# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Strepsils Intensive 8.75 mg Lozenges

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient flurbiprofen 8.75mg

Excipients with known effects:
Glucose 1.069 g / lozenge. Total maximum daily dose (MDD) is 5.345 g.
Sucrose 1.407 g / lozenge. Total MDD is 7.035 g.
Invert Sugar (Honey) 50.3 mg / lozenge. Total MDD is 0.2515 g.
Sulphites – Sulphur Dioxide (E220) 0.137 ppm / lozenge which is present in liquid glucose.
Wheat Starch (containing gluten), one lozenge contains no more than 21.38 micrograms of gluten which is present in liquid glucose.
Butylated hydroxyanisole (E320) present in Lemon flavour (0-1%).
Lemon flavour containing allergens (citral, citronellol, d-Limonene, farnesol, geraniol and linalool).

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Lozenge
Clear, round lozenge

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

For the symptomatic relief of sore throats.
Strepsils Intensive Lozenges are indicated in adults and adolescents over 12 years of age.

### 4.2 Posology and method of administration

**Posology:**
Treatment should be administered for the shortest duration necessary to control symptoms. It is recommended that this product should be used for a maximum of three days.

**Adults:** One lozenge sucked/dissolved slowly in the mouth every 3 – 6 hours as required. Maximum 5 lozenges in any 24 hour period.
**Paediatric population:**

**Adolescents over the age of 12 years**: As above for adults
**Children**: Not indicated for children under 12 years. (see section 4.3).

**Elderly:** No dose modification is required.
The elderly are at increased risk of the serious consequences of adverse reactions to NSAIDs (see section 4.4).

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

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

**Method of administration**
For oromucosal administration. To be dissolved slowly in the mouth.

As with all lozenges, to avoid local irritation, Strepsils Intensive Lozenges should be moved around the mouth whilst sucking. If mouth irritation occurs, treatment should be withdrawn.

**4.3 Contraindications**

- Hypersensitivity to flurbiprofen or any of the excipients listed in section 6.1.
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, bronchospasm or urticaria) in response to ibuprofen, acetylsalicylic acid (Aspirin) or other nonsteroidal anti-inflammatory drugs (NSAIDs).History of gastrointestinal bleeding or perforation, severe colitis, haemorrhagic or haematopoietic disorders related to previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Severe heart failure, severe hepatic impairment or severe renal impairment (see section 4.4).
- Use in children under 12 years of age.
- During last trimester of pregnancy

**4.4 Special warnings and precautions for use**

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (See section 4.2, and GI and cardiovascular risks below).

If the symptoms get worse or if new symptoms occur, the treatment should be re-evaluated by a healthcare professional. If mouth irritation occurs, treatment should be withdrawn.

**Other NSAIDs**: The use of Strepsils Intensive Lozenges with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2)

**Gastrointestinal Effects:**
Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without any 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 aspirin, 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 aspirin (see section 4.5).

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

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's Disease) as their condition may be exacerbated (see section 4.8 – undesirable effects).

**Cardiovascular and cerebrovascular effects:**
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 is insufficient data to exclude such a risk for flurbiprofen when given at a daily dose of 8.75mg to 43.75mg per day.

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 and oedema have been reported in association with NSAID therapy.

**Nervous System Effects:**
Analgesic induced headache. In the eventof prolonged use of analgesics or usebeyond the product posology, headachemay occur, which must not be treated with increased doses of the medicinal product.

**Renal and Hepatic Impairment:**
Caution is required in patients with renal or 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 flurbiprofen products.

**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 4.8). Patients appear to be at highest risk of 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. Strepsils Intensive Lozenges should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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

**Respiratory:**
Bronchospasm maybe precipitated in patients suffering from, or with a previous history of, bronchial asthma or allergic reactions.
Flurbiprofen should be used with caution in these patients.

**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 therapy.

Flurbiprofen can prolong bleeding time and caution is required in patients with potential for abnormal bleeding.

The use of flurbiprofen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of flurbiprofen should be considered.
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**Excipients**
This product contains glucose, sucrose and invert sugar. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This product 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 also contains fragrances with Citral, Citronellol, d-Limonene, Farnesol, Geraniol and Linalool which may cause allergic reactions and Sulphur Dioxide (E220) which may rarely cause severe hypersensitivity reactions and bronchospasm.

This medicine contains butylated hydroxyanisole (E320) which may cause local skin reactions) e.g. contact dermatitis) or irritation to the eyes and mucous membranes.

**4.5 Interaction with other medicinal products and other forms of interactions**

| **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 used with <u>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 |
| *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 (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.

**<u>Paediatric population</u>**: No additional information available.

**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.

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 olgio-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 (see section 4.3).

**Breast-feeding**
In limited studies, flurbiprofen appears in the breast milk in a 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, flurbiprofen is 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 NSAIDs. If affected, the patient should not drive or operate machinery.

**4.8 Undesirable effects**

Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of:

1. Non-specific allergic reactions and anaphylaxis,
2. Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea,
3. Assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The list of the following adverse effects relates to those experienced with flurbiprofen at OTC doses, in short-term use.

The frequencies of the adverse drug reactions (ADRs) reported below are based on the reporting of adverse events in all patients receiving flurbiprofen 8.75 mg in placebo-controlled, open-label, and active comparator clinical trials.

They are tabulated by system organ class and frequency. Frequencies are defined as Very

common (≥1/10); Common (≥1/100 and <1/10); Uncommon (≥1/1,000 to < 1/100); Rare (≥1/10,000 to <1/1,000); Very rare (< 1/10,000); Not known (cannot be estimated from the available data).

| System Organ Class | Frequency | Adverse Events |
|---|---|---|

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|---|---|---|
| Blood and Lymphatic System Disorders | Not known | Anaemia and thrombocytopenia. |
| Nervous System Disorders | Common | Dizziness, headache, paraesthesia |
| | Uncommon | Somnolence |
| Immune System Disorders | Rare | Anaphylactic reaction |
| Cardiac disorders | Not known | Cardiac failure, oedema, myocardial infarction |
| Vascular disorders | Not known | Hypertension |
| Respiratory, Thoracic and Mediastinal Disorders | Common | Throat irritation |
| | Uncommon | Exacerbation of asthma and bronchospasm, dyspnoea, 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 |
| 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 |
| Hepatobiliary Disorders | Not known | Hepatitis |
| Psychiatric Disorders | Uncommon | Insomnia |

**Reporting of Suspected Adverse Events**
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 Pharmacovigilance Section, Health Products Regulatory Authority, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

**4.9 Overdose**

**Symptoms:**
Most patients who have ingested clinically important amounts of NSAIDs will develop symptoms of overdose that may include nausea, vomiting, epigastric pain, gastrointestinal irritation or more rarely diarrhoea, drowsiness, blurred vision and dizziness. 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 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**

**5.1 Pharmacodynamic Properties**
**Pharmacotherapeutic group:** Respiratory System; 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 and respiratory cells.

According to studies using the whole body 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 relieve pain by acting on the central nervous system. Reduction in throat soreness was observed after 15 minutes while onset of pain relief and reduction of throat swelling was observed 30 minutes after taking a lozenge. Duration of action extended up to 3 hours.

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 conjugation in the liver 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**

Macrogol 300
Potassium Hydroxide
Lemon Flavour (butylated hydroxyanisole (E320), citral, citronellol, d-Limonene, farnesol, geraniol and linalool)
Levomenthol
Liquid Glucose (wheat starch containing gluten, sulphur dioxide (E220)
Liquid sucrose
Honey

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Store below 25°C.

**6.5 Nature and contents of container**

Lozenges are packed in blisters made up of white opaque 250micron Polyvinyl Chloride (PVC), coated with 40gsm or 90gsm Polyvinylidene Chloride (PVDC); heat sealed to 20 microns Aluminium lidding material coated with 7gsm of heat sealing lacquer containing 16 lozenges.

**6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Reckitt Benckiser Ireland Ltd
7 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA0979/041/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 07 March 2003

Date of last renewal : 07 March 2008

**10 DATE OF REVISION OF THE TEXT**