Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Medisils Intensive 8.75 mg lozenges

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lozenge contains 8.75 mg of flurbiprofen

Excipients with known effect
Each lozenge contains 2034 mg isomalt (E 953), 427.5 mg maltitol liquid (E 965), 10.796 mg orange flavour (contains limonene, citral, citronellol), 0.013 mg cochineal Red A (E 124) and 0.080 mg Sunset yellow FCF (E 110).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lozenge

A round orange lozenge of 19 mm diameter and 7.5 mm thickness.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Medisils Intensive is indicated for the local 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
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

Adults and adolescents 12 years or older
One lozenge should be slowly sucked/dissolved in the mouth every 3 to 6 hours as needed. Maximum 5 lozenges in every 24-hour period.

It is recommended that this product should be used no longer than three days.

Paediatric population
Not indicated for children under 12 years of age.
The safety and efficacy of Medisils Intensive in children below 12 years of age have not been established. No data are available.

Elderly population
Due to the limited clinical data available, a general dose cannot be recommended. Elderly patients are at higher risk of suffering serious consequences of adverse reactions (see section 4.4).

Renal impairment
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).

Hepatic impairment
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).

Method of administration

For oromucosal and short term use only.
As with all lozenges, Medisils Intensive lozenges should be moved around inside the mouth to avoid local irritation.

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 (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 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 may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease. Medisils Intensive 8.75 mg orange lozenges must be used with caution in these patients.

Other NSAIDs
Concomitant use of flurbiprofen lozenges 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 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 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 in 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
Mild to moderate hepatic dysfunction (see sections 4.3 and 4.8).

Nervous system effects
Analgesic-induced headache: In case of prolonged use of analgesics or use beyond the regulations, headaches 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 NSAID 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 flurbiprofen lozenges. Patients with a history of gastrointestinal toxicity, particularly elderly, should report any unusual abdominal symptoms (especially gastrointestinal 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 acetyl salicylic acid (see section 4.5).

If gastrointestinal bleeding or ulceration occurs in patients taking 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 NSAIDs (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.

In cases of purulent bacterial pharyngitis/tonsillitis, the patient is advised to consult a physician as the treatment needs to be re-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 Medisils Intensive is administered while the patient suffers from fever or pain in relation to infection, monitoring of infection is advised.

Treatment should be administered for three days maximum.

Excipients
Contains Isomalt and Maltitol which may have a mild laxative effect after multiple daily doses. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Isomalt and Maltitol have a calorific value of 2.3 kcal/g.

This medicinal product contains azo colouring agent: Cochineal Red A (E 124) and Sunset yellow FCF (E 110). May cause allergic reactions.

Medisils Intensive contains orange flavour containing limonene, citral and citronellol 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-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 acetylsalicylic acid (not above 75 mg 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. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the coadministration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking flurbiprofen concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring.
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:	Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
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 (SSRIs):	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.

Paediatric population
No additional information available.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no clinical data from the use of [product name] during pregnancy. The inhibition of prostaglandin synthesis may adversely affect pregnancy and/or 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.

Even if systemic exposure is lower compared with oral administration, it is not known if the systemic Medisils Intensive exposure reached after topical administration can be harmful to an embryo/foetus. During the first and second trimester of pregnancy, Medisils Intensive should not be used unless clearly necessary. If used, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, systemic use of prostaglandin synthetase inhibitors including Medisils Intensive may induce cardiopulmonary and renal toxicity in the foetus. At the end of the pregnancy prolonged bleeding time in both mother and child may occur, and labour can be delayed. Therefore, Medisils Intensive is contraindicated during the last trimester of pregnancy (see section 4.3).

Breast-feeding
In limited studies, flurbiprofen appears in the breast milk in very low concentrations and is unlikely to affect the breast-fed infant adversely. However, because of possible adverse effects of NSAIDs on breast-fed infants, Medisoothe Intensive 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 machines have been performed.

Dizziness, drowsiness and visual disturbances are possible undesirable side effects after taking flurbiprofen. If affected, the patient should not drive or operate machinery.

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 dyspnoea.
- 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 over-the-couter doses, for short-term use: (Very common (≥ 1/10, Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1 000, < 1/100), Rare (≥ 1/10 000, < 1/10 00), 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

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

Cardiac disorders
Not known: Oedema, cardiac failure

Vascular disorders
Not known: hypertension

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

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 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 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 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

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
A single dose of flurbiprofen 8.75 mg 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 (-5.5 mm), reaching a maximum at 70 minutes (-13.7 mm) and remaining significant for up to 240 minutes (-3.5 mm) including patients with streptococcal and non-streptococcal infections, reduction in difficulty swallowing from 20 minutes (-6.7 mm), reaching a maximum at 110 minutes (-13.9 mm) and for up to 240 minutes (-3.5 mm) and reduction in the feeling of a swollen throat at 60 minutes (-9.9 mm), reaching a maximum at 120 minutes (-11.4 mm) and for up to 210 minutes (-5.1 mm).

Multiple dose efficacy measured using Sum of Pain Intensity Differences (SPID) over 24 hours has demonstrated significant reduction in sore throat pain intensity (-473.7 mm*h to -529.1 mm*h), difficulty swallowing (-458.4 mm*h to -575.0 mm*h) and swollen throat (- 482.4 mm*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 8.75 mg 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 8.75 mg 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

Flurbiprofen 8.75 mg 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
Flurbiprofen is mainly metabolised by hydroxylation via the kidneys.

Elimination
Flurbiprofen is mainly 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.

Elderly and paediatric population
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 Sections 4.4, 4.6 and 4.8.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Isomalt (E 953)
Maltitol liquid (E 965)
Potassium acesulfame (E 950)
Macrogol 300 (E 1521)
Potassium hydroxide (E 525)
Cochineal Red A (E 124)
Sunset yellow FCF (E 110)
Orange flavour (limonene, decanal, citral, citronellol)
Levomenthol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC-PVdC/Aluminium blisters packs.

Pack sizes: 8, 10, 12, 16, 20, 24, 30, 36 lozenges

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
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8 MARKETING AUTHORISATION NUMBER

PA0126/405/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th September 2025

10 DATE OF REVISION OF THE TEXT