APPLICANT	**: Reckitt Benckiser Pharmaceuticals (Pty) Ltd**
PROPRIETARY NAME (DOSAGE FORM)	**: Strepsils Intensive Spray (Throat Spray)**
STRENGTH	**: Flurbiprofen 8,75 mg**

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S1

1 NAME OF THE MEDICINE

Strepsils Intensive Spray (flurbiprofen 8,75 mg throat spray)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

8,75 mg flurbiprofen per metered dose or 3 sprays.

Preservatives:

Methyl parahydroxybenzoate 0,22 % *m/v*

Propyl parahydroxybenzoate 0,04 % *m/v*

Contains sweetener (0,27 mg Saccharin sodium)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Throat spray, solution

Clear, colourless to slightly yellow solution with a taste of cherry and mint.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Strepsils Intensive Spray is indicated for the short-term symptomatic relief of acute sore throat in adults.

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STRENGTH	**: Flurbiprofen 8,75 mg**

4.2 Posology and method of administration

For short-term use only.

Adults aged 18 years and over:

One dose (3 sprays) administered to the back of the

throat every 3-6 hours as required, up to a maximum of 5 doses in a 24 hour period.

Do not inhale whilst spraying.

Strepsils Intensive Spray should be used for a maximum of three days.

Use the lowest effective dose for the shortest possible duration of treatment.

Paediatric population

The safety and efficacy of Strepsils Intensive Spray in children or adolescents under 18 years has not been established.

Elderly patients

A general dose recommendation cannot be given, since to date clinical experience is limited.

The elderly is at increased risk of the serious consequences of adverse reactions.

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

Method of administration

For Oromucosal administration

Before first use, activate the pump by pointing the nozzle away from

you and spraying a minimum of four times until a fine, consistent mist is produced.

The pump is then primed and ready for use.

Between each dose point the nozzle away from you and spray a minimum of once ensuring a fine, consistent mist is produced.

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Always ensure a fine consistent mist is produced before dosing the product.

4.3 Contraindications

- Hypersensitivity to flurbiprofen 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 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.
- First, second and last (third) trimester of pregnancy (See section 4.6)
- Severe heart failure, severe renal failure or severe hepatic failure (see section 4.4).
- Children and adolescents below 18 years.

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.

<u>Infections</u>

Cases of 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 should be advised to consult a medical practitioner immediately if signs of a bacterial infection occur or worsen during the Strepsils Intensive Spray therapy. It should be considered whether initiation of an anti-infective antibiotic therapy is indicated.

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In cases of purulent bacterial pharyngitis/tonsillitis, the patient should be advised to consult a medical practitioner as the treatment needs to be re-evaluated.

Treatment should be administered for three days maximum.

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

If mouth irritation occurs, treatment with Strepsils Intensive Spray should be withdrawn.

Elderly population

The elderly have an increased frequency of adverse reactions to NSAIDs including Strepsils Intensive Spray, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.

Respiratory

Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease. Strepsils Intensive Spray should be used with caution in these patients.

Other NSAIDs

The use of Strepsils Intensive Spray 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).

Cardiovascular, Renal and Hepatic Impairment

Strepsils Intensive Spray has been reported to cause nephrotoxicity in various forms including

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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.

Hepatic

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

Cardiovascular and cerebrovascular effects

Caution 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 Strepsils Intensive Spray therapy.

In view of the Strepsils Intensive Spray's inherent potential to cause fluid retention, heart failure may be precipitated in compromised patients.

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 Strepsils Intensive Spray when given at a daily dose of no more than 5 doses (3 sprays per dose).

Nervous System effects

Analgesic induced headache may occur with Strepsils Intensive Spray if used for longer than 3 days or exceeding the recommended dose. Analgesic induced headache must not be treated with increased doses of Strepsils Intensive Spray.

Gastrointestinal

Strepsils Intensive Spray should not be given to patients with a history of gastrointestinal

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disease (ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angio-dysplasia) as these conditions may be exacerbated (see section 4.3 and 4.8).

Gastrointestinal bleeding, ulceration, or perforation, which can be fatal, has been reported with NSAIDs, such as contained in Strepsils Intensive Spray. It may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of Strepsils Intensive Spray, in patients with a history of ulcers, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. Patients with a history of GI toxicity, particularly when elderly, should be advised to report any unusual abdominal symptoms (especially GI bleeding) to their medical practitioner.

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 Strepsils Intensive Spray, the treatment with Strepsils Intensive Spray should be withdrawn.

Haematological effects

Strepsils Intensive Spray, may inhibit platelet aggregation and prolong bleeding time. Strepsils Intensive Spray should be used with caution in patients with a potential for bleeding.

Dermatological

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens- Johnson syndrome and toxic epidermal necrolysis, have been reported in association with the use of NSAIDs (see section 4.8). Strepsils Intensive Spray should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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This product contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

Drug Reaction and Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as STREPSILS INTENSIVE SPRAY. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue DISPRIN MELTS and evaluate the patient immediately.

4.5 Interaction with other medicines 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 such as flurbiprofen in Strepsils Intensive Spray, 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:

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Anticoagulants:

Strepsils Intensive Spray 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 such as flurbiprofen in Strepsils Intensive Spray may reduce the effect of diuretics and other antihypertensive medicines 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 (e.g digoxin)

NSAIDs such as flurbiprofen in Strepsils Intensive Spray may exacerbate cardiac failure, reduce GFR and increase plasma glycosides levels – adequate control, if necessary, dose adjustment is recommended.

Ciclosporin

Increased risk of nephrotoxicity.

Corticosteroids

Increased risk of gastrointestinal ulceration or bleeding (PUBs) (see section 4.4).

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Lithium

May increase serum levels of lithium - adequate control and, if necessary, dose adjustment is recommended.

Methotrexate

The administration of NSAIDs such as flurbiprofen in Strepsils Intensive Spray 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 such as flurbiprofen in Strepsils Intensive Spray, 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

Medicines that contain probenecid or sulfinpyrazone may delay the excretion of flurbiprofen.

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Quinoline antibiotics

Animal data indicate that NSAIDs such as flurbiprofen in Strepsils Intensive Spray, can increase the risk of convulsions associated with quinoline antibiotics. Patients taking NSAIDs and quinolines 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 increase risk of nephrotoxicity when NSAIDs such as flurbiprofen in Strepsils Intensive Spray, are given with tacrolimus.

Zidovudine

Increased risk of haematological toxicity when NSAIDs such as flurbiprofen in Strepsils Intensive Spray, 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

The use of Strepsils Intensive Spray during pregnancy is contraindicated. 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

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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 as contained in Strepsils Intensive Spray should not be given (See section 4.3).

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors such as flurbiprofen contained in Strepsils Intensive Spray, 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-hydramnios.
- the mother and the neonate, at the end of pregnancy, to:
  - possible prolongation of bleeding time, a platelet anti-aggregating effect which may occur even at very low doses.
  - inhibition of uterine contractions resulting in delayed or prolonged labour.

In view of Strepsils Intensive Spray's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Consequently, flurbiprofen as contained in Strepsils Intensive Spray, is contraindicated during the third trimester of pregnancy (see section 4.3).

<u>Breastfeeding</u>

Women on treatment with Strepsils Intensive Spray, which contains flurbiprofen, should

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not breastfeed their infants. Flurbiprofen appears in the breast milk and may cause harm to the breastfeeding baby.

Fertility

There is some evidence that medicines such as flurbiprofen in Strepsils Intensive Spray, 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 such as flurbiprofen in Strepsils Intensive Spray. If affected, the patient should not drive or operate machinery.

4.8 Undesirable effects

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

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Psychiatric disorders:

Uncommon: insomnia

Nervous system disorders:

Common: dizziness, headache, parasthesia Uncommon: somnolence

Cardiac and vascular disorders:

Not Known: Oedema, hypertension, cardiac failure

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

Unknown: Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, vomiting, flatulence, constipation, dyspepsia, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn’s disease, gastritis

Hepatobiliary disorders:

Not known: hepatitis

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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, erythema multiforme and toxic epidermal necrolysis.

Not known: Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) [see Warnings and Special Precautions]

General disorders and administration site conditions:

Uncommon: pyrexia, pain

Description of selected adverse reactions

Hypersensitivity reactions to NSAIDs such as flurbiprofen in Strepsils Intensive Spray, 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. There is insufficient data to exclude such a risk for Strepsils Intensive Spray.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the risk/benefit balance of the medicinal product.

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Healthcare providers are to report any suspected reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form' found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop nausea, vomiting, epigastric pain, or 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, coma or 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

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Pharmacological Classification: A.16 Ear, nose and throat preparations

Flurbiprofen is a propionic acid derivative NSAID which acts through inhibition of prostaglandin synthesis. In humans flurbiprofen has 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.

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 8,75 mg delivered locally to the throat as three sprays has been demonstrated to relieve sore throat, including swollen and inflamed sore throats through a significant change in the severity of throat soreness area under the change (AUC) from baseline curve (mean difference (standard deviation)) for active treatment versus placebo from 0 to 2 hours (-1,82 (1,35) vs -1,13 (1,14)), 0 to 3 hours (-2,01 (1,405) vs -1,31 (1,233)) and 0 to 6 hours (-2,14 (1,551) vs -1,50 (1,385).

Significant differences in the AUC from baseline curve from 0 - 6 hours compared to placebo were also seen for other qualities of sore throat including pain intensity (- 22,50 (17,894) vs -15,64 (16,413)), difficulty swallowing (-22,50 (18,260) vs -16,01 (15,451)), swollen throat (-20,97 (18,897) vs -13,80 (15,565)) and sore throat pain relief (3,24 (1,456) vs 2,47 (1,248)). The change from baseline at individual time points across the different qualities of sore throat demonstrated significance starting from 5 minutes and lasting for up to 6 hours.

For those patients taking antibiotics for Streptococcal infection, there was statistically significant greater relief of sore throat pain intensity for flurbiprofen 8,75 mg lozenge from 7 hours and onwards after antibiotics were taken. The analgesic effect of flurbiprofen 8,75 mg lozenge was not reduced by the administration of antibiotics to treat patients with streptococcal sore throat.

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Multiple-dose efficacy over 3 days has also been demonstrated.

Paediatric Population

No specific studies in children less than 18 years of age have been undertaken with Strepsils Intensive Spray.

5.2 Pharmacokinetic properties

Absorption

A single dose of flurbiprofen 8,75 mg is delivered directly to the throat as three sprays and the flurbiprofen is readily absorbed, with detection in the blood between 2 and 5 minutes and plasma concentrations peaking at 30 minutes after administration, but remaining at a mean low level of 1,6 µg/mL which is approximately 4 times lower than a 50 mg tablet dose. Strepsils Intensive Spray demonstrates bioequivalence to flurbiprofen 8,75 mg lozenge. 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 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

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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

- Betadex
- Disodium phosphate dodecahydrate
- Citric acid monohydrate
- Methyl parahydroxybenzoate (E218)
- Propyl parahydroxybenzoate (E216)
- Sodium hydroxide
- Mint flavour Cherry flavour
- N,2,3-Trimethyl-2-isopropylbutanamide
- Saccharin sodium
- Hydroxypropylbetadex
- Purified water
- Qualitative composition of mint flavour:

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- Flavouring substance(s)
- Flavouring preparation(s)
- Propylene glycol E1520
- Glyceryl triacetate (Triacetin) E1518

- Qualitative composition of cherry flavour:
  - Flavouring substance(s)
  - Flavouring preparation(s)
  - Propylene glycol E1520
  - Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After first opening: 6 months

6.4 Special precautions for storage

Store at or below 25 °C.

Do not refrigerate or freeze.

6.5 Nature and contents of container

A white opaque HDPE bottle with a multi-component pump unit and protective polypropylene overcap. The pump is comprised of polyoxymethylene, low density polyethylene, high density polyethylene, polypropylene, stainless steel and PIB Compound (Polyisobutylene - Rubber).

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Pack size: Each bottle contains 15 ml of solution which provides approximately 83 actuations.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Reckitt Benckiser Pharmaceutical (Pty) Ltd

8 Jet Park Road

Elandsfontein 1601

0861 11 11 00

8 REGISTRATION NUMBER

50/16/0351

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 March 2021

10 DATE OF REVISION OF THE TEXT

25 November 2022