PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S1

1 NAME OF THE MEDICINE

Ibuprofen 200 mg Clicks (200 mg ibuprofen) film coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg ibuprofen.

Contains sugar (lactose monohydrate 8 mg/tablet).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Ibuprofen 200 mg Clicks: White, circular, film-coated tablets, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ibuprofen 200 mg Clicks is indicated for the treatment of mild pain of inflammatory origin and fever, including:

- Soft tissue injuries as sprains and strains
- headache
- back pain of musculoskeletal origin
- fever
- muscular aches and pain
- menstrual pain
- dental pain
- pain associated with migraine
- earache

4.2 Posology and method of administration

Adults:

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

The recommended dosage of Ibuprofen 200 mg Clicks is 1,200 mg daily in divided doses (1 to 2 tablets every four hours) for the relief of:

- mild to moderate pain of
- Soft tissue injuries such as sprains and strains
- Dental pain
- Back pain of musculoskeletal origin
- Earache
- Pain associated with migraine
- Muscular ache and pains
- Fever
- Menstrual pain

The total daily dose of Ibuprofen 200 mg Clicks should not exceed 1,200 mg. Once the acute phase has been brought under control, it is normal practice to revert to a maintenance dosage.

Paediatric Population:

Not to be given to children under 12 years of age.

Method of Administration

For oral use and short-term use only.

4.3 Contraindications

- Hypersensitivity to ibuprofen or any of the excipients in Ibuprofen 200 mg Clicks.
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, or urticaria) in response to aspirin or other non-steroidal anti-inflammatory medication.

- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Severe heart failure (NYHA Class IV), renal failure or hepatic failure (see section 4.4)
- Last trimester of pregnancy and during labour.

4.4 Special warnings and precautions for use

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 ibuprofen therapy. In view of ibuprofen's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and gastrointestinal and cardiovascular risks below).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory

Bronchospasm may be precipitated in patients suffering from, or with a previous history of, bronchial asthma or allergic disease.

Other NSAIDs

The use of Ibuprofen as in Ibuprofen 200 mg Clicks with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

SLE and mixed connective tissue disease

Systemic lupus erythematosus as well as those with mixed connective tissue disease – increased risk of aseptic meningitis (see section 4.8).

Renal

Patients with congestive heart 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 NSAID- induced inhibition of renal prostaglandin synthesis.

Renal impairment as renal function may further deteriorate (see sections 4.3 and 4.8). There is a risk of renal impairment in dehydrated children and adolescents.

Hepatic

Hepatic dysfunction (see sections 4.3 and 4.8).

Cardiovascular and cerebrovascular effects

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

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. ≤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, and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Impaired female fertility

There is limited evidence that medicines which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

Pregnancy: Regular use of NSAIDs such as Ibuprofen 200 mg Clicks 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 (see section 4.6).

Gastrointestinal

NSAIDs such as Ibuprofen 200 mg Clicks should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

GI bleeding, ulceration or perforation, which can be fatal has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti- platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Ibuprofen 200 mg Clicks, the treatment should be withdrawn.

Dermatological

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDs (see section 4.8).

Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Ibuprofen 200 mg Clicks should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Anti-coagulants

Care is required in those who are also receiving warfarin and other anti-coagulants.

Ibuprofen 200 mg Clicks should be discontinued in patients who experience blurred or diminished vision or changes in colour vision. Patients with collagen disease may be at increased risk of developing aseptic meningitis.

Information of excipients of Ibuprofen 200 mg Clicks

Ibuprofen 200 mg Clicks contains sugar (lactose monohydrate). Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take Ibuprofen 200 mg Clicks.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Ibuprofen (like other NSAIDs) should be avoided in combination with:

Aspirin (Acetylsalicylic Acid): Concomitant administration of ibuprofen as in Ibuprofen 200 mg Clicks and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects unless low-dose aspirin (not above 75mg daily) has been advised by a doctor (see Section 4.4).

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin (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).

Other NSAIDs including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4).

Ibuprofen as in Ibuprofen 200 mg Clicks should be used with caution in combination with:

Corticosteroids: as these may increase the risk of gastrointestinal ulceration or bleeding (see Section 4.4).

Antihypertensives and diuretics: since NSAIDs may diminish the effects of these medicines. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co- administration of an ACE inhibitor or Angiotensin II antagonist and medicines that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics can increase the risk of nephrotoxicity of NSAIDs such as Ibuprofen 200 mg Clicks.

Anticoagulants: NSAIDs such as Ibuprofen 200 mg Clicks may enhance the effects of anti-coagulants, such as warfarin (See section 4.4).

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Cardiac glycosides: NSAIDs such as Ibuprofen 200 mg Clicks may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: There is evidence for potential increase in plasma levels of lithium.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: NSAIDs such as Ibuprofen 200 mg Clicks should not be used for 8-12 days after

mifepristone administration as NSAIDs such as Ibuprofen 200 mg Clicks can reduce the effect of mifepristone.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs such as Ibuprofen 200 mg Clicks are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs such as Ibuprofen 200 mg Clicks are given with zidovudine. There is evidence of an increased risk haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Quinolone antibiotics: Patients taking NSAIDs such as Ibuprofen 200 mg Clicks and quinolones may have an increased risk of developing convulsions.

Aminoglycosides: Ibuprofen 200 mg Clicks may decrease the excretion of aminoglycosides.

Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with Ibuprofen 200 mg Clicks.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal 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. Administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryofoetal lethality. During the first and second trimester of pregnancy, Ibuprofen 200 mg Clicks should not be given unless clearly necessary. If Ibuprofen 200 mg Clicks 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 foetus 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 the 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, Ibuprofen 200 mg Clicks is contraindicated during the third trimester of pregnancy.

Breastfeeding

In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

Fertility

See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking Ibuprofen 200 mg Clicks. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Adverse events which have been associated with Ibuprofen are given below, listed by system organ class and frequency. Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

The list of the following adverse events relates to those experienced with ibuprofen at OTC doses for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse events may occur.

The adverse events observed most often are gastrointestinal in nature. Adverse events are mostly

dose-dependent, in particular the risk of occurrence of gastrointestinal bleeding is dependent on the dosage range and duration of treatment.

Clinical studies suggest that use of ibuprofen, particularly at a high dose 2400mg/day may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke), (see section 4.4).

Tabulated list of adverse reactions:

System Organ Class	**Frequency**	**Side effect**
Blood and the lymphatic system disorders	Less frequent	Haematopoietic disorders (anaemia, leukopenia, thrombocytopenia, neutropenia, eosinophilia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.
Immune system disorders	Less frequent Frequency unknown	Hypersensitivity reactions consisting of: Urticaria and pruritus Severe hypersensitivity reactions. Symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock). Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.
Psychiatric disorders	Frequent	Depression
Nervous system disorders	Frequent Less frequent	Dizziness, nervousness, tinnitus, drowsiness, insomnia Headache, aseptic meningitis
Eye disorders	Frequent	Visual impairment, changes in visual colour perception, toxic amblyopia
Cardiac disorders	Frequency	Cardiac failure and oedema

	unknown	
Vascular disorders	Frequency unknown	Hypertension
Gastrointestinal disorders	Frequent Less frequent	Diarrhoea, flatulence, constipation and vomiting Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis, dyspepsia, exacerbation of colitis and Crohn's disease Abdominal discomfort or pain, nausea, vomiting, gastrointestinal ulcers, sometimes with bleeding
Hepato-biliary disorders	Less frequent	Hepatotoxicity, abnormalities in liver function tests, liver disorders
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Various skin rashes Severe forms of skin reactions such as bullous reactions including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis can occur. Medicine reaction with eosinophilia and systemic symptoms (DRESS syndrome)
Renal and urinary disorders	Less frequent Frequency unknown	Acute renal failure, cystitis, haematuria, interstitial nephritis, nephrotic syndrome, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema. Renal insufficiency
Investigations	Less	Decreased haemoglobin levels

	frequent	

Description of Selected Adverse Reactions

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm, dyspnoea or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The pathogenic mechanism of medicine induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with medicine intake, and disappearance of symptoms after medicine discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen, in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued~~[s]~~ monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

Adverse reactions also must be reported to Unicorn Pharmaceuticals (Pty) Ltd to vigilance@unicornpharma.co.za. By reporting side effects, you can help provide more information on the safety of Ibuprofen 200 mg Clicks.

4.9 Overdose

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1,5-3 hours.

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs such as Ibuprofen 200 mg Clicks will develop no more than nausea, vomiting, epigastric pain, or diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. 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. Exacerbation of asthma is possible in asthmatics.

Management

Electrolytes may be corrected by intravenous infusions, if necessary. There is no specific antidote to Ibuprofen 200 mg Clicks. Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Class: A 2.7 Antipyretic or antipyretic and anti-inflammatory analgesics.

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, ATC Code: M01AE01.

Ibuprofen is described as a 2-(4-isobutylphenyl) propionic acid and is a non-steroidal compound which exhibits anti-inflammatory, analgesic and anti-pyretic activities. NSAIDs demonstrate its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swelling and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin (acetylsalicylic acid) on platelet aggregation when they are dosed concomitantly. Some pharmacodynamics studies show that when single doses of ibuprofen 400mg was taken within 8 h

before or within 30 min after immediate release aspirin (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 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 4.5).

5.2 Pharmacokinetic properties

Absorption

Ibuprofen is rabidly absorbed following oral administration. An oral dose taken on an empty stomach by human volunteers produced peak serum levels after three quarters of an hour. Absorption was slower and peak serum levels lower after food.

Distribution

Ibuprofen is rapidly distributed throughout the whole body.

Biotransformation

Two major metabolites of ibuprofen have been isolated from human urine. They are (+)2-4'hydroxy-2-methylpropyl) phenylpropionic acid (metabolite A) and (+)2,4'(2-carboxylpropyl) phenylpropionic acid (metabolite B). The levels in human serum of both metabolites have been measured after single and repeated doses.

Elimination

The excretion is rapid with no evidence of accumulation and complete via the kidneys. Elimination half-life is approximately 2 hours. About 60 % of a dose is excreted in the urine, and the excretory products are in the form of either free or conjugated metabolites A and B. No ibuprofen is found.
In limited studies, ibuprofen appears in the breast milk in very low concentrations.

Linearity/non-linearity

Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty

stomach. When taken with food, peak levels are observed after 1 to 2 hours. These times may vary with different dosage forms.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose Microcrystalline E460 (Avicel pH 101)

Lactose Monohydrate

Croscarmellose sodium

Silica Colloidal Anhydrous

Polyvinylpyrrolidone (PVPK-30)

Maize Starch

Sodium lauryl sulphate

Magnesium Stearate E572

Coating agent: *Ready-for-use mixture containing:*

Hydroxy propyl cellulose E463, Hypromellose – 3cps E464, Hypromellose – 6cps E464, Macrogol 400, Titanium Dioxide E171, Isopropyl alcohol.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

Ibuprofen 200 mg Clicks tablets are packed in White opaque PVC/ Aluminium blisters. The blisters are constructed of PVC (250 µ thickness) and Aluminium foil (0.02 mm thickness).

Ibuprofen 200 mg Clicks tablets are supplied in blister packs of 12, 20 and 24 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

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8 REGISTRATION NUMBER(S)

56/2.7/0645

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 May 2024

10 DATE OF REVISION OF THE TEXT

Not applicable