Public Assessment Report
Decentralised Procedure

Stufen Instants 8.75mg granules

UK/H/2403/01/DC

UK licence no: PL 00063/0563

Reckitt Benckiser Healthcare (UK) Limited
LAY SUMMARY

On 10 July 2012, the MHRA granted Reckitt Benckiser Healthcare (UK) Limited a Marketing Authorisation (licence) for the medicinal product Strefen Instants 8.75mg granules (PL 00063/0563). This pharmacy medicine (legals status P) contains the active ingredient flurbiprofen. Flurbiprofen belongs to a group of medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). It works by changing how the body responds to pain, swelling and high temperature. Strefen Instants 8.75mg granules are used to relieve the symptoms of sore throats, such as throat soreness, pain and swelling.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Strefen Instants 8.75mg granules outweigh the risks; hence a Marketing Authorisation has been granted.
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### Module 1

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<td>Article 8(3) – Full dossier for a known active substance</td>
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<td><strong>Form</strong></td>
<td>Granules</td>
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<tr>
<td><strong>Strength</strong></td>
<td>8.75mg</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Reckitt Benckiser Healthcare (UK) Limited, 103 – 105 Bath Road, Slough, SL1 3UH</td>
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<td><strong>Reference Member State</strong></td>
<td>United Kingdom</td>
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<td><strong>Concerned Member States</strong></td>
<td>Austria, Czech Republic, Germany, Hungary, Ireland, Italy, Poland, Romania, Slovak Republic</td>
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<td>UK/H/2403/001/DC</td>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Strefen Instants 8.75mg granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One sachet with 850 mg granules contains 8.75 mg of flurbiprofen

Excipient: 4.25 mg of aspartame/sachet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Granule
White to cream-coloured, free-flowing granule with a characteristic mint odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Strefen Instants are indicated for the short term symptomatic relief of sore throat.

Strefen Instants are indicated in children over the age 12 years.

4.2 Posology and method of administration
Method of Administration: For oral use only.

Indicated for adults and children over the age of 12 years:
One sachet of granules to be dissolved in the mouth, then swallowed. Strefen Instants can be taken every 3-6 hours as required, up to a maximum of 5 sachets of granules in a 24 hour period.

The product should not be used for more than 3 days. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).
There are no specific requirements in relation to food and drink.

Paediatric population
The safety and efficacy of Strefen Instants in children under 12 years has not been established.

Elderly population
A general dose recommendation cannot be given, since to date clinical experience is limited. The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.
4.3 Contraindications
Hypersensitivity to flurbiprofen or any of the excipients in the product.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, bronchospasm, rhinitis, angiodema or urticaria) in response to aspirin (acetylsalicylic acid) or other NSAIDs.

Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration) and intestinal ulceration.

History of gastrointestinal bleeding or perforation, severe colitis, haemorrhagic or haematopoietic disorders related to previous NSAIDs therapy.

Last trimester of pregnancy (See section 4.6)

Severe heart failure, renal failure or hepatic failure (see section 4.4).

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).

Phenylketonuria
Strefen Instants contains aspartame which is a source of phenylalanine and this may be harmful for people with phenylketonuria.

Elderly population
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 since NSAIDs have been reported to precipitate bronchospasm in such patients. Strefen Instants should be used with caution in these patients.

Other NSAIDs
The use of Strefen Instants with concomitant NSAIDs including cyclo-oxygenase-2 selective inhibitors should be avoided (see section 4.5).

Systemic lupus erythematosus (SLE) and mixed connective tissue disease
Patients with SLE and mixed connective tissue disease may have an increased risk of aseptic meningitis (see section 4.8).

Renal Impairment
NSAIDs have been reported to cause nephrotoxicity in various forms including interstitial nephritis, nephrotic syndrome and renal failure. The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also
section 4.3). The habitual administration of analgesics may lead to persistent kidney damage with the risk of renal failure, particularly in combination of several analgesic substances, but this is not usually seen with short term, limited use products such as Strefen Instants.

**Hepatic Impairment**
Flurbiprofen is hydrolysed in the liver and impaired hepatic function may reduce the rate at which the drug is removed from the body. At the short term, low doses of Strefen Instants this is not believed to be of significant concern.

**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 trial and epidemiological data suggest that use of some NSAIDs, (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for flurbiprofen.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with flurbiprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

**Effects on the Nervous System**
In the event of prolonged use of analgesics or use beyond the regulations cephalia may occur, which must not be treated with increased doses of the medicinal product.

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

It is recommended to discontinue the use of flurbiprofen treatment in women attempting to conceive, in women who have difficulties conceiving and women who are undergoing investigation of infertility.

**Gastrointestinal**
NSAIDs 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 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 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. Combination therapy with protective agents (e.g., misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly when 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 acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving flurbiprofen, the treatment should be withdrawn.

**Haematological effects**

Flurbiprofen, like other NSAIDs, may inhibit platelet aggregation and prolong bleeding time. Strefen Instant should be used with caution in patients with a potential for abnormal bleeding.

**Dermatological**

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely 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. Strefen Instant should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

**Infections**

Since in isolated cases an exacerbation of infective inflammations (e.g. development of necrotising fasciitis) has been described in temporal association with the use of systemic NSAIDs as a class, the patient is advised to consult a physician immediately if signs of a bacterial infection occur or worsen during the Strefen Instant therapy. It should be considered whether initiation of an anti-infective antibiotic therapy is indicated. In cases of purulent bacterial pharyngitis/tonsillitis, Strefen Instant should be used with antibiotic therapy.

If the symptoms get worse or if new symptoms occur the treatment should be re-evaluated.

If mouth irritation occurs, treatment should be withdrawn.

4.5 Interaction with other medicinal products and other forms of interaction

**Flurbiprofen should be avoided in combination with:**

Other NSAIDS including cyclooxygenase-2 selective inhibitors

Avoid concomitant use of two or more NSAIDs, unless advised by a doctor, as this may increase the risk of adverse effects (esp. gastrointestinal adverse events as ulcers and bleeding), (see section 4.4).
Acetylsalicylic acid (low dose)
As with other products containing NSAIDs, concomitant administration of flurbiprofen and aspirin is not generally recommended because of the potential for adverse events. Unless low-dose aspirin (not above 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see section 4.4).

**Flurbiprofen should be used with caution (not recommended) in combination with:**

**Anticoagulants**
NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

**Anti-platelet Agents**
Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

**Antihypertensive drugs (Diuretics, ACE inhibitors, angiotensin-II-antagonists)**
NSAIDs may reduce the effect of diuretics and other antihypertensive drugs may enhance nephrotoxicity caused by inhibition of cyclooxygenase, especially in patients with compromised renal function (Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter).

**Alcohol**
May increase the risk of adverse reactions, especially of bleeding in the gastrointestinal tract.

**Cardiac glycosides**
NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels - adequate control and, if necessary, dose adjustment is recommended.

**Ciclosporin**
Increased risk of nephrotoxicity.

**Corticosteroids**
May increase the risk of adverse reactions, especially of the gastrointestinal tract (see section 4.3).

**Lithium**
May increase serum levels of glycosides – adequate control and, if necessary, dose adjustment is recommended.

**Methotrexate**
The administration of NSAIDs within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.

**Mifepristone**
NSAIDs should not be used for 8 – 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
Oral antidiabetics
Alteration of blood glucose levels reported (increased check rate recommended).

Phenytoin
May increase serum levels of phenytoin – adequate control and, if necessary, dose adjustment is recommended.

Potassium sparing diuretics
Concomitant use may cause hyperkaliaemia (check of serum potassium is recommended).

Probenecid Sulfinpyrazone
Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of flurbiprofen.

Quinolone antibiotics
Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Selective serotonin reuptake inhibitors (SSRI’s)
Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Tacrolimus
Possible increased 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.

No studies so far have revealed any interactions between flurbiprofen and tolbutamide or antacids.

Paediatric Population
No clinical data is available for children under 12 and use below this age is not recommended. Children between 12 and 17 have been included in clinical assessment of flurbiprofen 8.75mg and no significant differences in efficacy or safety established.

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. In animals, administration of a prostaglandin synthesis inhibitor had been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increase incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, flurbiprofen should not be
given unless clearly necessary. If flurbiprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low as possible 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 oligo-hydroamniosis;

The mother and the neonate, at the end of pregnancy, to:
- Possible prolongation of bleeding time, an anti-aggregation effect which may occur even at very low doses.
- Inhibitions of uterine contractions resulting in delayed or prolonged labour.

Consequently, flurbiprofen is contraindicated during the third trimester of pregnancy.

**Breastfeeding**
In limited studies, flurbiprofen appears in the breast milk in very low concentration. However, because of possible adverse effects of NSAIDs on breast-fed infants, Strefen Instants are not recommended for use in nursing mothers.

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

**4.7 Effects on ability to drive and use machines**
No studies on the effects on the ability to drive and use machines have been performed.

Dizziness and visual disturbances are possible undesirable effects after taking NSAIDS. If affected, patients should not drive or operate machinery.

**4.8 Undesirable effects**

a) **Summary of safety profile**

Low dose Flurbiprofen indicated for the short term treatment of sore throats exhibits primarily gastrointestinal adverse events. These are non-serious and transient in nature. Other non-serious, transient events noted during clinical assessment are typical of the patient group likely to be seeking alleviation of sore throat and similar symptoms associated with colds and influenza-type illness.

Common undesirable effects include a burning sensation or discomfort in the mouth, alteration of taste, headache and diarrhoea. All of these effects are transient and non-serious in nature.

b) **Summary of adverse reactions**

The following list of adverse effects relates to clinical assessment with flurbiprofen 8.75mg at OTC doses for short-term use.
(Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10000 to <1/1000), Very rare (<1/10000), not known (cannot be estimated from the available data))

**Blood and lymphatic system disorders**
Uncommon: Lymphadenopathy
Rare: Anaemia
Very Rare: Haematopoietic disorders

**Cardiac disorders**
Rare: Palpitations

**Ear and labyrinth disorders**
Uncommon: Ear pain
Rare: Ear congestion, Deafness, Ear discomfort, Vertigo

**Eye disorders**
Rare: Conjunctivitis, Eye irritation, Photophobia, Lacrimation increased, Occular hyperaemia, Vision blurred

**Gastrointestinal disorders**
Common: Abdominal pain (general, upper or lower), Diarrhoea, Mouth ulceration, Nausea, Oral discomfort, Oral pain, Paraesthesia oral,
Uncommon: Abdominal discomfort, Abdominal distension, Constipation, Dry mouth, Dyspepsia, Dysphagia, Glossodynia, Hypoaesthesia oral, Oral dysaesthesia, Stomatitis, Tongue ulceration, Vomiting
Rare: Flatulence, Gastroesophageal reflux, Gingival bleeding, Gingival pain, Gingival ulceration, Malaena, Oral pruritis, Swollen tongue, Tongue coated, Tongue dry
Very Rare: Hepatitis and cholestatic icterus (jaundice)

**General disorders and administration site conditions**
Common: Influenza-like illness
Uncommon: Chest discomfort, Fatigue, Malaise, Pain, Pyrexia
Rare: Asthenia, Chest pain, Oedema peripheral, Thirst, Chills, Feeling hot, Sensation of a foreign body, Swelling, Ulcer

**Immune system disorders**
Rare: Seasonal allergy

**Infections and infestations**
Common: Upper respiratory tract infection
Uncommon: Ear infection, Eye infection, Gingival infection, Influenza, Laryngitis, Lower respiratory tract infection, Nasopharyngitis, Oral herpes, Pharyngitis, Rhinitis, Sinusitis, Tonsillitis, Viral infection
Rare: Bronchitis, Peritonsilar abcess, Urinary tract infection, Vulvovaginal candidasis

**Investigations**
Rare: Blood glucose increased, Body temperature increased

**Metabolism and nutrition disorders**
Rare: Dehydration.
**Musculoskeletal and connective tissue disorders**
Uncommon: Arthralgia, Back pain
Rare: Joint swelling, Neck pain, Muscle spasms, Pain in extremity,

**Nervous system disorders**
Common: Dizziness, Dysgeusia, Headache, Parasthesia,
Uncommon: Aphonia, Burning sensation, Migraine, Somnolence
Rare: Hypoaesthesia, Lethargy, Ageusia,

**Psychiatric disorders**
Uncommon: Insomnia,
Rare: Confusional state, Sleep disorder, Abnormal dreams

**Renal and urinary disorders**
Rare: Pollakiuria, Urinary abnormality, Chromaturia, Interstitial nepritis, Nephritis syndrome

**Reproductive system and breast disorders**
Rare: Menorrhagia

**Respiratory, thoracic and mediastinal disorders**
Common: Cough, Oropharyngeal pain, Throat irritation, Wheezing
Uncommon: Asthma, Dry throat, Dysphonia, Dysponoea, Epistaxis, Increased upper airway secretion, Nasal congestion, Nasal discomfort, Pharyngeal erythema, Pharyngeal hypoaesthesia, Productive cough, Rales, Rhinalgia, Rhinorrhoa, Sneezing,
Rare: Bronchospasm, Haemoptysis, Oropharangeal blistering, Pharyngeal oedema, Sinus congestion, Aggravation of asthma

**Skin and subcutaneous tissue disorders**
Uncommon: Hyperhidrosis, Pruritus, Rash, Rash pruritic,
Rare: Acne, Dry skin, Eczema, Psoriasis, Skin nodule, Swelling face
Very Rare: Stevens-Johnson syndrome, Lyell syndrome

**Vascular disorders**
Rare: Hot flush

**Adverse reactions reported with flurbiprofen, tablet form (i.e. at a higher dose and/or in the treatment of chronic conditions, under long-term treatment, not indicated for the Strefen Instants).**

(Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10000 to <1/1000), Very rare (<1/10000), not known (cannot be estimated from the available data))

**Cardiac disorders**
Very rare: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.
Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses) and in long-term treatment may be associated with a small increased
risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

**Blood and lymphatic system disorders**

Rare: haematological reactions (including anaemia, prolonged bleeding time)

Very rare: thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia).

**Respiratory, thoracic and mediastinal disorders**

Rare: bronchospasm, dyspnoea

**Gastrointestinal disorders**

Rare: GI bleeding, ulceration and perforation and ulcerative stomatitis

**Renal and urinary disorders**

Rare: renal dysfunction (including interstitial nephritis, nephritic syndrome and renal failure)

**Skin and subcutaneous tissue disorders**

Very rare: skin reactions (including Stevens Johnson syndrome and Lyell’s syndrome)

**General disorders and administration site conditions**

Rare: Fever

**Immune System disorders**

Very rare: anaphylactic shock

**Hepatobiliary disorders**

Very rare: hepatic disorders (including hepatitis and cholestatic jaundice)

**Adverse events associated with use of NSAIDs in general**

(Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10000 to <1/1000), Very rare (<1/10000), not known (cannot be estimated from the available data))

**Cardiac disorders**

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of NSAIDs (particularly at high doses 2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke), (see section 4.4).

**Blood and lymphatic system disorders**

Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

**Nervous System disorders**
Uncommon: Headache
Very rare: Aseptic meningitis – single cases have been reported very rarely.

**Respiratory, thoracis and mediastinal disorders**
Exacerbation of asthma and bronchospasm.

**Gastrointestinal disorders**
The most commonly-observed adverse events are gastrointestinal in nature.
Uncommon: abdominal pain, nausea, dyspepsia.
Rare: diarrhea, flatulence, constipation and vomiting.
Very rare: peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis. Exacerbation of colitis and Crohn’s disease (see section 4.4).

**Renal and Urinary disorders**
Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

**Skin and subcutaneous tissue disorders**
Uncommon: Various skin rashes.
Very rare: Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis can occur.

**Immune System disorders**
Uncommon: Hypersensitivity reactions with urticaria and pruritus.
Very rare: severe hypersensitivity reactions. Symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).
In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see section 4.4).

**Hepatobiliary disorders**
Very rare: liver disorders.

c) **Description of selected adverse events.**
Consumers of low-dose flurbiprofen indicated for the treatment of sore throat may experience sensations described variously as burning, tingling or prickling in the mouth. The sense of taste may also be affected. These phenomenon are non-serious and transient in nature.

Headaches may also be experienced which are also transient and non-serious.

Some individuals may suffer minor, temporary gastrointestinal discomfort.

Flurbiprofen belongs to the pharmacological class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs) Hypersensitivity reactions to NSAIDs have occasionally been reported and these may consist of:

(a) Non-specific allergic reactions and anaphylaxis
(b) Respiratory tract reactivity, e.g. asthma, aggravated asthma, bronchospasm, dyspnoea
(c) Various skin reactions, e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

d) Paediatric population.
Efficacy and safety studies on Strefen 8.75mg lozenges have included children 12 – 17 years. Although no overall comparison between subjects aged 12-17 years and those greater than or equal to 18 years was made in relation to GI adverse events, it is noted that in the largest clinical study conducted to date the observed rate for flurbiprofen 8.75mg in the 12-17 year old population was lower than in adults and there was no suggestion of increased risk of significant GI events in the younger subjects. There were no serious, severe or moderate GI events experienced by subjects aged 12-17 years.

4.9 Overdose
Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache, and gastrointestinal bleeding are also possible. In more serious poisoning with NSAIDs, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation, blurred vision and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning with NSAIDs 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
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 or gastric lavage and if necessary correction of serum electrolytes if the patient presents within one 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. There is no specific antidote to flurbiprofen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: Anti-inflammatory and anti-rheumatic products, non-steroids, propionic acid derivatives.

ATC Code: R02 AX01

Flurbiprofen is a propionic acid derivative NSAID which acts through inhibition of prostaglandins synthesis. In humans flurbiprofen has potent analgesic, antipyretic and anti-inflammatory properties. According to studies using the whole blood assay, flurbiprofen is a mixed COX-1/COX-2 inhibitor with some selectivity towards COX-1.
Pre-clinical studies suggest that the R (-) enantiomer of flurbiprofen and related NSAIDs may act on the central nervous system; the suggested mechanism is by inhibition of induced COX-2 at the level of the spinal cord.

Strefen Instants have been demonstrated to relieve sore throat through a reduction in severity of throat soreness from 1 minute (-0.95; SD=1.45) and over 6 hours (-2.25; SD=1.76), sore throat pain relief with significance from 1 minutes (2.58; SD=1.37) and over 6 hours (3.26; SD=1.52), relief from difficulty swallowing with significance from 5 minutes (-13.63; SD=16.15) and over 6 hours (-23.50; SD=15.96) and reduction in sore throat pain intensity from 5 minutes (-13.81; SD=15.96) and over 6 hours (-22.62; SD=18.63). Multiple dose efficacy has also been observed. Patients also recorded a significant improvement in wellbeing at 3 hours and after 3 days treatment.

The mint flavoured granule format dissolves quickly in the mouth and contains polymers for adherence and retention.

**Paediatric Population**

No specific studies in children have been undertaken, although efficacy and safety studies on Strefen 8.75mg lozenges have included children 12 – 17 years, although small sample size means that no statistical conclusions can be drawn.

### 5.2 Pharmacokinetic properties

**Absorption**

Strefen Instants dissolve rapidly and the flurbiprofen is readily absorbed, with plasma concentrations peaking at 60 - 70 minutes. Absorption of flurbiprofen can occur from the buccal cavity by passive diffusion. Rate of absorption is dependent on pharmaceutical form with peak concentrations achieved more rapidly than, but of similar magnitude to, those achieved after an equivalent swallowed dose, but more slowly than an equivalent lozenge dose.

**Distribution**

Flurbiprofen is rapidly distributed throughout the body and is extensively bound to plasma proteins.

**Metabolism / Excretion**

Flurbiprofen is mainly metabolised by hydroxylation and excreted via the kidneys. It has an elimination half-life of 3 to 6 hours. Flurbiprofen is excreted in very small amounts in human milk (less than 0.05ug/ml). Approximately 20-25% of a flurbiprofen oral dose is excreted unchanged.

**Special Groups**

No difference in pharmacokinetic parameters between elderly and young adult volunteers has been reported following oral administration of flurbiprofen tablets. No pharmacokinetic data have been generated in children below 12 years of age following administration of Flurbiprofen 8.75 mg however administration of both flurbiprofen syrup and suppository formulations indicate no significant differences in pharmacokinetic parameters compared with adults.
5.3 Preclinical safety data
Flurbiprofen displays dose dependent effects typical of NSAIDS, including gastrointestinal effects such as ulceration, bleeding and perforation in rats, delayed onset and duration of parturition in pregnant rats, especially when exposure occurs late in pregnancy.

Genotoxicity
In-vitro and in-vivo studies to assess the genotoxicity potential of flurbiprofen demonstrate that the drug is unlikely to pose a risk of genotoxicity among humans. The chemical structure of flurbiprofen does not contain structural alerts for genotoxicity and NSAIDS are not considered to be mutagenic.

Systemic Toxicity
The principle toxic reaction to flurbiprofen is gastrointestinal erosion and ulceration in all species studies, with death at high doses due to ulceration and associated peritonitis. Renal papillary necrosis, liver toxicity and anaemia have been documented in several species.

Carcinogenicity
Carcinogenicity studies in mice and rats revealed no evidence of treatment related carcinogenicity.

Reproductive and Developmental toxicology
Fertility, reproductive performance and foetal development have been studies in rats and mice. Dose-dependent effects on dams (female rats) and offspring observed in these studies included prolonged pregnancy and labour, increased numbers of stillbirths, gastrointestinal ulceration and reduction in number of pups born to rats. Transfer of flurbiprofen to foetus and transfer from mother’s milk to the neonate have been observed, but no evidence of teratogenic effects has been seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Xylitol
Mannitol
Carbomer
Sodium hydrogen carbonate
Cool Mix for Mint Flavour
Peppermint Flavour
Aspartame
Citric Acid anhydrous
Silicon Dioxide
Sodium Chloride

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months
6.4 **Special precautions for storage**
Do not store above 25°C

6.5 **Nature and contents of container**
Each sachet is composed of:
12 micron Polyester (PET) 12 micron Polyethylene (PE)/9 micron Aluminium/37 gsm Polyethylene (PE)
Or
12 micron Polyester (PET) 12 micron Polyethylene (PE)/12 micron Aluminium/37 gsm Polyethylene (PE)

Pack sizes contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 sachets. Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Reckitt Benckiser Healthcare (UK) Limited
103 – 105 Bath Road
Slough
SL1 3UH

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00063/0563

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
10/07/2012

10 **DATE OF REVISION OF THE TEXT**
10/07/2012
Strefen®
INSTANTS 8.75 mg GRANULES
Flurbiprofen 8.75 mg

INFORMATION FOR THE USER
Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However, you still need to use this medicine carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask your doctor or pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve after 3 days.
- If any side effects get serious, or if you notice any side effects not listed, stop taking this medicine and tell your doctor or pharmacist.

In this leaflet
1. What Strefen Instants 8.75mg Granules are and what they are used for
2. Before you take Strefen Instants 8.75mg Granules
3. How to take Strefen Instants 8.75mg Granules
4. Possible side effects
5. How to store Strefen Instants 8.75mg Granules
6. Further information

1. WHAT STREFEN INSTANTS 8.75MG GRANULES ARE AND WHAT THEY ARE USED FOR
Strefen Instants 8.75mg Granules contain flurbiprofen. Flurbiprofen belongs to a group of medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). It works by changing how the body responds to pain, swelling and high temperature. Strefen Instants 8.75mg Granules are used to relieve the symptoms of sore throats such as throat soreness, pain and swelling.

2. BEFORE YOU TAKE STREFEN INSTANTS 8.75MG GRANULES
Do not take the medicine if you have or ever have suffered from:
- allergic (hypersensitive) reactions to flurbiprofen or to any of the other ingredients (see Section 6)
- allergic (hypersensitive) reactions to aspirin or to any other NSAIDs medicine
- heart, kidney or liver failure
- vomiting, an enlarged liver or fatty liver
- ulceration of the stomach or intestines, or severe colitis
- blood problems including where your blood did not clot properly.

Do not take the medicine if you:
- are taking high dose aspirin (75mg or above daily). If you are on low-dose aspirin (up to 75mg daily), speak to your doctor or pharmacist before you take The Medicine
- are taking another NSAIDs medicine (such as celecoxib, ibuprofen, diclofenac sodium etc.)
- are in the last 3 months of pregnancy
- are under 12 years of age.

Take special care with the medicine and speak to your doctor before taking these medicines if you are suffering from:
- allergy
- a new bacterial infection (yellow-green pus or cough, painful sinuses, sore throat)
- cancer or ulcer problems
- a previous stroke or think that you might be at risk of these conditions (e.g. if you have had high blood pressure, diabetes or high cholesterol or are a smoker)
- high blood pressure
- a chronic autoimmune disease (including systemic lupus erythematosus)
- hepatitis
- have any serious skin conditions, including Stevens-Johnson syndrome
- phenylketonuria as the medicine contains asparagine which is a source of phenylalanine and this may be harmful for people with phenylketonuria
- are elderly as you are more likely to experience the side effects listed in this leaflet.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, consult them before using these medicines if you are taking:
- low dose aspirin (up to 75 mg daily)
- medicines for high blood pressure or heart failure
- water tablets (diuretics, including potassium sparing drugs)
- medicines for thinning the blood (anti-coagulants)
- medicines for heart failure (e.g. Probenecid, Sulfapyridine)
- another NSAIDs medicine or steroids (such as celecoxib, ibuprofen, diclofenac sodium or prednisolone)
- mifepristone (a medicine used for pregnancy termination)
- quinolone antibiotics (such as ciprofloxacin)
- progestogen or tamoxifen (to suppress the immune system)
- phenytoin (to treat epilepsy)
- methotrexate (to treat cancer)
- lithium or SSRIs (for depression)
- oral anticoagulants (to treat diabetes)
- zidovudine (to treat HIV)
- corticosteroids (steroid hormones)
- tacrolimus (an immunosuppressant drug).

TAKING THE MEDICINE WITH FOOD AND DRINK
Food should be avoided during treatment with Strefen Instants 8.75mg Granules. There are no known effects of taking this medicine with or without food.

Pregnancy and breast-feeding
Strefen Instants 8.75mg Granules belong to a group of medicines which may impair fertility in women. This effect is reversible on stopping the medicine. It is unlikely that the occasional use of the medicine will affect your chances of becoming pregnant. If you have problems becoming pregnant, tell your doctor before taking this medicine if you have problems becoming pregnant.

Further information
Do not take this medicine after the expiration date and before the 6 months of pregnancy. If you are in the first 6 months of pregnancy or are breast-feeding, speak to your doctor before taking this product. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Strefen Instants 8.75mg Granules should not affect your ability to drive or use machines. Dizziness and visual disturbances are possible undesirable side effects after taking NSAIDs. If affected you should not drive or operate machines.

Important Information for sufferers of phenylketonuria
Strefen Instants 8.75mg Granules contains asparagine which is a source of phenylalanine and this may be harmful for people with phenylketonuria.

Special warnings
Medicines such as Strefen Instants 8.75mg Granules may be associated with a small increased risk of heart attack (myocardial infarction) or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment (3 days).

If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker), you should discuss your treatment with your doctor or pharmacist.

3. HOW TO TAKE STREFEN INSTANTS 8.75MG GRANULES
For adults and children 12 years and older. (Do not give Strefen Instants to children under 12 years).

Open the contents of the sachet into your mouth and allow to dissolve in the mouth before swallowing.
- The granules should start to work within 30 minutes.
- Then take one sachet every 3-4 hours, if required.
- There are no known effects of the medicine with or without food.
- Do not take more than 5 sachets in 24 hour period.

These sachets are for short-term use only. You should take as few sachets as you need for the shortest time to relieve your symptoms. Do not take Strefen Instants 8.75mg Granules for more than 3 days, unless your doctor tells you to. If you do not get better or you get worse, or if new symptoms occur such as a bacterial infection, talk to a doctor or pharmacist.

If you take more than you should
Talk to a doctor or pharmacist or go to your nearest hospital straight away. Symptoms of overdose may include: feeling sick or being sick, stomach ache or more rarely diarrhoea, ringing in the ears, headache and gastrointestinal bleeding is also possible. If you have any questions on the use of this product, ask your doctor or pharmacist.
PAR Strefen Instants 8.75mg granules

UK/H/2403/01/DC

4. POSSIBLE SIDE EFFECTS

Like all medicines, Strefen Instants 8.75mg Granules can cause side effects, although not everyone gets them. STOP TAKING this medicine and contact a doctor IMMEDIATELY if you develop:

- Signs of gastrointestinal bleeding such as:
  - passing blood in the stools (black red stools)
  - black tarry stools
  - vomitting blood or dark particles that look like coffee grounds.
- Very rare allergic reactions such as:
  - asthma
  - unexpected wheezing, shortness of breath
  - swelling of the face, lips or tongue
  - skin reactions (such as hives, itching rash)
  - swelling
- Abdominal symptoms such as:
  - indigestion, heartburn
  - stomach ache/pain or
  - other usual stomach symptoms.

Tell your doctor or pharmacist if you notice any of the following effects or any effects not listed:

Very common (occur in more than 1 in 10 patients)
- Oral discomfort such as burning or warm feeling in the mouth.

Common (occur in more than 1 in 100 patients)
- Stomach ache, feeling sick, diarrhoea
- Dry or tingling mouth, mouth ulcers
- Influenza like illness
- Upper respiratory tract infection (throat infection)
- Headache, dizziness
- Cough, throat irritation or wheezing.

Uncommon (occur in more than 1 in 1000 patients)
- Enlarged lymph nodes
- Ear pain, ear infection, eye infection
- Dry throat, dry mouth, burning sensation in the mouth, inflammation in the mouth (stomatitis), mouth and throat ulcers,
  - difficulty in swallowing, gum infection, decreased oral sensitivity
- Inflammation of the larynx (laryngitis), inflammation of the
  - pharynx (pharyngitis), infection of the tonsils (tonsillitis), oral
  - herpes, aphthous, aphthous, aphthous
- Throat redness, throat numbness
- Sneezing, nasal congestion, nasal discomfort
- Feeling sick (vomiting), upset stomach, constipation, abdominal discomfort
- Back pain, joint pain
- Sleeping disorders: feeling sleepy, drowsiness, difficulty sleeping
- Breathing disorders: shortness of breath, asthma, crackling lung
  - sounds (rales), chest discomfort, lower respiratory tract infections
- Nose bleed, runny nose, pain in the nose, inflammation of the
  - lining of the sinuses (sinusitis)
- Skin rashes and itching
- Fever, productive cough, common cold, migraine
- Increased perspiration
- Viral infection, influenza
- Increased upper airway secretions.

Rare (occur in less than 1 in 1000 patients):
- Eye irritation, itching eyes, red eyes, conjunctivitis, blurred
  - vision, increased tear production
- Dry tongue, exfoliation tongue, coated tongue, loss of taste
  - function
- Mouth ulcers (ulcerative stomatitis), pharyngeal swelling, tonsilitis complications (Peritonsillar abscess)
- Heart palpitations, chest pain
- Dizziness (vertigo), sensitivity to light, sinus congestion
- Wind (flatulence), black tarry stools
- Coughing blood (haemoptysis)
- Gum pain, gum bleedling, gum ulcers
- Heartburn
- Acne, dry skin, eczema, psoriasis, skin rashes
- Hot flush, thirst, dehydration, increase in body temperature
- Knee swelling, neck pain, muscle spasm, pain in extremities
- Sensation of a foreign body, chills
- Confusional state, abnormal dreams
- Bronchitis, bronchospasm, seasonal allergy, shortness of breath
- Physical weakness, exhaustion
- Facial swelling, lower limb swelling
- Urinary tract infection, vulvovaginal candidiasis, increased
  - urinary frequency, abnormal urine colour
- Prolonged menstruation
- Increased in blood glucose
- Kidney dysfunction (including interstitial nephritis, nephritic
  - syndrome and renal failure)
- Haematological reactions (including anaemia, prolonged
  - bleeding time)
- Gastrointestinal bleeding, ulceration, perforation.

Very Rare (effects less than 1 user in 10000):
- Liver problem causing jaundice (yellowing of the skin and white
  - of the eyes)
- Severe skin conditions such as Steven-Johnson Syndrome
  - (skin rash and blisters, mouth and eye ulcers), and Lyell's
  - syndrome (red tender peeling skin).

Other side effects (reported in similar NSAIDs medicine such as ibuprofen):
- Inflammation of the stomach (very rare)
- Rare and small increased risk of heart attack, high blood
  - pressure, inflammation of the brain.

If any of the side effects get serious, or if you notice any side

4. HOW TO STORE STREHEN INSTANTS 8.75mg GRANULES

- Keep all medicines out of the reach and sight of children.
- Do not use this medicine after the expiry date, which is stated
  - on the pack.
- Do not store above 25°C.

Medicines should not be disposed of via wastewater or

4. FURTHER INFORMATION

What Strefen Instants 8.75mg Granules contain:
The active ingredient (the ingredient which makes the medicine
work) is flurbiprofen 8.75 mg. The other ingredients are Mannitol,
Xylitol, Sodium bicarbonate, Carbomer, Citric acid Anhydrous,
Cool Mix flavour. Sodium chloride, Peppermint flavour,
Aspartame and Silicon dioxide.

What Strefen Instants 8.75mg Granules look like and

The medicine is a white to cream coloured free-flowing granule
with a characteristic mint odour and taste of mint.

The pack contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or
16 sachets. Not all pack sizes may be marketed.

Marketing Authorisation Holder: Reckitt Benckiser Healthcare
(UK) Ltd, 103-105 Bath Road, Slough, SL1 3UH
Manufacturer: RECKITT BENCKISER HEALTHCARE
INTERNATIONAL, Nottingham NG90 2DB

Product License Number: PL 0066/0563

Date of Revision: April 2012

P
Module 4
Labelling

Streffen®
Instants 8.75mg Granules

For oral administration only

Licence Holder:
Reckitt Benckiser Healthcare (UK) Ltd, Slough SL1 3UH

RB005068
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the UK, Austria, Czech
Republic, Germany, Hungary, Ireland, Italy, Poland, Romania and the Slovak Republic
agreed to grant a marketing authorisation for the medicinal product Strefen Instants 8.75mg
granules (PL 00063/0563) on 25 April 2012. This product was assessed by the Decentralised
Procedure (UK/H/2403/001/DC), with the UK as Reference Member State. A subsequent
national licence was granted in the UK on 10 July 2012.

The product is a pharmacy medicine (legal status P), containing the active substance
flurbiprofen and is indicated for the short term symptomatic relief of a sore throat.

This application was made as a full dossier application for a known active substance, under
Article 8.3 of Directive 2001/83 EC.

Flurbiprofen is a non-steroidal anti-inflammatory drug (NSAID), with excipients; as granules
designed to be dissolved on the tongue. Flurbiprofen, as an NSAID, has anti-inflammatory,
anti-pyretic and analgesic properties, modulated by the COX system.

No new non-clinical studies were conducted, which is acceptable given that flurbiprofen is a
well-known active substance.

The data from five clinical studies have been provided with this application, one
bioequivalence study, one clinical efficacy study and three further supportive studies. All
studies were conducted in-line with current Good Clinical Practice.

The RMS has been assured that acceptable standards of GMP are in place for this product
type at all sites responsible for the manufacture and assembly of this product. Evidence of
compliance with GMP has been provided for the named manufacturing and assembly sites.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Strefen Instants 8.75mg granules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the active substance (INN)</td>
<td>Flurbiprofen</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Anti-inflammatory and anti-rheumatic products, non-steroids, propionic acid derivatives (R02 AX01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strengths</td>
<td>8.75mg granules</td>
</tr>
<tr>
<td>Reference number for the Decentralised Procedure</td>
<td>UK/H/2403/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Austria, Czech Republic, Germany, Hungary, Ireland, Italy, Poland, Romania, Slovak Republic</td>
</tr>
<tr>
<td>Marketing Authorisation Number</td>
<td>PL 00063/0563</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Reckitt Benckiser Healthcare (UK) Limited, 103 – 105 Bath Road, Slough, SL1 3UH</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Flurbiprofen
Chemical Name: (RS)-2-(2-fluorobiphenyl-4-yl)propanoic acid
Molecular Formula: C_{15}H_{13}FO_{2}

Structure:

![Structure of Flurbiprofen]

Molecular Weight: 244.3
Appearance: White or almost white crystalline powder

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

P Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients xylitol, mannitol, carbomer, sodium hydrogen carbonate, cool mix for mint flavour, peppermint flavour, aspartame, citric acid anhydrous, silicon dioxide and sodium chloride.

All excipients used comply with respective European Pharmacopoeia monographs, with the exception of silicon dioxide (which is controlled to a suitable US Pharmacopoeia formulation), and cool mix for mint flavour and peppermint flavour (which are controlled to a suitable in-house specification). Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the pharmaceutical development program was to develop a consumer-perceived, in-mouth, fast-dissolving, sugar-free, granular, unit-dose formulation, delivering 8.75mg flurbiprofen for the treatment of the symptoms of a sore throat. The applicant has provided a suitable product development rationale and data.

Manufacture

Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and has shown satisfactory results.

Control of Drug Product

The finished product specification proposed is acceptable and provides an assurance of the quality of the finished product. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specification.

Satisfactory data on the characterisation of impurities have been provided.
Reference Standards or Materials
Certificates of Analysis for all reference standards used have been provided and are satisfactory.

Container Closure System
The finished product is packaged in polyester (PET)/aluminium/polyethylene (PE) sachets in pack sizes of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 sachets. Not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting mock-ups for any pack size before it is marketed.

Stability of the Drug Product
Stability data provided to support a shelf-life of 24 months, with the storage instructions “Do not store above 25°C”.

Bioequivalence/Bioavailability
Certificates of Analysis have been provided for batches of test and reference product used in the bioequivalence studies.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

CONCLUSION
It is recommended that a Marketing Authorisation is granted for this application.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of flurbiprofen are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

The Environmental Risk Assessment (ERA) report states that the default Market Penetration Factor (Fpen) can be substituted by a specific Fpen, as sales volumes for 2008 were available for the European market where the use of the proposed formulation is intended. This is accepted. Based on the revised Fpen value of 0.0008, the Phase I – Predicted Environmental Concentration (PECSURFACEWATER) was determined to be below the action limit of 0.01 μg/l (0.002 μg /l). No other environmental concerns are apparent. It is assumed that the medicinal product is unlikely to represent a risk to the environment following its prescribed usage in patients. The bibliographic data presented states that the Log Kow (concentration in octanol phase/concentration in aqueous phase) value for flurbiprofen is 4.16. Since the Log Kow is less than the action limit of 4.5, the drug substance does not need to be screened for persistence, bioaccumulation or toxicity as per the guidance.

There are no objections to the approval of this product from a non-clinical viewpoint.
IIII.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

The data from five clinical studies have been provided with this application, one bioequivalence study, one clinical efficacy study and three further supportive studies. All studies were conducted in-line with current Good Clinical Practice.

Pharmacokinetics

In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product flurbiprofen 8.75mg granules versus the reference product flurbiprofen 8.75mg lozenge (Reckitt Benckiser Healthcare (UK) Limited, UK) in healthy volunteers under fasting conditions.

Volunteers received the test or reference treatment after an overnight fast of at least 10 hours and no liquids for 2 hours prior to dosing. Post dose, volunteers were not allowed to eat for 4 hours or drink for 2 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 12 hours post dose. The two treatment arms were separated by a 4-day washout period.

The pharmacokinetic results (arithmetic means [SD], ratio [%] and 90% confidence intervals) for flurbiprofen are presented below:

<table>
<thead>
<tr>
<th>Clarithromycin</th>
<th>AUC₀→₄ µg/ml/h</th>
<th>AUC₀→∞ µg/ml/h</th>
<th>Cₘₐₓ µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>6014 (1018)</td>
<td>6790 (1253)</td>
<td>1452 (338)</td>
</tr>
<tr>
<td>Reference</td>
<td>6325 (1025)</td>
<td>7144 (1269)</td>
<td>1635 (234)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>94.90 (92.02-97.88)</td>
<td>94.84 (91.63-98.16)</td>
<td>87.26 (80.40-94.71)</td>
</tr>
</tbody>
</table>

AUC₀→₄ area under the plasma concentration-time curve from time zero to 4 hours
AUC₀→∞ area under the plasma concentration-time curve from time zero to infinity
Cₘₐₓ maximum plasma concentration

The 90% confidence intervals for Cₘₐₓ and AUC for test versus reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.

Pharmacodynamics

No new pharmacodynamic studies have been submitted with this application. As the pharmacodynamics of flurbiprofen are well-known and a dose-response relationship has already been established with the lozenge formulation, no further studies are required.
Efficacy
The below clinical efficacy study has been submitted with this application:
**An double-blind, randomised, multicentre, parallel-group, multiple-dose, placebo-controlled study to test for superiority of the test product flurbiprofen 8.75mg granules (Reckitt Benckiser Healthcare (UK) Limited, UK) versus placebo in patients with a sore throat due to an upper respiratory tract infection.**

Method
Patients were randomised into the study if they had a sore throat that had started during the 4 previous days due to a respiratory tract infection, which scored ≥6 on the Throat Soreness Scale just after swallowing (assessed by the patient). Additionally, it was required that the sore throat be confirmed objectively by attainment of a score of ≥5 on the expanded 21-point Tonsillo-Pharyngitis Assessment (assessed by site staff).

The primary objective was to determine the analgesic properties of 8.75mg flurbiprofen micro granules in patients with sore throat due to upper respiratory tract infection (URTI). The analgesic properties were assessed by comparing throat soreness in patients treated with 8.75mg flurbiprofen microgranules or placebo. In addition to this primary endpoint, sore throat relief, sore throat pain intensity and a functional measure of difficulty in swallowing was also assessed.

The secondary objective of this study was to determine additional patient/consumer benefits associated with 8.75mg flurbiprofen micro granules. These benefits were assessed by measuring freedom from symptoms and also by a consumer questionnaire. The consumer questionnaire included opinions on pain relief, what the relief felt like e.g. cooling, soothing, site of action of the micro granules within the mouth, how fast acting the product was, duration of action, how satisfied the patient was with the pain relief attained and how their sore throat affected their daily activities.

The primary efficacy analysis was the area under the change from baseline curve (AUC) in severity of throat soreness from 0–2 hours first post dose.

Secondary analyses included:
- AUC for change from baseline in severity of throat soreness, sore throat pain intensity and difficulty in swallowing from 0–3 and 0–6 hours post dose.
- AUC for sore throat pain relief ratings from 0–3 and 0–6 hours post dose.
- Change from baseline in severity of throat soreness, sore throat pain intensity at individual time points from one minute to 6 hours post-dose.
- Sore throat pain relief from baseline at individual time points from one minute to 6 hours post dose.
- Overall treatment rating at 3 hours and the end of Day 3.
- Sore throat relief, the change from baseline in severity of throat soreness and difficulty in swallowing at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3.
- Whether the patient was symptom free (i.e. having a throat soreness score of 0 or 1) at the end of Day 1, at 24 hours post-first dose and at the end of Days 2 and 3.
- Time to first reporting ‘moderate pain relief’ on the sore throat pain relief 7-point scale.
- Proportion of patients with a change of ≥1 in throat soreness and time to reporting the change ≥1.
The proportion of patients who discontinued trial medication due to the resolution of sore throat.
Overall granule sachet and rescue (paracetamol) consumption up to end of Day 3.
Change from baseline in health related quality of life assessed using the EQ5D questionnaire.
Response to questions in the consumer questionnaire.
Change from baseline in oral temperature at 60, 120 and 180 minutes.
Safety and tolerability assessed in terms of the overall proportion of patients with adverse events.

Analyses were performed on both patients who received at least one dose of study medication (the Intention-To-Treat [ITT] population) and patients who completed the study with no major protocol violations (the Per-Protocol [PP] population).

**Results**

The results for the primary efficacy analysis for the ITT population are presented below:

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC baseline to 3 hours</td>
<td>-2.14 (1.72)</td>
<td>1.35</td>
<td>1.68</td>
</tr>
<tr>
<td>AUC baseline to 6 hours</td>
<td>-2.29</td>
<td></td>
<td></td>
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<td>Difference between LS means</td>
<td>-0.48</td>
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<td>95% CI</td>
<td>-0.81, -0.15</td>
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<tr>
<td>p-value for treatment</td>
<td>0.0049</td>
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Similar results were observed in the PP population (p=0.0097).

The results of the secondary efficacy analyses include:

- AUC from baseline to 3 and 6 hours on a throat soreness scale showed that both had a statistically significant improvement in favour of the active treatment (p < 0.005)
- Change in baseline of throat soreness over time was statistically significant at every time point apart from at 360 minutes
- Change in throat soreness scale at the end of Day 1, 2 and 3 and at 24 hours post dose did not show any statistically significant difference from placebo
- AUC from baseline to 3 and 6 hours post dose of a sore throat pain scale showed that there was a statistically significant improvement in favour of the active treatment
- Change in baseline of sore throat pain relief over time was statistically significant at every time up to and including 360 minutes.
- Change in sore throat pain relief scale at the end of Day 1, 2 and 3 and at 24 hours post dose did not show any statistically significant difference from placebo, except at the end of Day 1
- AUC from baseline to 3 and 6 hours post dose of a sore throat VAS showed that there was a statistically significant improvement in favour of the active treatment
- Change in baseline of sore throat VAS over time was statistically significant at every time up to and including 360 minutes
- AUC from baseline to 3 and 6 hours post dose of a difficulty in swallowing VAS showed that there was a statistically significant improvement in favour of the active treatment
- Change in baseline of sore throat VAS over time was statistically significant at every time up to 360 minutes, apart from at the initial 5 minute timepoint
- Change in a difficulty in swallowing VAS at the end of Day 1, 2 and 3 and at 24 hours post dose showed statistically significant difference from placebo at Day 1, 2 and 3, but not at 24 hours post dose
Patients overall treatment rating, measured on a 11-point scale, showed a difference at both 0-3 hours and also at the end of Day 3

• No statistically significant differences were seen in rescue medication use between the active treatment and placebo at any point

Conclusions
The primary efficacy analysis shows a statistically significant improvement over placebo for the granule formulation.

The secondary analyses generally support the application and posology as a short-term symptomatic treatment. This is borne out by the significant differences in the different scales used and also that the effect does seem to have a fast onset (most were significant at 5 minutes). However, the large amount of subjective data from patient questionnaires on soft end points is not of any clinical relevance in this assessment.

Supportive studies
In addition to the above study, supportive data from three studies were submitted, two performed using the lozenge and one using the granule formulation. These in general support the data shown above, with changes of similar magnitude, even when different endpoints and analyses are used.

Conclusions on Clinical Efficacy
Clinical efficacy is supported by the fact that the granule formulation is bioequivalent to the lozenge formulation. In the clinical efficacy study itself, the data provided shows that the granules are efficacious and do have an effect over that of the placebo comparator.

Safety
No new or unexpected safety issues were raised by the new data submitted with this application.

SmPC, PIL, Labels
The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with those for the originator products.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Strefen Instants 8.75mg granules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.
PAR Stufen Instants 8.75mg granules

PHARMACOKINETICS
Bioequivalence has been demonstrated between this granule formulation and Stufen 8.75mg Lozenges.

PHARMACODYNAMICS
The pharmacodynamics of flurbiprofen are well-known and a dose-response relationship has been established for the lozenge formulation. On this basis of these points, no new pharmacodynamic data have been submitted and none were required.

EFFICACY
One clinical efficacy study has been submitted, which showed a statistically significant improvement in patients given flurbiprofen granules versus placebo from baseline to 2 hours post dose. Secondary analyses also supported the product for short-term, symptomatic use.

SAFETY
No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with flurbiprofen is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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