SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Edolfen Dual Action 200 mg/500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg ibuprofen and 500 mg paracetamol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, oval shaped, film-coated tablets, with dimensions 19.7 mm x 9.2 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The medicinal product is used for the temporary treatment of mild to moderate pain associated with migraine, headache, backache, menstrual pain, toothache, rheumatic pain, muscular pain, pain associated with mild forms of arthritis, cold and flu, sore throat or fever. The medicinal product is particularly suitable for the treatment of pain requiring stronger analgesics than ibuprofen or paracetamol used alone.

Edolfen Dual Action is intended for adults aged 18 years and over.

4.2 Posology and method of administration

Posology
For short-term oral administration.

Use the lowest effective dose for the shortest time necessary to relieve symptoms. The patient should contact a doctor if the symptoms persist or worsen or if it is necessary to use the medicinal product for more than 3 days.

Adults: one tablet up to 3 times a day with water. Wait at least 6 hours between successive doses.

If after taking one tablet the symptoms are not controlled, you can take a maximum of two tablets up to three times a day. Wait at least 6 hours between successive doses.

Do not take more than six tablets (3,000 mg paracetamol, 1,200 mg ibuprofen) in 24 hours.

Undesirable effects may be reduced by using the lowest effective dose for the shortest period necessary to relieve symptoms (see section 4.4).

To reduce the risk of undesirable effects, Edolfen Dual Action should be taken with food.

Elderly: No dose adjustment is required (see section 4.4).

Adverse effects are more common in the elderly. If an NSAID is required, the lowest effective dose should be used in the shortest time necessary to relieve the symptoms. During treatment with NSAIDs the patient should be regularly monitored because of the risk of gastrointestinal bleeding.

Paediatric population
Not for use by children below 18 years of age.

Method of administration
For oral administration.

4.3 Contraindications

The medicinal product is contraindicated:

- in patients with known hypersensitivity to ibuprofen, paracetamol or to any of the excipients listed in section 6.1.
- in patients with a history of hypersensitivity reactions (e.g., bronchospasm, angioedema, asthma, rhinitis or urticaria) related to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- in patients with active or history of gastrointestinal ulceration, perforation, or bleeding including those related to the use of NSAIDs (see section 4.4).
- in patients with coagulation disorders.
- in patients with severe hepatic failure, severe renal failure, or severe heart failure (NYHA class IV) (see section 4.4).
- in concomitant use with other NSAIDs including selective cyclooxygenase-2 (COX-2) inhibitors and acetylsalicylic acid at doses greater than 75 mg per day - increased risk of undesirable effects (see section 4.5).
- in concomitant use with other paracetamol-containing products - increased risk of serious undesirable effects (see section 4.5).
- in the last trimester of pregnancy due to risk of premature foetal occlusion of the ductus arteriosus and pulmonary hypertension (see section 4.6).

4.4 Special warnings and precautions for use

The risk of paracetamol overdose is higher in patients with alcoholic liver failure without signs of cirrhosis. In case of overdose, contact a doctor immediately even if the patient feels well, as there is a risk of delayed serious liver damage.

To reduce the risk of adverse reactions, the lowest effective dose should be used for the shortest time necessary to control the symptoms (see section 4.2 and gastrointestinal and cardiovascular disorders below) and take the medicinal product with food (see section 4.2).

Elderly:
Elderly patients are more likely to develop adverse reactions following the use of NSAIDs, especially gastrointestinal bleeding and perforations, which may be fatal (see section 4.2).

Caution is required in patients who have:

Respiratory disorders:
In patients with active or a history of bronchial asthma, cases of sudden bronchospasm following NSAIDs have been reported.

Cardiac, renal and hepatic disorders:
The administration of NSAIDs may lead to a dose-dependent inhibition of prostaglandin synthesis and may accelerate the onset of renal dysfunction. The risk of these reactions is highest in patients with impaired renal, cardiac or hepatic function, in patients taking diuretics and in the elderly. Renal function should be monitored in these patients (see section 4.3).

Cardiovascular and cerebrovascular effects:
Patients with a history of hypertension or mild to moderate congestive heart failure, should be adequately monitored and appropriate recommendations made as fluid retention and oedema have been reported in association with NSAID treatment.

Clinical studies suggest that the use of ibuprofen, especially at high doses (2,400 mg/day), may be associated with a small increase in the risk of arterial thromboembolic events (for example, myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low-dose ibuprofen intake (e.g., ≤ 1,200 mg/day) is associated with an increased risk of arterial embolic-thrombotic incidents.

In patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), known ischemic heart disease, peripheral vascular disease and/or cerebrovascular disease, ibuprofen treatment should be administered after careful consideration and high doses (2,400 mg/day) should be avoided.
The initiation of long-term treatment of patients with risk factors for cardiovascular incidents (hypertension, hyperlipidaemia, diabetes mellitus, smoking) should also be carefully considered, especially if high doses of ibuprofen (2,400 mg/day) are required.

Gastrointestinal bleeding, ulceration or perforation:
Fatal gastrointestinal bleeding, ulceration or perforation have been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation increases with increasing NSAID doses, in patients with a history of peptic ulcer disease, especially if complicated by bleeding or perforation (see section 4.3), and in the elderly. In these patients the treatment should commence with the lowest possible dose. In these patients, and in patients requiring concomitant treatment with low doses of acetylsalicylic acid or other drugs that increase gastrointestinal risk, combination therapy with protective agents (e.g., misoprostol or proton pump inhibitors) should be considered (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, especially the elderly, are advised to report any abdominal symptom of concern (especially gastrointestinal bleeding), particularly in the initial stages of treatment.

Caution should be exercised in patients taking concomitant medicinal products that may 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 (see section 4.5).

In patients taking ibuprofen who have experienced gastrointestinal bleeding or ulceration, treatment should be discontinued.

NSAIDs should be used with caution in patients with a history of gastrointestinal diseases (ulcerative colitis, Crohn's disease) as these conditions may worsen (see section 4.8).

SLE and mixed connective tissue diseases:
Patients with systemic lupus erythematosus (SLE) or mixed connective tissue diseases have an increased risk of aseptic meningitis (see section 4.8).

Skin reactions:
Very rarely, severe and sometimes fatal skin reactions including exfoliative dermatitis, Stevens-Johnson syndrome and toxic necrotic epidermal necrolysis have been reported after NSAID use (see section 4.8). Patients are at greatest risk of developing these reactions early in the course of therapy. In most cases the onset of reactions occurred within the first month of treatment. Administration of this medicinal product should be discontinued at the first sign of skin rash, mucosal lesions or other signs of hypersensitivity.

Fertility disorders:
The use of this medicinal product may interfere with fertility in women and is therefore not recommended in women planning to become pregnant. Discontinuation of the drug

should be considered in women with difficulty in becoming pregnant or women undergoing fertility testing.

4.5 Interaction with other medicinal products and other forms of interaction

This medicinal product (like all other medicinal products containing paracetamol) is contraindicated for use concomitantly with other medicinal products containing paracetamol - increased risk of adverse reactions (see section 4.3).

This medicinal product (like all other medicines containing ibuprofen and NSAIDs) is contraindicated for concomitant use with:

- acetylsalicylic acid. Concomitant administration of ibuprofen and acetylsalicylic acid is not recommended as the risk of undesirable effects increases.
- other NSAIDs, including selective cyclooxygenase-2 (COX-2) inhibitors, as the risk of adverse reactions increases (see section 4.3).

This medicinal product (like all other medicines containing paracetamol) should be used with caution when used concurrently with:

- chloramphenicol: increase in plasma concentration of chloramphenicol.
- cholestyramine: cholestyramine reduces the rate of absorption of paracetamol. Therefore, if maximum pain relief is required, cholestyramine should not be taken within one hour of taking the medicinal product.
- metoclopramide and domperidone: metoclopramide and domperidone increase the rate of absorption of paracetamol. However, concomitant use of these medicines need not be avoided.
- warfarin: after prolonged regular use, paracetamol may increase the anticoagulant effect of warfarin and other drugs of the coumarin group, which may lead to an increased risk of bleeding; doses taken sporadically have no significant effect on this property.

This medicinal product (like all other medicines containing ibuprofen and NSAIDs) should be used with caution when used concurrently with:

- anticoagulants: NSAIDs may increase the effect of anticoagulants such as warfarin.
- antihypertensive drugs: NSAIDs may reduce the effects of these drugs.
- antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).
- acetylsalicylic acid: Experimental data suggest that ibuprofen may competitively inhibit the platelet aggregation inhibitory effect of low doses of acetylsalicylic acid when these drugs are administered concomitantly. Although it is uncertain whether these data can be extrapolated to clinical situations, it cannot be excluded that regular long-term use of ibuprofen may reduce the cardioprotective effect of low doses of acetylsalicylic acid. Occasional use of ibuprofen is not considered to be of clinical significance (see section 5.1).
- cardiac glycosides: NSAIDs may increase the risk of heart failure, decrease GFR values and increase plasma concentrations of glycosides.
- cyclosporine: increased risk of nephrotoxic effects.

- Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- diuretics: impairment of the effect of diuretics. Diuretics may increase the risk of nephrotoxic effects from NSAIDs.
- lithium: decreased lithium excretion.
- methotrexate: decreased methotrexate excretion.
- mifepristone: do not use NSAIDs for 8-12 days after mifepristone administration as the effect of mifepristone may be reduced.
- quinolone antibiotics: data from animal studies indicate that NSAIDs may increase the risk of seizures associated with the use of quinolone antibiotics. Patients taking NSAIDs and quinolones may be at increased risk of seizures.
- tacrolimus: possible increased risk of nephrotoxic effects when NSAIDs and tacrolimus are used concomitantly.
- zidovudine: increased risk of haematological toxicity when zidovudine is co-administered with NSAIDs. There are data on an increased risk of joint bleeding and hematoma formation in HIV (+) patients with haemophilia treated with concomitant zidovudine and ibuprofen.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on the use of this medicinal product in pregnant women.

Based on human data on the use of NSAIDs, congenital anomalies have been reported, but their incidence was low and they did not follow a specific pattern. Based on the effects of NSAIDs on foetal cardiovascular development (risk of premature closure of the ductus arteriosus), the medicinal product is contraindicated in the last trimester of pregnancy. The medicinal product may delay and prolong labour and increase the risk of bleeding in both mother and child (see section 4.3). NSAIDs should not be used in the first and second trimester of pregnancy and during labor unless the potential benefit to the mother outweighs the potential risk to the foetus.

Epidemiological data in pregnant women have not shown any harmful effects of paracetamol used in the recommended doses.

Therefore, if possible, the use of this medicinal product should be avoided in the first 6 months of pregnancy and the medicinal product is contraindicated in the last 3 months of pregnancy (see section 4.3).

Breast-feeding
Ibuprofen and its metabolites may pass into breast milk in very low doses (0.0008% of the dose administered to the mother). No adverse effects in infants are known.

Paracetamol passes into breast milk, but to a clinically insignificant extent. Based on available data there are no contraindications for breastfeeding.

Therefore, it is not necessary to interrupt breastfeeding during short-term use of the medicinal product at the recommended doses.

Fertility
For fertility in women see section 4.4.

4.7 Effects on ability to drive and use machines

The use of NSAIDs may be followed by undesired effects such as dizziness, drowsiness, fatigue and visual disorders. If these symptoms occur, do not drive or use machines.

4.8 Undesirable effects

Clinical studies conducted with ibuprofen/paracetamol medicinal products have not indicated any adverse reactions other than those observed with ibuprofen or paracetamol used alone.

The table below presents adverse reactions collected from pharmacovigilance data in patients using ibuprofen alone or paracetamol alone in short and long term use.

Blood and lymphatic system disorders	Very rare (≤1/10,000)	Blood disorders (agranulocytosis, anemia, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia and thrombocytopenia). **The first symptoms are** fever, sore throat, superficial ulcerations of the oral mucosa, flu-like symptoms, severe weakness, bleeding and bruising, and nosebleeds of unknown etiology.
Immunological system disorders	Very rare (≤1/10,000)	Hypersensitivity reactions such as non-specific hypersensitivity reactions and anaphylactic reactions have been reported. Serious hypersensitivity reactions. **Symptoms may include:** swelling of the face, tongue and larynx, dyspnea, tachycardia, drop in blood pressure, (anaphylactic reaction, vascular edema or life-threatening shock).
Psychiatric disorders	Very rare (≤1/10,000)	Confusion, depression and hallucinations.
Nervous system disorders	Uncommon (≥1/1,000 to ≤1/100)	Headache and dizziness.

	Very rare (≤1/10,000)	Paresthesia, optic neuritis and somnolence. In isolated cases aceptic meningitis has been reported in patients with immune system disorders (such as systemic lupus erythematosus or mixed connective tissue disease) **manifesting as** neck rigidity, headache, nausea, vomiting, fever and confusion (see section 4.4).
Eye disorders	Very rare (≤1/10,000)	Vision disorders.
Ear and labyrinth disorders	Very rare (≤1/10,000)	Tinnitus and dizziness.
Vascular disorders	Very rare (≤1/10,000)	The occurrence of edema, increased blood pressure and heart failure have been reported after administration of NSAIDs. Clinical studies indicate that the use of ibuprofen, especially at a high dose (2400 mg/day), may be associated with a small increase in the risk of arterial thromboembolic events (for example myocardial infarction or stroke) (see section 4.4).
Respiratory, thoracic and mediastinal disorders	Very rare (≤1/10,000)	Respiratory tract reactivity including asthma, exacerbation of asthma symptoms, bronchospasm and dyspnea.
Gastrointestinal disorders	Common (≥1/100 to ≤1/10)	Abdominal pain, diarrhea, indigestion, nausea, gastric discomfort and vomiting.
	Uncommon (≥1/1,000 to ≤1/100)	Flatulence with gas and constipation.
	Uncommon (≥1/1,000 to ≤1/100)	Gastrointestinal ulceration, perforation or bleeding manifested by tarry stools or bloody vomit, sometimes fatal especially in elderly patients (see section 4.4). Ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration of the medicinal product (see section 4.4). Gastritis and pancreatitis have been reported less frequently.

Hepatic and bile duct disorders	Very rare (≤/10 000)	Hepatic impairment, hepatitis or jaundice. Paracetamol overdose can cause acute hepatic failure, liver failure, hepatic necrosis and liver damage (see section 4.9).
Skin and subcutaneous tissue disorders	Common (≥1/100 to ≤1/10)	Excessive sweating.
	Uncommon (≥1/1,000 to ≤1/100)	Various types of rashes including itching and urticaria. Angioedema and facial edema.
	Very rare (≤1/10,000)	Excessive sweating, purpura and photophobia. Exfoliative dermatosis. The appearance of blisters including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
	Unknown (cannot be determined from the available data)	Post-drug reaction with eosinophilia and systemic symptoms (DRESS syndrome).
Renal and urinary tract disorders	Very rare (≤1/10,000)	Various forms of nephrotoxic effects including interstitial nephritis, nephrotic syndrome and acute or chronic renal failure.
General and administration site disorders	Very rare (≤1/10,000)	Fatigue and bad mood.
Diagnostic tests	Common (≥1/100 to ≤1/10)	Increased alanine aminotransferase, increased gamma- glutamyl transferase and altered hepatic parameters after paracetamol administration. Increased plasma creatinine and increased blood urea.
	Uncommon (≥1/1,000 to ≤1/100)	Increased aspartate aminotransferase, increased alkaline phosphatase, increased creatinine phosphokinase, increased plasma creatinine, decreased hemoglobin, and increased platelet count.

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 national reporting system:

Cyprus
Pharmaceutical Services

Ministry of Health
CY-1475 Nicosia
Tel: +357 22608607
Fax: +357 22608669
Website: www.moh.gov.cy/phs

4.9 Overdose

Paracetamol
There is a risk of liver damage in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. In patients who have one or more of the below there is a risk of liver damage after taking 5 g (equivalent to 10 tablets) or more of paracetamol:

a) During long-term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymes.
b) In people who regularly consume alcohol in excess of acceptable levels.
c) In individuals with possible glutathione deficiency due to e.g., eating disorders, cystic fibrosis, HIV-related infections, starvation, cachexia.

Symptoms of overdose
Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Symptoms of liver damage may occur 12 to 48 hours after overdose - abnormal liver function is observed in tests. Abnormalities in glucose metabolism and metabolic acidosis may occur. In severe poisoning, liver failure may lead to encephalopathy, bleeding, hypoglycemia, cerebral oedema and death. Even in the absence of signs of severe kidney damage, acute renal failure with renal tubular necrosis may occur, manifested by low back pain, hematuria and proteinuria. Cases of cardiac arrhythmias and pancreatitis have been reported.

Overdose treatment
In the event of a paracetamol overdose, immediate action should be taken. Although there are no significant early symptoms the patient should be urgently referred to a hospital emergency department. Symptoms may be limited to nausea or vomiting and may not reflect the severity of the overdose and the risk of internal organ damage. The established standard of care should be followed.

If the overdose has occurred within one hour, the administration of activated charcoal should be considered. Determination of paracetamol plasma concentration should be performed at 4 or more hours after overdose (earlier measurements are not reliable).

Treatment with N-acetylcysteine may be used up to 24 hours after paracetamol overdose; however, its best efficacy is achieved up to 8 hours after overdose. The efficacy of this antidote declines rapidly after this time.

If necessary, N-acetylcysteine can be administered intravenously according to the established dosage regimen. If the patient is not vomiting and the patient is at a considerable distance from the hospital, methionine can be given orally.

Patients who develop symptoms of severe renal failure 24 hours after paracetamol overdose should be treated according to established standards of management.

Ibuprofen

Symptoms of overdose
Most patients will experience symptoms limited to nausea, vomiting, epigastric pain or, more rarely, diarrhoea after taking large amounts of NSAIDs. Furthermore, tinnitus, headache and gastrointestinal bleeding may occur. In more severe cases of overdose, symptoms of poisoning involve the central nervous system and are manifested by drowsiness, occasionally agitation and disorientation or coma. In rare cases convulsions may develop. In severe overdose, metabolic acidosis and prolonged prothrombin time / INR may occur, possibly due to effects on blood clotting factors. Acute renal failure and liver damage may occur in dehydrated patients. Asthmatic patients may experience a worsening of symptoms.

Treatment of overdose
Symptomatic and supportive treatment should be given, airways should be maintained clear, and the patient's heart rate and vital signs should be monitored until stabilized. If an overdose has occurred within one hour, the administration of activated charcoal should be considered. For frequent or prolonged convulsions, intravenous diazepam or lorazepam should be administered. A bronchodilator should be used for asthma, if it occurs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non-steroids, ATC code: M01AE51

The pharmacological actions of ibuprofen and paracetamol differ in terms of their site and mode of action. These complementary modes of action are also synergistic in nature which results in the product having stronger analgesic and antipyretic properties than its active ingredients when used alone.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) whose efficacy in inhibiting prostaglandin synthesis has been confirmed in conventional animal models of inflammation. Prostaglandins sensitize nociceptive afferent nerve terminals to mediators such as bradykinin. The analgesic action of ibuprofen is induced by peripheral inhibition of the cyclooxygenase-2 (COX-2) isoenzyme and subsequent reduction of sensitivity of nociceptive nerve terminals. Ibuprofen also inhibits the migration of induced lymphocytes to sites of inflammation. Ibuprofen has significant effects in the spinal cord, partly due to its ability to inhibit COX activity. The antipyretic action of ibuprofen is based on central inhibition of prostaglandin synthesis in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swelling and fever.

Experimental data suggest that ibuprofen may competitively inhibit the platelet aggregation inhibitory effect of low doses of acetylsalicylic acid when these drugs are administered concomitantly. Some pharmacodynamic studies have shown that when a single dose of ibuprofen (400 mg) is administered within 8 hours prior to, or 30 minutes after, a dose of immediate-release acetylsalicylic acid (81 mg), there is an attenuation of the effect of acetylsalicylic acid on thromboxane formation or platelet aggregation. Although it is uncertain whether these data can be extrapolated to clinical situations, it cannot be excluded that regular long-term use of ibuprofen may reduce the cardioprotective effect of low doses of acetylsalicylic acid. Occasional intake of ibuprofen is not considered to be clinically relevant (see section 4.5).

The exact mechanism of action of paracetamol has still not been definitively elucidated, however there is ample evidence to support the hypothesis of its central analgesic effect. Results of various biochemical studies demonstrate central inhibition of COX-2 enzyme activity. Paracetamol may also stimulate 5-hydroxytryptamine (serotonin) activity in the descending pathway, which blocks the transmission of pain stimuli in the spinal cord. Studies have shown a very weak ability of paracetamol to inhibit the peripheral activity of COX-1 and COX-2 isoenzymes.

The clinical efficacy of ibuprofen and paracetamol has been demonstrated in the treatment of headache, toothache and menstrual pain and fever; in addition, efficacy has been demonstrated in patients for the treatment of pain and fever associated with cold and flu and pain associated with sore throat, myalgia, soft tissue injuries and back pain.

This medicinal product is particularly helpful in the treatment of pain requiring stronger analgesics than 400 mg ibuprofen or 1000 mg paracetamol taken alone or as an analgesic product controlling pain faster than ibuprofen.

Summary of clinical studies after 2 taking tablets

A randomized, double-blind study with the combination product in a model of acute, postoperative toothache. The study showed the following:

- the medicinal product has greater analgesic efficacy than 1,000 mg paracetamol ($p<0.0001$) and 400 mg ibuprofen ($p<0.05$) which is clinically and statistically significant.
- the medicinal product has a fast onset of action with a "confirmed perceived analgesic effect" - achieved at a median of 18.3 minutes. The onset of action was significantly faster than for ibuprofen 400 mg (23.8 minutes, $p=0.0015$). "Stronger analgesic effect" for the medicinal product was achieved at a median of 44.6 minutes, which is significantly faster than for ibuprofen 400 mg (70.5 minutes, $p<0.0001$).
- the duration of the analgesia was significantly longer for this product (9.1 hours) than with 500 mg paracetamol (4 hours) or 1000 mg paracetamol (5 hours).
- the overall evaluation of the tested medicinal product by the subjects showed a high level of satisfaction with 93.2% of the subjects rating the product as “good”,

"very good" or "excellent" in pain relief. This combination product performed significantly better than 1000 mg paracetamol ($p<0.001$).

A randomized, double-blind study with the medicinal product in the treatment of chronic knee pain. The study showed the following:

- the medicinal product has greater analgesic efficacy than 1,000 mg of paracetamol ($p<0.0001$) used in short-term treatment ($p<0.01$) and in long-term treatment ($p<0.01$).
- the overall evaluation of the product by the subjects showed a high level of satisfaction in the long-term treatment of knee pain with 60.2 % of the subjects rating the product as "good" or "excellent." The product performed significantly better than 1,000 mg paracetamol ($p<0.001$).

5.2 Pharmacokinetic properties

Ibuprofen is well absorbed from the gastrointestinal tract and binds strongly to plasma proteins. Ibuprofen diffuses into the synovial fluid. Ibuprofen, a component of this medicinal product, is detected in the plasma after 5 minutes and reaches maximum plasma concentrations 1-2 hours after ingestion on an empty stomach. When the medicinal product was administered with food the plasma concentration of ibuprofen was lower and delayed by a median of 25 minutes, with a similar degree of absorption.

Ibuprofen is metabolized in the liver to two major metabolites, which are excreted in this form or in a conjugated form mainly via the kidneys together with negligible amounts of unchanged ibuprofen. Renal excretion is rapid and complete. The elimination half-life is approximately 2 hours.

Based on limited data, ibuprofen passes into breast milk in very low doses.

No significant differences in the pharmacokinetic properties of ibuprofen were observed in the elderly.

Paracetamol is well absorbed from the gastrointestinal tract. The ability to bind to plasma proteins appears to be insignificant when used in therapeutic doses, although this is dose-dependent. The paracetamol component of this medicinal product is detected in plasma after 5 minutes and reaches its maximum plasma concentration 0.5-0.67 hours after ingestion on an empty stomach. When the medicinal product was administered with food, plasma concentrations of paracetamol were lower and delayed by a median of 55 minutes, with a similar degree of absorption.

Paracetamol is metabolized in the liver and excreted in the urine mainly in the conjugated form - glucuronides and sulfates, with about 10% in the glutathione conjugated form. Less than 5% of paracetamol is excreted unchanged. The elimination half-life is about 3 hours.

A less important metabolite formed by hydroxylation, which is usually produced in very small amounts by multifunctional hepatic oxidases and is detoxified by the

reaction of coupling with hepatic glutathione, may accumulate in the liver and cause liver damage in case of paracetamol overdose.

No significant differences in the pharmacokinetic properties of paracetamol in the elderly.

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

This medicinal product has been formulated using a technology that releases ibuprofen and paracetamol simultaneously so that the combined effect of both active substances is achieved.

5.3 Preclinical safety data

Data on the toxicological safety profile of ibuprofen and paracetamol have been established in experimental animal studies and from extensive human clinical experience. There are no new non-clinical data of relevance to the prescriber other than those presented in this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Maize starch
Crospovidone (Type A) (E1202)
Silica, colloidal anhydrous (E551)
Povidone K-30 (E1201)
Starch, pregelatinised (maize)
Talc (E553b)
Stearic acid (50)

Film-coating
Poly(vinyl alcohol) (E1203)
Talc (E553b)
Macrogol 3350 (E1521)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the blisters in the outer carton in order to protect from light.

6.5 Nature and contents of container

Cardboard box containing perforated Aluminium-PVC/PVDC blisters of 10 film-coated tablets. Pack sizes of 10 or 20 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

23789

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 March 2023
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

27/03/2023

For internal use only: cy-spc-edolfen-dual-action-fc-tabs-v01-r00-a2f