**Approved Professional Information for Medicines for Human Use:**

# AUSTIFEN

## SCHEDULING STATUS

S3

## 1. NAME OF THE MEDICINE

AUSTIFEN-200 TABLETS

AUSTIFEN-400 TABLETS

AUSTIFEN-600 TABLETS

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AUSTIFEN–200 TABLETS

Each film-coated tablet contains ibuprofen 200 mg.

Contains sugar: lactose monohydrate 8,00 mg.

AUSTIFEN-400 TABLETS

Each film-coated tablet contains ibuprofen 400 mg.

Contains sugar: lactose monohydrate 16,00 mg.

AUSTIFEN–600 TABLETS

Each film-coated tablet contains ibuprofen 600 mg.

Contains sugar: lactose monohydrate 24,00 mg.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets.

AUSTIFEN-200 TABLETS:

White, circular, film-coated tablets, plain on both the sides.

AUSTIFEN-400 TABLETS:

White capsule shaped film-coated tablets, plain on both the sides.

AUSTIFEN-600 TABLETS:

White capsule shaped film coated tablets, plain on one side and breakline on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

AUSTIFEN is indicated for the treatment of:

- rheumatoid arthritis
- juvenile rheumatoid arthritis or 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 dysmennorhoea, dental, post-episiotomy and post-partum pain
- soft tissue injuries such as sprains and strains
- anti-pyretic.

### 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 AUSTIFEN is 1 200 mg daily in divided doses. Some patients can be maintained on 600 to 1 200 mg daily. In severe conditions, it can be advantageous to increase the

dosage until the acute phase has been brought under control. To relieve early morning stiffness, the first dose of the day can be given immediately after the patient awakes.

For the relief of mild to moderate pain, the following doses are recommended:

- dysmenorrhoea – 1 200 mg per day in three divided doses
- in cases of dental or post-episiotomy pain an initial dose of 800 mg may be given.

**The total daily dose of AUSTIFEN should not exceed 2 400 mg. Once the acute phase has been brought under control, a maintenance dosage should be reverted to.**

*Acute gout*

2 400 mg daily either as 800 mg 8 hourly or 600 mg 6 hourly until the acute symptoms have been relieved. If the acute symptoms do not resolve within three days, consult a health professional.

*Children*

In Juvenile Rheumatoid Arthritis, the total daily dosage of AUSTIFEN is

20 mg/kg of body mass given in divided doses.

Safety in children under one year of age has not been proven (see section 4.3).

*Pain*

Initial dose 5 mg/kg of body weight. A second dose of 5 mg/kg may be given after 2 hours if pain is not controlled. Thereafter 5 mg/kg every 4 - 6 hours.

DO NOT EXCEED 20 mg/kg of bodyweight per day. If pain persists for more than 7 days, consult a medical professional.

*Fever*

5 mg/kg of bodyweight every 4 - 6 hours.

DO NOT EXCEED 20 mg/kg of bodyweight per day.

If fever persists for more than 3 days, consult a medical professional.

**Method of administration**

For oral use.

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

**Paediatric population**

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

## 4.3 Contraindications

- Hypersensitivity to ibuprofen or to any of the excipients listed in section 6.1.
- Peptic ulcer disease, gastro-intestinal bleeding, haemorrhage or perforation (PUBs) related to previous NSAIDs.
- Active or history of recurrent ulcer/ haemorrhage/ perforations.
- Patients sensitive to aspirin or another nonsteroidal anti-inflammatory drugs (NSAIDs).
- History of severe allergic reactions such as anaphylaxis or angio-edema, induced by aspirin or other NSAIDs because of the possibility of cross-sensitivity due to structural relationships which exist among non-steroidal anti-inflammatory medicines, acute allergic reactions are likely to occur in patients who have exhibited allergic reactions to these compounds.
- Aspirin-induced nasal polyps associated with bronchospasm.
- Children under the age of 12 years.
- Patients with severe heart failure (NYHA Class IV), hepatic failure or renal failure (see section 4.4).
- The use of AUSTIFEN 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)
- Safety in lactation has not been established.
- Pregnancy and during labour (see section 4.4 and 4.6).

## 4.4 Special warnings and precautions for use

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

**Caution is advised in the following groups of patients**

- Patients receiving coumarin anticoagulants.
- Patients with collagen disease (mixed connective tissue disorders) and systemic lupus erythematosus may be at risk of developing aseptic meningitis.
- Patients with mild reactions such as allergic rhinitis, urticaria or skin rash induced by aspirin or other NSAIDs.
- Patients suffering from, or with a previous history of, bronchial asthma, chronic rhinitis, bronchospasm or allergic diseases since NSAIDs, such as in AUSTIFEN have been reported to precipitate bronchospasm, urticaria or angioedema in such patients.
- Patients with anaemia.
- Patients with bleeding disorders.

**Concomitant use with other NSAIDs**

Use of AUSTIFEN with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors should be avoided due to the increased risk of ulceration or bleeding (see section 4.5).

**Medication overuse headache**

The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of analgesic medication. Patients with medication overuse headache should not be treated by increasing the dose of the analgesic. In such cases the use of analgesics should be discontinued.

**Concomitant alcohol**

The concomitant consumption of excessive alcohol with NSAIDs, including ibuprofen may increase

the risk of adverse effects on the gastrointestinal tract, such as GI haemorrhage or the central nervous system, possibly due to an additive effect.

**Cardiovascular and cerebrovascular effects**

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention 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 such as myocardial infarction or stroke. Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200mg/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 AUSTIFEN 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.

**Risk of foetal renal dysfunction**

The use of nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen such as in AUSTIFEN around 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Oligohydramnios is often, but not always, reversable with treatment discontinuation. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation (see section 4.3 and 4.6). Invasive procedures such as exchange transfusion or dialysis may be required. If AUSTIFEN treatment is deemed necessary between 20 to 30 weeks of pregnancy, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if AUSTIFEN treatment extends beyond 48 hours. Discontinue AUSTIFEN if oligohydramnios occurs

and follow up according to clinical practice (see section 4.3 and 4.6).

**Closure of foetal ductus arteriosus**

Regular use of NSAIDs such as AUSTIFEN 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.

**Masking of symptoms of underlying infections**

The antipyretic, analgesic and anti-inflammatory action of ibuprofen may mask symptoms of the occurrence or worsening 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 bacteria complications to varicella.

When AUSTIFEN is 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.

**Renal effects**

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration. There is a risk of renal impairment especially in dehydrated children, adolescents and the elderly.

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen at higher than recommended doses. This risk is increased with the use of codeine/ibuprofen as patients may become dependent on the codeine component (see warning on Opioid use disorder, section 4.8 and section 4.9). Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

As with other NSAIDs, long-term administration of ibuprofen, such as in AUSTIFEN has resulted in renal papillary necrosis and other renal pathologic changes. 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. Other patients at risk include those with liver dysfunction, those taking diuretics and ACE inhibitors and the elderly.

For these patients, use the lowest effective dose, for the shortest possible duration and monitor renal function especially in long-term treated patients (see also section 4.3).

Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

**Gastrointestinal (GI) bleeding and perforation**

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

The risk of GI bleeding, ulceration or perforation is higher with increasing AUSTIFEN 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. Combination therapy with protective medicines (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other medicines likely to increase gastrointestinal risk (see below and section 4.5).

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

Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective

serotonin-reuptake inhibitors or antiplatelet medicines such as aspirin (see section 4.5).

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

AUSTIFEN 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.

**Severe Skin Reactions**

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported.

Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring within the first month of treatment in the majority of cases. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing medicines. AUSTIFEN should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

In exceptional cases, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of AUSTIFEN in case of varicella.

Also see DRESS below.

**Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS)**

DRESS has been reported in patients taking NSAIDs such as ibuprofen, the active ingredient contained in AUSTIFEN. 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 AUSTIFEN and evaluate the patient immediately.

**Changes in vision**

AUSTIFEN should be discontinued in patients who experience blurred or diminished vision, or changes in colour vision.

**Ulcerative stomatitis**

Patients may develop ulcerative stomatitis.

**Haematological effects**

Ibuprofen, like other NSAIDs, can interfere with platelet aggregation and prolong bleeding time in normal subjects.

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Ibuprofen, like other NSAIDs, can interfere with platelet aggregation and prolong bleeding time in normal subjects.

**Aseptic meningitis**

Aseptic meningitis has been observed in patients on ibuprofen therapy, such as AUSTIFEN. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

**Opioid use disorder (abuse and dependence)**

Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids such as codeine. Abuse or intentional misuse of codeine may result in overdose and/or death.

Serious clinical outcomes, including fatalities, have been reported in association with abuse and dependence with codeine/ibuprofen combinations, particularly when taken for prolonged periods at higher than recommended doses. These have included reports of gastrointestinal perforations, gastrointestinal haemorrhages, severe anaemia, renal failure, renal tubular acidosis and severe hypokalaemia associated with the ibuprofen component.

Patients should be informed about the risks and signs of OUD as well as serious clinical outcomes. If these signs occur, patients should be advised to contact their doctor.

Withdrawal symptoms, such as restlessness and irritability may occur once the medicine is stopped.

**Elderly**

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

AUSTIFEN should be given with care to the elderly.

**Paediatric population**

There is a risk of renal impairment in dehydrated children and adolescents.

**Excipients: lactose**

AUSTIFEN contains lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take AUSTIFEN.

## 4.5. Interaction with other medicines and other forms of interaction

- Anticoagulants – Enhancement of anticoagulant effect and the possibility of gastro-intestinal ulceration or bleeding. Anti-coagulants: AUSTIFEN may enhance the effects of anti-coagulants such as warfarin.
- Anti-platelet medicines and selective serotonin re-uptake inhibitors (SSRIs): increased risk of gastro-intestinal bleeding.

- Alcohol, corticosteroids, clopidogrel, ticlopidine, bisphosphonates, oxpentifylline – increased risk of gastro-intestinal bleeding and ulceration.
- Antidiabetic medicines including sulphonylureas – Hypoglycemic effects of these medicines may be increased.
- Digoxin (cardiac glycosides) – May exacerbate cardiac failure, reduce GFR and ~~[]~~increase in serum digoxin concentrations.
- Lithium – Increase in the steady-state concentration of lithium.
- Methotrexate – Increased and prolonged Methotrexate plasma concentration and an increased risk of Methotrexate toxicity.
- Nephrotoxic medicines e.g – ciclosporin – Increased risk of nephrotoxicity.
- Anti-hypertensives, beta-blockers or diuretics – Reduction or reversal of the anti-hypertensive effect may occur. Diuretics can also increase the risk of nephrotoxicity of AUSTIFEN.
- Bone marrow depressants – The leucopenic and / or thrombocytopenic effects of these medicines may be increased.
- Corticosteroids: increased risk of gastro-intestinal ulceration or bleeding (PUBs).
- NSAIDs: Use of two or more NSAIDs, including cox-2 inhibitors concomitantly could result in an increase in side effects.
- Aspirin (Acetylsalicylic acid): As with other medicines containing NSAIDs, concomitant administration of AUSTIFEN and aspirin 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 aspirin 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 use.
- Cholestyramine: The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical

significance is unknown.

- Mifepristone: A decrease in the efficacy can theoretically occur due to the anti-prostaglandin properties of AUSTIFEN. Limited evidence suggests that coadministration of AUSTIFEN 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: Animal data indicates that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking AUSTIFEN and quinolones may have an increased risk of developing convulsions.
- Aminoglycosides: AUSTIFEN may decrease the excretion of aminoglycosides.
- Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with AUSTIFEN.
- Tacrolimus: Possible increase risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
- CYP2C9 Inhibitors: Concomitant administration of ibuprofen such as in AUSTIFEN with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen exposure by approximately 80 to 100 % has been shown. Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

Use of AUSTIFEN in pregnancy and during labour is contraindicated.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of

cardiac malformation and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy.

The use of NSAIDs, such as AUSTIFEN used at 20 weeks gestation or later may cause serious kidney problems in an unborn baby.

After around 20 weeks of pregnancy, the unborn babies' kidneys produce most of the amniotic fluid. Amniotic fluid provides a protective cushion and helps the unborn babies' lungs, digestive system, and muscles develop. Foetal renal dysfunction can lead to oligohydramnios due to the low levels of amnionic fluid. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation (see section 4.2 and 4.4).

Regular use of NSAIDs such as AUSTIFEN 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 newborn. The onset of labour may be delayed and its duration increased (see section 4.4).

**Lactation**

In the limited studies so far available, NSAIDs can appear in the breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

**Fertility**

The use of AUSTIFEN 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 AUSTIFEN should be considered.

### 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

### Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during reported clinical trials and recorded post-market spontaneous reports with ibuprofen.

| System Organ Class | Frequency | | |
|---|---|---|---|
| | **Frequent** | **Less Frequent** | **Not known** |
| Infections and infestations | | Rhinitis, aseptic meningitis | |
| Blood and lymphatic system disorders | | Agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, neutropenia, eosinophilia, leukopenia | |
| Immune system disorders | | Hypersensitivity, anaphylactic reaction | |
| Metabolism and nutrition disorders | | | Hypokalaemia* |
| Psychiatric disorders | | Insomnia, anxiety, depression, confusional state | |

| | | | |
|---|---|---|---|
| Nervous system disorders | Headache, dizziness | Nervousness, paraesthesia, somnolence, optic neuritis, and drowsiness | |
| Eye disorders | | Blurred vision, visual impairment, changes in visual colour perception and other toxic amblyopia | |
| Ear and labyrinth disorders | | Hearing impaired, tinnitus, vertigo | |
| Cardiac disorders | | Tachycardia, cardiac failure, myocardial infarction | |
| Vascular disorders | | Flushing, hypertension. | |
| Respiratory, thoracic and mediastinal disorders | | Asthma, bronchospasm, dyspnoea | |
| Gastrointestinal disorders | Abdominal discomfort, peptic ulceration, gastrointestinal bleeding, nausea, vomiting, abdominal cramps and pain, | Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation, pancreatitis | Exacerbation of colitis and Crohn’s disease. |

| | | | |
|---|---|---|---|
| | dyspepsia, diarrhoea, haematemesis, flatulence, constipation, melaena | | |
| Hepatobiliary disorders | | Hepatitis, jaundice, abnormal hepatic function, hepatic failure, hepatotoxicity | Abnormal liver function tests |
| Skin and subcutaneous tissue disorders | Rash | Urticaria, pruritus, purpura, angioedema, photosensitivity reaction, allergic dermatitis, erythema multiforme, bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis | [a)]Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematous pustulosis (AGEP) |
| Renal and urinary disorders | | Impairment of renal function, acute reversible renal failure, tubulointerstitial nephritis and nephrotic syndrome, cystitis, haematuria | Renal tubular acidosis* |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | Fatigue | Oedema, fever | |

[a)] Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4)

**Description of selected adverse reactions**

*Gastrointestinal disorders:*

The most frequently observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, gastrointestinal haemorrhage and exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following ibuprofen administration. Less frequently, gastritis, duodenal ulcer, gastric ulcer and gastrointestinal perforation have been observed.

*Immune system disorders:*

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

**Renal tubular acidosis and hypokalaemia:*

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 due to dependence on the codeine component.

*Cardiac disorders and vascular disorders:*

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical studies suggest that use of ibuprofen, particularly at high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke (see section 4.4).

*Infections and infestations:*

Rhinitis and aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).
Exacerbation of infection-related inflammations coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of Ibuprofen the patient is therefore recommended to go to a doctor without delay.

*Skin and subcutaneous tissue disorders:*

In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and

infestations").

***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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za.

## 4.9 Overdose

*Toxicity*

Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults. However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400 mg/kg or greater.

*Symptoms*

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours. The most likely symptoms of overdosage are epigastric pain, nausea, vomiting, lethargy and drowsiness.

Central nervous system (CNS) effects include headache, tinnitus, dizziness, convulsion, and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea, diarrhoea and depression of the CNS and respiratory system have also been rarely reported.

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. Disorientation, excitation, fainting and cardiovascular toxicity, including hypotension, bradycardia and tachycardia have been reported. In cases of significant overdose, renal failure and liver damage are possible.

Large overdoses are generally well tolerated when no other medicines are being taken.

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).

Exacerbation of asthma is possible in asthmatics.

*Management*

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Electrolytes may be corrected by intravenous infusions if necessary.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition. There is no specific antidote for AUSTIFEN.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 3.1 Antirheumatics (Anti-inflammatory agents).

Pharmacotherapeutic group**:** Propionic acid derivatives.

ATC Code: M01AE01

Ibuprofen has analgesic, antipyretic and anti-inflammatory activities. Its analgesic activity is exerted through a peripheral action of blocking pain-impulse generation. The peripheral action of ibuprofen may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation. Ibuprofen exerts its antipyretic effects by acting centrally on the hypothalamic heat-regulating centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss.

Ibuprofen exerts its anti-inflammatory action peripherally in inflamed tissue by reducing prostaglandin activity and by inhibiting synthesis and / or actions of other local mediators of the inflammatory response.

### 5.2 Pharmacokinetic properties

Rapidly absorbed after oral administration. Onset of action for pain relief is 30 minutes and the time for peak effect for fever is 2 to 4 hours. The half-life of Ibuprofen is about 2 hours and the duration of action for fever is 6 to 8 hours or more and is 4 to 6 hours for pain. The excretion of ibuprofen is rapid and complete with more than 90% of an ingested dose excreted in the urine as metabolites or their conjugates.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Lactose monohydrate

Croscarmellose sodium

Colloidal anhydrous silica

Polyvinyl povidone

Maize starch

Magnesium stearate

Sodium lauryl sulphate

Film coating:

Hydroxypropyl cellulose

Hydroxypropyl methyl cellulose

Polyethylene glycol

Titanium dioxide

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store in a dry place at or below 25 °C. Protect from light.

Keep blister packs in the outer carton until required for use.

Keep the HDPE containers well closed.

### 6.5 Nature and contents of container

AUSTIFEN-200 tablets

Opaque Aluminium/PVC blister packs of 1 x 12, 2 x 12, 4 x 12, 7 x 12, 1 x 15,

1 x 16 and 3 x 14 tablets.

Bulk pack (White HDPE jars) of 1000 tablets.

AUSTIFEN-400 tablets

Opaque Aluminium/PVC blister packs of 1 x 12, 2 x 12, 4 x 12, 7 x 12, 1 x 15,

1 x 16 and 3 x 14 tablets.

Bulk pack (White HDPE jars) of 1000 tablets.

AUSTIFEN-600 tablets

Opaque Aluminium/PVC blister packs of 1 x 12, 2 x 12, 4 x 12, 7 x 12, 1 x 15,

1 x 16 and 3 x 14 tablets.

Bulk pack (White HDPE jars) of 1000 tablets.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd.

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## 8. REGISTRATION NUMBERS

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