PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

UNIFEN 200 (film-coated tablets)

UNIFEN 400 (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Unifen 200

Each film coated tablet contains ibuprofen 200 mg.

Unifen 400

Each film coated tablet contains ibuprofen 400 mg.

Sugar free.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

Unifen 200

Peach-red coloured, round biconvex film coated tablets with intact coating.

Unifen 400

Peach-red coloured, round, biconvex film coated tablets with intact coating

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Unifen is indicated for the treatment of:

- Rheumatoid arthritis
- Idiopathic juvenile arthritis (Still's disease)
- Ankylosing spondylitis
- Osteo-arthritis
- Acute gouty arthritis
- Non-articular rheumatism including fibrositis
- Non-rheumatic inflammatory conditions such as frozen shoulder (capsulitis), bursitis, tendonitis, tenosynovitis and low back pain.
- Relief of mild to moderate pain such as dysmenorrhoea, dental, post-episiotomy and post-partum pain.
- Soft tissue injuries such as sprains and strains.
- Pyrexia

4.2 Posology and method of administration

Posology

Use the lowest effective dose for the shortest possible duration of treatment.

Adults:

The recommended dosage of **Unifen** is 600 mg 6-8 hourly.

The total daily dose of Unifen should not exceed 2 400 mg.

Paediatric population

This formulation is not suitable for children under the age of 12 years.

Method of administration

For oral use

To minimize gastrointestinal side-effects or if gastrointestinal disturbances occur, **UNIFEN** should be given with food or milk.

4.3 Contraindications

- Hypersensitivity (allergy) to ibuprofen or to any of the excipients of **Unifen** listed in section 6.1.
- Heart failure.
- Peptic ulcer disease or gastrointestinal bleeding.
- History of gastrointestinal bleeding, ulceration or perforation (PUBs) related to previous NSAIDs.
- Active or history of recurrent ulcer/haemorrhage/perforations.
- Patients sensitive to aspirin or another nonsteroidal anti-inflammatory medicine.
- History of severe allergic reaction such as anaphylaxis or angioedema, induced by aspirin or other NSAIDs. Because of the possibility of cross-sensitivity due to structural relationships which exists among non-steroidal anti-inflammatory medicines, acute allergic reactions are likely to occur in patients who have exhibited allergic reactions to these compounds.
- **UNIFEN** is contraindicated in patients with renal failure.
- Aspirin-induced nasal polyps associated with bronchospasm.
- Children under the age of 12 years.

- The use of **UNIFEN** around 20 weeks gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. (see Section 4.4 and 4.6)
- Third trimester of pregnancy and during labour (See section 4.6)
- Safety in lactation has not been established.

4.4 Special warnings and precautions for use

The antipyretic, analgesic and anti-inflammatory action of ibuprofen may mask symptoms of the occurrence or worsening of infection.

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with **Unifen** therapy. In view of **UNIFEN**'s inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal.

The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of **Unifen**, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving **Unifen**, treatment with **Unifen** should be stopped.

Unifen should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolyis have been reported. **Unifen** should be

discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

The use of **UNIFEN** around 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis. If NSAID treatment is determined necessary, limit use to the lowest effective dose and shortest duration possible.
Regular use of NSAIDs during the third trimester of pregnancy may result in premature closure of the *foetal ductus arteriosus in utero* and possibly in persistent pulmonary hypertension of the new born. The onset of labour may be delayed and its duration increased.
Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue the NSAID if oligohydramnios occurs (see Section 4.3 and 4.6).

Risk benefit should be considered when the following medical conditions exist:

- **Unifen** should be given with care to the elderly, to patients with asthma or bronchospasm, bleeding disorders, cardiovascular disease, a history of peptic ulceration and in liver or renal impairment.
- Patients with congestive cardiac failure, cirrhosis, diuretic-induced volume depletion, or renal insufficiency require local synthesis of vasodilating prostaglandins to maintain renal perfusion, and therefore these patients are at greater risk of developing renal dysfunction due to inhibition of renal prostaglandin synthesis.

- Because of the possibility of cross-sensitivity due to structural relationships which exists among non-steroidal anti-inflammatory medicines, acute allergic reactions are likely to occur in patients who have exhibited allergic reactions to these compounds.
- Serious interactions have been reported after the use of high dose methotrexate with ibuprofen.
- Patients receiving warfarin and other anti-coagulants. Patients who are sensitive to aspirin or other NSAIDs should generally not be given ibuprofen.
- **Unifen** should be discontinued in patients who experience blurred or diminished vision, or changes in colour vision.
- Patients with collagen disease may be at risk of developing aseptic meningitis.
- Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as **UNIFEN.** Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue **UNIFEN** and evaluate the patient immediately.
- Mild reactions such as allergic rhinitis, urticaria or skin rash induced by aspirin or other NSAIDs.
- Anaemia
- Stomatitis

- System lupus erythematosus

Renal Tubular Acidosis

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of NSAIDs at higher than recommended doses. Presenting signs and symptoms included generalised weakness. NSAID induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

4.5 Interaction with other medicines and other forms of interaction

- Anti-hypertensives, beta-blockers and diuretics: **UNIFEN** may reduce the effect of anti-hypertensives, such as ACE inhibitors, beta-blockers and diuretics.
- NSAIDs - use of two or more NSAIDs concomitantly could result in an increase in side effects.
- Corticosteroids: increased risk of gastrointestinal ulceration, perforation or bleeding (PUBs).
- Anti-coagulants - **Unifen** may enhance the effects of anti-coagulants such as warfarin and the possibility of gastrointestinal bleeding.
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) - increased risk of gastrointestinal bleeding.
- Diuretics can also increase the risk of nephrotoxicity of **UNIFEN.**
- Digoxin – Increase in serum digoxin concentrations. More frequent monitoring is mandatory and may exacerbate cardiac failure and reduce GFR.
- Lithium – Increase in the steady-state concentration of lithium. More frequent monitoring is mandatory.
- Immunosuppressive medicines e.g. ciclosporin – Increased risk of nephrotoxicity.

- Mifepristone: A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of **UNIFEN.** Limited evidence suggests that coadministration of **UNIFEN** 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 medicinal termination of pregnancy.
- Quinolone antibiotics: Patients taking **UNIFEN** and quinolones may have an increased risk of developing convulsions.
- Aminoglycosides: **UNIFEN** may decrease the excretion of aminoglycosides.
- Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with **UNIFEN.**
- Alcohol, corticosteroids, clopidogrel, ticlopidine, bisphosphonates, pentoxifylline – Increased risk of gastrointestinal bleeding and ulceration.
- Antidiabetic agents – Hypoglycaemic effects of these medicines may be increased.
- Methotrexate – Increased and prolonged methotrexate plasma concentration and an increased risk of methotrexate toxicity. More frequent monitoring is mandatory.
- Bone marrow depressants – The leucopenic and/or thrombocytopenic effects of these medicines may be increased.

4.6 Fertility, pregnancy and lactation

- Pregnant women should not use **UNIFEN** at 20 weeks or later unless specifically advised to do so by a health care professional because it may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

- Additionally it should be avoided at 30 weeks and later in pregnancy because of the additional risk of premature closure of the fetal ductus arteriosus (see Section 4.3 and 4.4).

Breastfeeding

- Safety and efficacy in lactation have not been established (see section 4.3)

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking **UNIFEN**. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The frequency of adverse reactions reported with UNIFEN are summarised in Table 1 as per the MedDRA system organ classification (SOC).

Table 1: Tabulated list of adverse reactions		
System Organ Class	***Frequency***	**Adverse effect**
Blood and lymphatic system disorders	*Less frequent*	Agranulocytosis, thrombocytopenia, anaemias, neutropenia, eosinophilia.
Immune system disorders	*Less frequent*	Aseptic meningitis, angioedema, anaphylaxis, fever, rashes, exacerbation of asthma and bronchospasm
Metabolism and nutrition disorders	*Frequency not known*	Hypokalaemia
Psychiatric disorders	*Frequent*	Depression

Nervous system disorders	*Frequent*	Dizziness, nervousness, tinnitus, drowsiness, insomnia.
	Less frequent	Headache,
Eye disorders	*Less frequent*	Blurred vision
	Frequency not known	Visual impairment, changes in visual colour perception and other toxic amblyopia.
Cardiac disorders	*Less frequent*	Tachycardia, flushing,
	Frequency not known	increase in blood pressure / hypertension, oedema, cardiac failure.
Gastrointestinal disorders	*Frequent*	Nausea, abdominal cramps and pain. Vomiting, diarrhoea, flatulence, constipation, dyspepsia, peptic ulcers, perforation or gastro-intestinal bleeding (sometimes fatal), melaena, haematemesis, gastritis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease.
	Less frequent	Abdominal discomfort

		or pain, gastro-intestinal ulcers, sometimes with bleeding.
Hepato-biliary disorders	*Less frequent*	Hepatitis. Hepatotoxicity, abnormalities in liver function tests
Skin and subcutaneous tissue disorders	*Less frequent*	Allergic dermatitis, erythema multiforme
	Frequency not known	Bullous reactions including Stevens Johnson syndrome and toxic epidermal necrolysis. Drug reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4)
Renal and urinary disorders	*Less frequent*	Oedema, impairment of renal function, cystitis, haematuria, acute reversible renal impairment, interstitial nephritis and nephrotic syndrome.
	Frequency not known	Renal tubular acidosis

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"**6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The most likely symptoms of overdosage are epigastric pain and nausea.

Electrolytes may be corrected by intravenous infusions if necessary.

There is no specific antidote for **Unifen**.

Treatment is symptomatic and supportive.

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 4.8).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 3.1 Antirheumatics (anti-inflammatory agents)

ATC Code: M01A E01

PHARMACOLOGICAL ACTION

Ibuprofen has analgesic, antipyretic and anti-inflammatory activities.

5.2 Pharmacokinetic properties

Ibuprofen is absorbed following oral administration, and peak concentrations are observed after 1 to 2 hours. The half-life in plasma is about 2 hours. Ibuprofen is extensively bound to plasma-proteins. It is rapidly excreted in the urine, approximately 90 % of the dose being recovered as metabolites and their conjugates. Ibuprofen passes slowly into the synovial spaces, remaining there in higher concentrations, as the plasma concentration of ibuprofen declines.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide,

Magnesium stearate,

Maize starch,

Microcrystalline cellulose,

Polysorbate-80,

Sodium starch glycolate

Tablet film coating:

Hydroxypropyl methyl

Cellulose,

Polyethylene glycol-400,

Talc,

Titanium dioxide and ponceau 4R supra.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months – Unifen 200

24 months – Unifen 400

6.4 Special precautions for storage

Unifen 200: Store in well closed containers, at or below 25 °C, protected from moisture.

Unifen 400: Store in well closed containers, at or below 25 °C, protected from moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Unifen 200

White HDPE bottle containing 28, 500 or 1000 tablets.

Silver aluminium patient ready packs of different pack sizes.

Unifen 400

White HDPE bottle containing 100 or 1000 tablets.

Silver aluminium patient ready packs of different pack sizes.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Block A, 1st Floor, Office No 1,

Signet Terrace Office Park,

19 Guinea Fowl Street,

Ext 1, Lenasia,1827

South Africa

8 REGISTRATION NUMBER(S)

Unifen 200: 30/3.1/0440

Unifen 400: 34/3.1/0446

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORIZATION

Date of registration: 20 June 1996 – Unifen 200

Date of registration: 20 September 2002 – Unifen 400

10 DATE OF REVISION OF THE TEXT

31 July 2023