SCHEDULING STATUS: **S1**

1. NAME OF THE MEDICINE

BETAGESIC, 200 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Ibuprofen	200 mg
Preservatives:	
Methyl hydroxybenzoate	0,14 % m/m
Propyl hydroxybenzoate	0,06 % m/m

Sugar free

For a full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Film-coated tablets

Red coloured, circular, biconvex shaped, and film-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

BETAGESIC is indicated for the relief of headache from musculo-skeletal origin, feverishness, muscular aches and pain, menstrual pain, and dental pain.

4.2 Posology and method of administration

Posology

Adults and children over 12 years: Initial dose 2 tablets with water, then if necessary, 1 or 2 tablets every four hours. Do not take more than 6 tablets in 24 hours.

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

If symptoms persist for more than 7 days, consult your doctor.

Paediatric population

Not to be given to children under 12 years.

Method of administration

To be taken orally.

4.3 Contraindications

- Contraindications
- Hypersensitivity to ibuprofen or to any of the excipients found in section 6.1
- Heart failure.
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including BETAGESIC.
- BETAGESIC should not be given to patients with bleeding disorders, cardiovascular disease, peptic ulceration, or a history of such ulceration.
- Active or history of recurrent ulcer, haemorrhage, or perforations.
- Patients who are sensitive to aspirin should not be given BETAGESIC.
- Severe renal failure or hepatic failure (see section 4.4).

- Do not use NSAIDs in women from 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/ foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.6).

4.4 Special warnings and precautions for use

General:

Asthma sufferers should only take BETAGESIC after consulting a doctor. Caution is advised in those patients who are receiving coumarin anticoagulants.

Renal:

Ibuprofen should be used with care in patients with mild to moderate impaired renal function.

Hepatic:

Hepatic dysfunction (see section 4.3 and section 4.8).

Foetal Toxicity:

Limit use of NSAIDs, including BETAGESIC, between 20 to 30 weeks of pregnancy due to the risk of oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.3).

If NSAID treatment is prescribed between 20 weeks and 30 weeks gestation, limit BETAGESIC use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if BETAGESIC treatment extends beyond 48 hours. Discontinue BETAGESIC if oligohydramnios occurs and follow up according to clinical practice.

DRESS:

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as BETAGESIC. 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. Eosinophilia 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 BETAGESIC and evaluate the patient immediately.

Cardiovascular and cerebrovascular effects:

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

Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) and should only be treated with diclofenac after careful consideration.

Respiratory:

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

Other NSAIDs:

Concomitant use of BETAGESIC with other 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 patients with mixed connective tissue disease and are receiving ibuprofen have increased risk of aseptic meningitis. Studies suggest that the use of ibuprofen, particularly at high doses and in long term treatment may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke.

Elderly:

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

Gastrointestinal:

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 gastrointestinal perforation, ulceration, or bleeding (PUBs) is higher with increasing doses of BETAGESIC, in patients with a history of ulcers, and in the elderly.

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

BETAGESIC 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.

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 medicines such as aspirin (see section 4.5).

Severe skin reactions:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing. BETAGESIC should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Masking of symptoms of underlying infections:

BETAGESIC can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When BETAGESIC is

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

Impaired female fertility:

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

Excipients:

BETAGESIC contains methyl hydroxybenzoate and propyl hydroxybenzoate and may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per 200 mg film-coated tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

Anti-coagulants: BETAGESIC may enhance the effects of anti-coagulants such as warfarin. Caution is advised in those patients who are receiving coumarin anticoagulants.

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding. Patients who are sensitive to aspirin should not be given BETAGESIC.

Aspirin (acetylsalicylic acid): BETAGESIC should be avoided in combination with aspirin unless low-dose aspirin (not above 75 mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see section 4.4). Studies suggest that NSAIDS including BETAGESIC may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. No firm conclusions have been made for regular NSAIDs use and no clinically relevant effect is considered to be likely for occasional NSAIDs use like BETAGESIC.

NSAIDs: use of two or more NSAIDs concomitantly could result in an increase in side effects.

Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Antihypertensives and diuretics: 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.

Cardiac glycosides: BETAGESIC may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: Potential increase in plasma levels of lithium.

Methotrexate: There is evidence for the potential increase in plasma levels of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: BETAGESIC should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Tacrolimus: Possible increased risk of nephrotoxicity when BETAGESIC is given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk haemarthroses and haematoma in HIV-positive haemophiliacs receiving concurrent treatment with zidovudine and BETAGESIC.

Quinolone antibiotics: BETAGESIC can increase the risk of convulsions associated with quinolone antibiotics. Patients taking BETAGESIC and quinolones may have an increased risk of developing convulsions.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Use of NSAIDs, including BETAGESIC, can cause premature closure of the foetal ductus arteriosus and foetal renal dysfunction leading to oligohydramnios and, neonatal renal impairment. Due to these risks, do not use NSAIDs in women from 30 weeks gestation and later in pregnancy. If NSAIDs treatment is prescribed between 20 weeks and 30 weeks gestation, limit BETAGESIC

use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if BETAGESIC treatment extends beyond 48 hours, (see section 4.3 and section 4.4).

Fertility

BETAGESIC may cause impairment of female fertility by an effect of ovulation. This is reversible upon withdrawal of treatment.

Lactation

Patients using BETAGESIC should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

BETAGESIC may affect the ability to drive and use machines due to possible undesirable side effects such as drowsiness, dizziness, blurred vision, and other visual field defects, (see section 4.8**)**.

4.8 Undesirable effects

Side-effects are classified according to MedRA System Organ Class using the following convention:

Frequent, Less frequent and frequency unknown*.

*Frequency unknown: the frequency of the side effect cannot be estimated from the available data.

Frequency	System organ class	Undesirable effects
Less frequent	Blood and lymphatic system disorders	Agranulocytosis, haemopoietic disorders including anaemia, neutropenia, eosinophilia and thrombocytopenia have been observed.
	Immune system disorders	Hypersensitivity reactions consisting of urticaria and pruritus. Severe hypersensitivity reactions, including facial, tongue and throat swelling, dyspnoea, tachycardia, and hypotension (anaphylaxis, angioedema, or severe shock).
	Nervous system disorders	Headache, aseptic meningitis.
	Gastrointestinal disorders	Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain. Peptic ulcers, perforation, or gastrointestinal bleeding, sometimes fatal. Melaena, haematemesis, ulcerative stomatitis.
	Hepato-biliary disorders	Hepatotoxicity, abnormalities in liver function tests.
	Skin and subcutaneous tissue disorders	Skin rash.

		Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.
	Renal and urinary disorders	Cystitis, haematuria, acute renal failure, interstitial nephritis, nephrotic syndrome.
Frequency Unknown	Cardiac disorders	Oedema and cardiac failure.
	Vascular disorders	Hypertension.
	Respiratory, thoracic and mediastinal disorders	Provocation of bronchospasm in patients with asthma.
	Skin and subcutaneous tissue disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS) (see Section 4.4). Acute generalised exanthematous pustulosis (AGEP), photosensitivity reaction.
	Psychiatric disorders	Nervousness; depression, insomnia.
	Nervous system disorders	Drowsiness, headache, dizziness.
	Eye disorders	Blurred vision and other visual field defects.
	Ear and labyrinth disorders	Tinnitus.
	Gastrointestinal disorders	Exacerbation of colitis and Crohn's disease, gastritis.

	Renal and urinary disorders	Impairment of renal function.

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 the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

May also report to Adcock Ingram Limited using the following email:

Adcock.AEReports@adcock.com

4.9 Overdose

Symptoms

The most likely symptoms of overdosage are epigastric pain, nausea, vomiting, or more rarely diarrhoea may develop.

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. 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. Dialysis may be done as ibuprofen is not strongly protein bound. There is no specific antidote to BETAGESIC.

Management should be symptomatic and supportive. 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 bronchospasm.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.7 Anti-pyretic or antipyretic and anti-inflammatory analgesic.

Mechanism of action:

BETAGESIC is a non-steroidal compound, with analgesic, anti-inflammatory and antipyretic activities.

5.2. Pharmacokinetic properties

When taken with food, peak levels are observed after 1 to 2 hours. The half-life of Ibuprofen is about 2 hours. Excretion is via the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica, Maize starch, Methyl hydroxybenzoate, Propyl hydroxybenzoate, Stearic acid, Opadry Pink 04A84530 (HPMC 2910/Hypromellose 15cP, Light liquid paraffin, Erythrosine Aluminium Lake, Sodium acetate trihydrate, Talc, Titanium dioxide).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ºC.

6.5 Nature and contents of container

15’s, 20’s and 42’s in PVC/Al blister packs.

Not all pack sizes may be marketed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

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8. REGISTRATION NUMBER

U/2.7/20

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