SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Strefen Honey and Lemon
Strefen Orange flavour Sugar Free

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient; Flurbiprofen 8.75mg

Excipient(s) with known effect:

Strefen Honey and Lemon

Glucose

Sucrose

Wheat Starch*

Sulphites – sulphur Dioxide (E220)*

d-Limonene**

Linalool**

Citral**

Citronellol**

Farnesol**

Geraniol**

Butylate Hydroxyanisole (E220)**

*present in liquid glucose

**present in Lemon Flavour

Strefen Orange flavour Sugar Free

Maltitol Liquid 0.509 g/lozenge. Total maximum daily dose (MDD) is 2.55 g.

Isomalt 2.033 g/lozenge. Total maximum daily dose (MDD) is 10.195 g.

Citral**

Citronellol**

d-Limonene**

Geraniol**

Linalool**

**present in Orange flavour

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Lozenges.

Strefen Honey and Lemon:

A round, pale yellow to brown lozenge with an icon intagliated on both sides of the lozenge.

Strefen Orange flavour Sugar Free.

A white to pale yellow circular lozenge, with a characteristic orange taste with an icon intagliated on both.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Strefen Honey and Lemon & Strefen Orange flavour Sugar Free are indicated for the short term relief of symptoms of sore throat such as throat pain and soreness in adults and children over the age of 12 years.

4.2 Posology and method of administration

Posology

Adults, the elderly and children over the age of 12 years:

One lozenge sucked/dissolved slowly in the mouth every 3 - 6 hours as required. Maximum 5 lozenges in a 24 hour period.

It is recommended that this product should be used for a maximum of three days.

Children: Not indicated for children under 12 years.
Elderly: 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.

Impaired hepatic: In patients with mild to moderate impairment of hepatic function no dose reduction is required. In patients with severe hepatic insufficiency flurbiprofen is contraindicated (see section 4.3).

Impaired renal: In patients with mild to moderate impairment of renal function no dose reduction is required. In patients with severe renal insufficiency flurbiprofen is contraindicated (see section 4.3).

Method of administration
For oromucosal administration and short-term use only.
As with all lozenges, to avoid local irritation, Strefen Honey and Lemon & Strefen Orange flavour Sugar Free should be moved around the mouth whilst sucking.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4)

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, angioedema, or urticaria) in response to 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 NSAID therapy.

Last trimester of pregnancy. (See section 4.6)

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

Use in children under 12 years of age.

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

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. Flurbiprofen lozenges should be used with caution in these patients.

Other NSAIDs:

The use of Strefen Honey and Lemon & Strefen Orange flavour Sugar Free lozenges with concomitant NSAIDS including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Systemic lupus erythematosus and mixed connective tissue disease:

Patients with systemic lupus erythematosus and mixed connective tissue disease may have an increased risk of aseptic meningitis (see section 4.8), however this effect is not usually seen with short term limited use products such as flurbiprofen lozenges.

Cardiovascular, Renal and Hepatic 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, however, this effect is not usually seen with short term, limited use products such as flurbiprofen lozenges.

Cardiovascular and cerebrovascular effects:
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.
Clinical trial and epidemiological data suggest that the use of 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 when given at a daily dose of no more than 5 lozenges.

Hepatic:
Mild to moderate hepatic dysfunction (see sections 4.3 and 4.8)

Nervous System effects
Analgesic induced headache- In the event of prolonged use of analgesics or use beyond the regulations headache may occur, which must not be treated with increased doses of the medicinal product.

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)

Gastrointestinal 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, however this effect is not usually seen with short term limited use products such as flurbiprofen lozenges.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) to their healthcare professional. 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).
If GI bleeding or ulceration occurs in patients receiving flurbiprofen, the treatment should be withdrawn.

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

very rarely in association with the use of NSAIDSs (see section 4.8). Flurbiprofen lozenges 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 flurbiprofen lozenges therapy. It should be considered whether initiation of an anti-infective antibiotic therapy is indicated.

Masking of symptoms of underlying infections:
Epidemiological studies suggest that systemic non-steroidal anti-inflammatory drugs (NSAIDs) 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 Strefen is administered while the patient suffers from fever or pain in relation to infection, monitoring of infection is advised.

Important Information about some of the ingredients of **Strefen Honey and Lemon**

• This medicine contains only very low levels of gluten (from wheat starch). It is regarded as 'gluten-free' and is very unlikely to cause problems if you have coeliac disease. One lozenge contains no more than 21.38 micrograms of gluten. If you have wheat allergy (different from coeliac disease) you should not take this medicine.
• This medicine contains 1.407 g Sucrose per lozenge and 1.069 g Glucose per lozenge. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase isomaltase insufficiency should not take this medicine.
• This medicine contains sulphites, which may rarely cause severe hypersensitivity reactions and bronchospasm.
• This medicine contains fragrance with Citral, Citronellol, d-Limonene, Farnesol, Geraniol and Linalool. Citral, Citronellol, d-Limonene, Farnesol, Geraniol and Linalool may cause allergic reactions.
• This medicine contains Butylated hydroxyanisole (E320) (present in Lemon flavour) which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

Important Information about some of the ingredients of **Strefen Orange flavour Sugar Free**

This product contains liquid maltitol (510 mg/lozenge) and Isomalt (2039 mg/lozenge), patients with rare hereditary problems of fructose intolerance should not take this medicine. May have a mild laxative effect. Calorific value 2.3 kcal/g for liquid maltitol and isomalt .

It also contains fragrances in the orange flavour containing Citral, Citronellol, d-Limonene, Geraniol and Linalool which may cause allergic reactions.

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

4.5 Interaction with other medicinal products and other forms of interaction

Flurbiprofen should be <u>avoided</u> in combination with:	
Other NSAIDS including cyclooxygenase-2 selective inhibitors:	Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (esp. gastrointestinal adverse events such as ulcers and bleeding), (see section 4.4).
Acetylsalicylic acid (low dose)	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 <u>used with caution</u> 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)
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 lithium – 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 hyperkalaemia
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.

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

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 has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased 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 and duration of treatment as short as possible.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose
the fœtus 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-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.
Consequently, flurbiprofen is contraindicated during the third trimester of pregnancy.

Lactation
In limited studies, flurbiprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely. However, because of possible adverse effects of NSAIDs on breast-fed infants, Strefen Honey & Lemon lozenges are not recommended for use in nursing mothers.

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 of machines have been performed.

4.8 Undesirable effects
Hypersensitivity reactions to NSAIDs have 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)
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). There is insufficient data to exclude such a risk for flurbiprofen 8.75 mg lozenges.a

The following list of adverse effects relates to those experienced with flurbiprofen 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:
Not known: anaemia, thrombocytopenia.

Immune System disorders:
Rare: anaphylactic reaction

Psychiatric disorders:

Uncommon: insomnia

Cardiovascular and cerebrovascular disorders
Not known: Oedema, hypertension and cardiac failure

Nervous System disorders:
Common: dizziness, headache, parasthesia
Uncommon: somnolence

Respiratory, thoracic and mediastinal disorders:
Common: throat irritation
Uncommon: exacerbation of asthma and bronchospasm, dyspnoea, wheezing, oropharyngeal blistering, pharyngeal hypoaesthesia.

Gastrointestinal disorders:
Common: diarrhoea, mouth ulceration, nausea, oral pain, paraesthesia oral, oropharyngeal pain, oral discomfort (warm or burning feeling or tingling of the mouth).
Uncommon: abdominal distension, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, glossodynia, dysgeusia, oral dysaesthesia, vomiting

Hepatobiliary disorders:
Not known: hepatitis

Skin and subcutaneous tissue disorders:
Uncommon: various skin rashes, pruritus.
Not known: severe forms of skin reaction such as bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

General disorders and administration site conditions:
Uncommon: pyrexia, pain

Reporting of Suspected Adverse Reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL)

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 and if necessary correction of serum electrolytes and if the patient presents within 1 hour of ingestion or 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: Throat preparations, other throat preparations.

ATC Code: R02AX01

Flurbiprofen is a propionic acid derivative NSAID which acts through inhibition of prostaglandin synthesis. In humans flurbiprofen has potent analgesic, antipyretic and anti-inflammatory properties and the 8.75mg dose dissolved in artificial saliva has been shown to reduce prostaglandin synthesis in cultured human respiratory cells. 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.

A single dose of flurbiprofen 8.75mg delivered locally to the throat in a lozenge has been demonstrated to relieve sore throat, including swollen and inflamed sore throats through a significant reduction (LS Mean Difference) in sore throat pain intensity from 22 minutes (-5.5mm), reaching a maximum at 70 minutes (-13.7mm) and remaining significant for up to 240 minutes (-3.5mm) including patients with streptococcal and non-streptococcal infections, reduction in difficulty swallowing from 20 minutes (-6.7mm), reaching a maximum at 110 minutes (-13.9mm) and for up to 240 minutes (-3.5mm) and reduction in the feeling of a swollen throat at 60 minutes (-9.9mm), reaching a maximum at 120 minutes (-11.4mm) and for up to 210 minutes (-5.1mm).

Multiple dose efficacy measured using Sum of Pain Intensity Differences (SPID) over 24 hours has demonstrated significant reduction in sore throat pain intensity (-473.7mm*h to -529.1mm*h), difficulty swallowing (-458.4mm*h to -575.0mm*h) and swollen throat (-482.4mm*h to -549.9mm*h) with statistically significant greater summed reduction in pain at each hourly interval over 23 hours for all three measures and statistically significantly greater sore throat relief each hour over the 6 hour assessment time. Efficacy of multiple doses after 24 hours and over 3 days has also been demonstrated.

For those patients taking antibiotics for streptococcal infection, there was statistically significant greater relief of sore throat pain intensity for flurbiprofen 8.75mg from 7 hours and onwards after antibiotics were taken. The analgesic effect of flurbiprofen 8.75 mg was not reduced by the administration of antibiotics to treat patients with streptococcal sore throat.
At 2 hours post first dose, flurbiprofen 8.75mg lozenges provided significant resolution of some of the associated symptoms of sore throat present at baseline including coughing (50% vs 4%), loss of appetite (84% vs 57%) and feverishness (68% vs 29%). The lozenge format dissolves in the mouth over 5 - 12 minutes and provides a measurable soothing and coating effect at 2 minutes.

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

5.2 Pharmacokinetic properties

Absorption
Flurbiprofen 8.75mg lozenges dissolve over 5 – 12 minutes and the flurbiprofen is readily absorbed, with detection in the blood at 5 minutes and plasma concentrations peaking at 40 - 45 minutes after administration but remaining at a mean low level of 1.4µg/mL which is approximately 4.4 times lower than a 50mg tablet dose.
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.

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 0.05 µg/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
There are no preclinical data of relevance additional to information already included in other relevant sections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Strefen Honey and Lemon

Macrogol 300
Potassium hydroxideLemon flavour (d-Limonene, Citral, Citronellol, Farnesol, Geraniol, Linalool and Butylated Hydroxyanisole (E320))
Levomenthol
Liquid sucrose
Liquid glucose (Wheat Starch, Sulphur Dioxide (E220))
Honey

Strefen Orange Sugar Free

Macrogol 300 (Polyethylene glycol 300)
Potassium hydroxide
Orange Flavour PHL-010300 (citral, citronellol, d-Limonene, geraniol and linalool)
Levomenthol
Acesulfame Potassium
Liquid Maltitol Isomalt

6.2 **Incompatibilities**

Not applicable.

6.3 **Shelf life**

Strefen Honey and Lemon 36 months.

Strefen Orange Sugar Free 24 months.

6.4 **Special precautions for storage**

Store below 25ºC.

6.5 **Nature and contents of container**

A push through strip consisting of 250 microns opaque PVC/PVdC (polyvinyl chloride/polyvinyl di-chloride) blister, heat sealed to hard tempered 20 micron aluminium foil. Blisters are enclosed in a cardboard carton in pack sizes of 2, 4, 6, 8, 10, 12, 16, 24or 36 lozenges.

6.6 **Special precautions for disposal and other handling**

None

7. MANUFACTURER

Reckitt Benckiser Healthcare Int., 1 Thane Road, Nottingham NG90 2DB, England.

8. MARKETING AUTHORISATION HOLDER

Reckitt Benckiser (Near East) Ltd., 6 Hanagar St., Hod- Hasharon, Israel 4527704.

Revised in December 2025