, hallucinations, dream abnormalities

	Very Rare: Paradoxical stimulation, optic neuritis, psychomotor impairment, extrapyramidal effects, tremor and convulsions.
Renal and urinary disorders	**Uncommon**: Urinary retention **Very Rare**: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure. Adverse renal effects are most often observed after overdose, after chronic abuse (often with multiple analgesics), or in association with paracetamol-related hepatotoxicity. Acute tubular necrosis usually occurs in conjunction with liver failure, but has been observed as an isolated finding in rare cases. A possible increase in the risk of renal cell carcinoma has been associated with chronic paracetamol use as well. One case-control study of patients with end-stage renal disease suggested that long term consumption of paracetamol may significantly increase the risk of end-stage renal disease particularly in patients taking more than 1000 mg per day. **Not Known:** Renal tubular acidosis[2]
Respiratory and thoracic and mediastinal disorders	**Uncommon**: Thickened respiratory tract secretions **Very Rare**: Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea.
Skin and subcutaneous tissue disorders	**Common**: Rash (including maculopapular type), pruritus. **Very Rare**: Hyperhiddrosis, purpura and photosensitivity. Very rare cases of serious skin reactions have been reported, such as exfoliative dermatoses and 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).

1.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) (see section 4.4).

2. Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.

3. High anion gap metabolic acidosis. Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Paracetamol:

Liver injury and even failure can occur following paracetamol overdose. Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. 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 proceed to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop in the absence of severe liver damage. Cardiac arrhythmias have been reported. Liver damage is possible in adults who have taken 10 g or more of paracetamol, due to excess quantities of a toxic metabolite.

Ibuprofen

Symptoms include nausea, abdominal pain and vomiting, dizziness, convulsion and rarely, loss of consciousness. Clinical features of overdose with ibuprofen which may result are depression of the central nervous system and the respiratory system.

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).

Treatment

Paracetamol**:**

Prompt treatment is essential in the management of paracetamol overdose even when there are no obvious symptoms, because of the risks of liver injury, which presents after some hours or even days delay. Medical treatment is advised, without delay in any patient who has ingested 7.5 g or more of paracetamol in the preceding 4 hours. Gastric lavage should be considered. Specific therapy to reverse liver injury with an antidote such as acetylcysteine (intravenous) or methionine (oral) should be instituted as soon as possible.

Acetylcysteine is most effective when administered during the first 8 hours following ingestion of the overdose and the effect diminishes progressively between 8 and 16 hours. It used to be believed that starting treatment more than 15 hours after overdose was of no benefit and might possibly aggravate the risk of hepatic encephalopathy. However, late administration has now been shown to be safe, and studies of patients treated up to 36 hours after ingestion suggest that beneficial results may be obtained beyond 15 hours. Furthermore, administration of intravenous acetylcysteine to patients who have already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.

An initial dose of 150 mg/kg of acetylcysteine in 200 mL 5% glucose is given intravenously over 15 minutes, followed by an I.V. infusion of 50 mg/kg in 500 mL 5% glucose over 4 hours and then 100 mg/kg in 1 litre 5% glucose over 16 hours. The volume of I.V. fluids should be modified for children.

Methionine is given orally as 2.5 g every 4 hours up to 10 g. Methionine treatment must be started within 10 hours after ingestion of paracetamol; otherwise it will be ineffective and may exacerbate liver damage.

Evidence of serious symptoms may not become apparent until 4 or 5 days following overdose and patients should be carefully observed for an extended period.

Ibuprofen**:**

In cases of acute overdose, the stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour has elapsed since ingestion. Because the drug is acidic and is excreted in the urine, it is theoretically beneficial to administer alkali and induce diuresis. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption and reabsorption of ibuprofen tablets.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N02BE51 – paracetamol, combinations excl.psycholeptics

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.

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 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).

Clinical trials

Randomized, double-blind studies were conducted with the combination using the acute dental pain model of post-operative pain. The studies showed that:

- Over the 48 hours, this product (Maxigesic® = Combogesic) had a faster onset than either of its two active ingredients and provided superior analgesia than the same daily dose of paracetamol (p=0.007 at rest, p=0.006 on activity) and ibuprofen (p=0.003 at rest, p=0.007 on activity)

- All three doses evaluated (half tablet or one tablet or two tablets) were effective when compared with placebo (p=0.004-0.002) and the highest dose [two tablets] had the greatest response rate (50%), lowest maximum VAS pain scores, longest time to rescue medication and lowest % of patients requiring rescue medication. All these measures were significantly different to placebo ($p<0.05$).

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.

The rate and absorption of both paracetamol and ibuprofen from the combination product is slightly delayed following administration after food.

Distribution

As for any product containing paracetamol, it is distributed into most body tissues.

Ibuprofen is highly bound (90-99%) to plasma proteins.

Metabolism

Paracetamol is metabolised extensively in the liver and excreted in the urine, mainly as inactive glucuronide and sulphate conjugates. Less than 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 overdose 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.

Ibuprofen is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation.

The metabolic pathways of paracetamol and ibuprofen are distinct and there should be no drug interactions where the metabolism of one affects the metabolism of the other. A formal study using human liver enzymes to investigate such a possibility failed to find any potential drug interaction on the metabolic pathways.

In another study, the effect of ibuprofen on the oxidative metabolism of paracetamol was evaluated in healthy volunteers under fasting conditions. The study results indicated that ibuprofen did not alter the amount of paracetamol undergoing oxidative metabolism, as the amount of paracetamol and its metabolites (glutathione-, mercapturate-, cysteine-, glucuronide- and sulfate-paracetamol) were similar when administered alone, as paracetamol, or with the concomitant administration of ibuprofen (as a fixed combination Maxigesic®) This study clears any added hepatic risks from the hepatotoxic metabolite, NAPQI, from paracetamol if administered with Ibuprofen.

Elimination

Paracetamol elimination half-life varies from about 1 to 3 hours.

Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion. The elimination half-life if ibuprofen is around 2 hours.

Pharmacokinetic relationship

A specific study to investigate possible effects of paracetamol on the plasma clearance of ibuprofen and vice versa did not identify any drug interactions.

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

Maize starch

Pregelatinised maize starch

Microcrystalline cellulose

Crosscarmellose sodium

Magnesium stearate

Opadry white OY-LS-58900 containing:

- HPMC 2910/Hypromellose 15cP (E464)
- Lactose Monohydrate
- Titanium dioxide (E171)
- Macrogol/PEG -4000
- Sodium Citrate- Dihydrate (E331)
- Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30 °C. Store in the original packaging to protect from light.

6.5 Nature and contents of container

Each pack contains 8, 10, 16, 20, 24, 30 and 32 film-coated tablets packed in 250 μm PVC film/alumiunium foil 25 μm blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

AFT Pharma UK Limited
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Unit 13, 2nd Floor, Armitage Road
London, NW11 8RQ
England

8 MARKETING AUTHORISATION NUMBER(S)

PL 57592/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/11/2014

10 DATE OF REVISION OF THE TEXT

23/09/2025