

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vocafen sugar free honey and lemon flavour 8.75 mg lozenges

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lozenge contains 8.75 mg of flurbiprofen.

Excipients with known effect:

Isomalt (E953): 2,047 mg/lozenge

Maltitol, liquid (E965) (contains sorbitol): 682.33 mg/lozenge

Honey flavour (contains citronellol): 2.4 mg/lozenge

Lemon flavour (contains citral, citronellol, geraniol, limonene and linalool): 9.0 mg/lozenge

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lozenge

White to pale yellow coloured, round, flat bevelled lozenges with honey and lemon and with a thickness of 7,0 to 8,0 mm and a diameter of 18,0 to 19,00 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vocafen sugar free honey and lemon flavour 8.75 mg lozenges are indicated for the short-term symptomatic relief of sore throat in adults and adolescents

over the age of 12 years.

4.2 Posology and method of administration

Posology

Adults and adolescents over the age of 12 years:

One lozenge every 3 to 6 hours as needed. Maximum 5 lozenges in 24-hour period. This product should be used for a maximum of three days.

Paediatric population:

Not indicated for children under 12 years of age.

Elderly population

Due to the limited clinical trials available, a general dose cannot be recommended. Elderly patients are at higher risk of suffering serious consequences of adverse reactions.

Impaired hepatic function

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 function

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, flurbiprofen 8.75 mg lozenges should be moved around the mouth whilst sucking.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, bronchospasm, rhinitis, angioedema or urticaria) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- Active or history of recurrent peptic ulcer/hemorrhage (two or more distinct episodes of proven ulceration) and intestinal ulceration.
- History of gastrointestinal bleeding or perforation, severe colitis, hemorrhage, or hematopoietic disorders related to previous treatment with NSAIDs.
- Last trimester of pregnancy (see section 4.6).
- Severe heart failure, severe renal failure, or severe hepatic failure (see section 4.4)

4.4 Special warnings and precautions for use

Undesirable effects may be minimized by using the lowest effective dose for the shortest possible duration necessary to control symptoms.

Elderly population

Elderly patients have an increased frequency of adverse reactions to NSAIDs, particularly gastrointestinal bleeding and perforation, which may be fatal.

Respiratory disorders

Bronchospasm can be triggered in patients suffering from, or with history of bronchial asthma or allergic diseases. Flurbiprofen must be used with caution in these patients.

Other NSAIDs

Concomitant use of flurbiprofen and other NSAIDs, including selective cyclooxygenase -2 inhibitors, should be avoided (see section 4.5).

SLE (Systemic Lupus Erythematosus) 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). 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 could trigger 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 to starting treatment in patients with 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 administration of some NSAIDs (particularly at high doses and long-term treatment) may be associated with a small increased risk of arterial thrombotic events (for example, myocardial infarction or stroke). There is not enough data to exclude this risk for flurbiprofen when administered at a maximum daily dose of 5 lozenges.

Hepatic impairment

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 in patients with history of gastrointestinal diseases (ulcerative colitis, Crohn's disease), as these conditions could be exacerbated (see section 4.8).

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

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAIDs doses, in patients with history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in elderly, however this effect is not usually seen with short term limited use products such as Vocafer sugar free honey and lemon flavour 8.75 mg lozenges. Patients with a history of gastrointestinal toxicity, particularly elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding), to their treating physician.

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 acetyl salicylic acid (see section 4.5).

In patients taking flurbiprofen, the treatment should be withdrawn if gastrointestinal bleeding or ulceration occurs.

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). Flurbiprofen should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Infections

The patient should immediately see a doctor if symptoms of bacterial infection occur or get worse during the treatment with flurbiprofen as in isolated cases, exacerbation of infectious inflammations was described (e.g. development of necrotizing fasciitis) in connection with the time when the systemic NSAIDs were used. The need to start antibiotic treatment with an anti-infective agent should be evaluated.

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 Vocaferen sugar free honey and lemon flavour is administered while the patient suffers from fever or pain in relation to infection, monitoring of infection is advised.

Others

The treatment should be reevaluated if symptoms get worse or if new symptoms occur.

The lozenge should be moved around inside the mouth as it dissolves. Treatment should be withdrawn in case of mouth irritation.

Excipients

This medicinal product contains isomalt and maltitol, liquid. Patients with rare hereditary problems of fructose intolerance should not use this medicinal product.

Vocaferen sugar free honey and lemon flavour contains fragrance with citral, citronellol, geraniol, limonene and linalool which may cause allergic reactions.

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 s-2 selective inhibitors:	Avoid concomitant use of two or more NSAIDs, since this may increase the risk of adverse effects particularly, gastrointestinal adverse events such as ulcers and bleeding) (see section 4.4).

Acetylsalicylic acid (low dose)	Unless low-dose acetylsalicylic acid has been recommended by the doctor (not above 75 mg/day), as it may increase the risk of adverse reactions (see section 4.4).
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Flurbiprofen should be taken <u>with caution</u> in combination with:	
Anticoagulants:	NSAIDs may increase the effects of anticoagulants, such as warfarin (see section 4.4).
Antiplatelet agents:	Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
Antihypertensive: drugs (diuretics, ACE-inhibitors, Angiotensin II Receptor Blockers):	NSAIDs may reduce the effect of diuretics and other antihypertensive drugs; they may increase the nephrotoxicity caused by inhibition of cyclooxygenase, particularly in patients with compromised renal function (patients should be adequately hydrated)
Alcohol	May increase the risk of adverse reactions, particularly gastrointestinal tract bleeding.
Cardiac glycosides:	NSAIDs may exacerbate cardiac failure, reduce the glomerular filtration rate and increase plasma glycosides levels - appropriate monitoring is recommended and, if necessary, dose adjustment
Cyclosporine:	Increased risk of nephrotoxicity.
Corticosteroids:	May increase the risk of adverse reactions, particularly in the gastrointestinal tract (see section 4.3).
Lithium:	May increase serum concentrations of lithium-appropriate monitoring is recommended and, if necessary, dose adjustment.
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 8-12 days after the administration of mifepristone, as NSAIDs can reduce the effect of mifepristone.
Oral antidiabetics	Alteration of blood glucose levels have been reported (increased check rate is recommended).
Phenytoin	May increase serum levels of phenytoin - appropriate monitoring and, if necessary, dose adjustment is recommended

Potassium-sparing diuretics	Concomitant use may cause hyperkalemia
Probenecid Sulfinpyrazone	Medicines containing probenecid or sulfinpyrazone may delay the excretion of flurbiprofen.
Quinolones antibiotics:	Animal data suggest that NSAIDs may increase the risk of seizures associated with quinolones. Patients taking NSAIDs and quinolones may have a higher risk of developing convulsions.
Selective serotonin Reuptake Inhibitors (SSRIs)	Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
Tacrolimus:	Possible increase of the nephrotoxicity risk when NSAIDs are administered with tacrolimus.
Zidovudine:	Increased risk of hematological toxicity when NSAIDs are administered with zidovudine.

So far, studies have not revealed any interaction between flurbiprofen and tolbutamide and antacids.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect 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 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-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, Vocafer sugar free honey and lemon flavour are not recommended for use in nursing mothers. See section 4.4 regarding female fertility.

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.

4.8 Undesirable effects

Hypersensitivity reactions to NSAIDs have been reported and these may consist of:

- Non-specific allergic reactions and anaphylaxis
- Respiratory tract reactivity such as asthma, asthma worsening, bronchospasm and dyspnea.
- Several skin reactions, such as itching, 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

The following list of adverse effects refers to those reported with flurbiprofen at OTC doses, for short-term use:

(Very common ($\geq 1/10$), Common ($\geq 1/100, < 1/10$), Uncommon ($\geq 1/1,000 < 1/100$), Rare ($\geq 1/10,000 < 1/1,000$), Very rare ($< 1/10,000$), not known (cannot be estimated from 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, paraesthesia

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, and more rarely diarrhea. 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 prothrombin time/INR (International Normalized Ratio) may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. In asthmatic patients, exacerbation of asthma is possible.

Management

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until they become stable.

Consider the use of activated charcoal or gastric lavage, and if needed serum electrolyte correction, if less than one hour has elapsed since ingestion or a potentially toxic amount was ingested. Frequent or prolonged convulsions should be treated with intravenous diazepam or lorazepam. Administer bronchodilators for asthma. There is no specific antidote for flurbiprofen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Throat preparations, other throat preparations,
ATC Code:
R02AX01

Mechanism of action

Flurbiprofen is a propionic acid derivative NSAID which acts through

inhibition of prostaglandin synthesis.

Pharmacodynamic effects

In humans, flurbiprofen has potent analgesic, antipyretic and anti-inflammatory properties and the 8.75 mg 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.

Preclinical 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.

Clinical efficacy and safety

Flurbiprofen from the 8.75 mg lozenge has been shown to penetrate into the layers of the whole human pharynx tissue including the deeper layer in an ex vivo model.

In patients that experienced a meaningful pain relief at a median time of 42.9 minutes by a single dose of flurbiprofen 8.75 mg delivered locally to the throat in a lozenge, the first perceived relief (onset of analgesia) occurred at a median time of 13.2 minutes.

Relief of 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 adolescents aged 12 – 17 years, although small sample size means that no statistical conclusions can be drawn.

5.2 Pharmacokinetic properties

Absorption

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 1.4 µg/mL which is approximately 4.4 times lower than a 50 mg 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.

Biotransformation/Elimination

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 0.08 µg/ml). Approximately 20-25% of a flurbiprofen oral dose is excreted unchanged.

Special populations

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

Isomalt (E953)

Maltitol liquid (E965) (contains sorbitol)

Acesulfame potassium (E950)

Macrogol 400

Levomenthol

Honey flavour (contains citronellol)

Lemon flavour (contains citral, citronellol, geraniol, limonene, and linalool)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC - PVDC Aluminum blisters in a printed cardboard box.
Pack size: 16 lozenges

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mapaex Consumer Healthcare (Ireland) Private Limited
IDA Business Park, Green Road, Newbridge
KILDARE
W12 X902
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8 MARKETING AUTHORISATION NUMBER(S)

PL 57980/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

24/04/2025