Safeguarding public health

Public Assessment Report

CALPROFEN 100MG/5ML ORAL SUSPENSION IBUPROFEN

(IBUPROFEN)

PL 15513/0147

Medicines and Healthcare products Regulatory Agency

CALPROFEN 100MG/5ML ORAL SUSPENSION IBUPROFEN

(Ibuprofen) PL 15513/0147

UKPAR

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CALPROFEN 100MG/5ML ORAL SUSPENSION IBUPROFEN (IBUPROFEN)
PL 15513/0147

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Pfizer Consumer Healthcare a Marketing Authorisation (licence) for the medicinal product Calprofen 100mg/5ml Oral Suspension Ibuprofen (PL 15513/0147). This is a general sale list (GSL) medicine for treating mild to moderate pain, post-immunisation pyrexia, headache, reduction of fever, sore throat, teething pain, toothache, minor aches and pains and symptoms of cold and influenza in children aged 3 months to 12 years.

Calprofen 100mg/5ml Oral Suspension Ibuprofen contains Ibuprofen. Ibuprofen is a well-established analgesic, anti-inflammatory and antipyretic drug

This is an abridged application made under Article 10c [formerly Article 10.1(a)(i)] of EC Directive 2001/83 and it is associated with a reclassification application for general sale availability of a multi-dose bottle presentation of Calprofen 100mg/5ml Oral Suspension Ibuprofen.

No new or unexpected safety concerns arose from this abridged application and it was therefore judged that the benefits of using Calprofen 100mg/5ml Oral Suspension Ibuprofen outweigh the risks, hence a Marketing Authorisation has been granted.

CALPROFEN 100MG/5ML ORAL SUSPENSION IBUPROFEN

(IBUPROFEN)

PL 15513/0147

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Calprofen 100mg/5ml Oral Suspension Ibuprofen (PL 15513/0147) to Pfizer Consumer Healthcare on 21st July 2006. The product is a general sale list (GSL) medicine.

This is an abridged application made under Article 10c [formerly Article 10.1(a)(i)] of EC Directive 2001/83 and it is associated with a reclassification application for general sale (GSL) availability of a multi-dose bottle presentation of Calprofen 100mg/5ml Oral Suspension Ibuprofen. The effect of this reclassification would be to extend the current conditions for general sale of ibuprofen oral suspension to include supply in multidose containers in addition to sachets.

No new quality data were submitted for this application, nor were any necessary, as the data are identical to that of the previously granted cross-referenced product: essential similarity is claimed to a Pinewood licence, Fenpaed 100mg/5ml Oral Suspension (PL 04917/0044), on which Pfizer are included as an own label supplier. The reference product has P (Pharmacy) legal status.

The simultaneous reclassification application from P to GSL legal status was proposed as 2% (100mg/5ml) ibuprofen oral suspension can already be supplied on general sale, but only if presented in unit dose packaging (sachets). The oral suspension was reclassified to GSL in December 2001.
This application proposes GSL sale and supply of liquid ibuprofen preparations of strength of 2% or less in multi-dose containers of up to 100ml.

The approved use of the product in bottles is identical to that already approved for the sachet presentation, and the maximum volume to be supplied in bottles is the same as that permitted for sachets (100ml). The principle of having sachets and multidose bottles of the same product available GSL has already been accepted, in relation to liquid paracetamol preparations.

PHARMACEUTICAL ASSESSMENT

PL number:	PL 15513/0147
Name of Product:	Calprofen 100mg/5ml Oral Suspension Ibuprofen
Active(s):	Ibuprofen
Company Name:	Pfizer Consumer Healthcare
E.C. Article:	10.1c (previously 10.1(a)(i)
Legal Status:	GSL

1 INTRODUCTION

1.1 Legal Basis

This is a simple abridged application for Calprofen 100mg/5ml Oral Suspension Ibuprofen. The cross-referral product is Fenpaed 100mg/5ml Oral Suspension PL 04917/0044; the licence for this is held by Pinewood Laboratories Limited. A letter of informed consent has been provided.

This application is associated with a POM to P reclassification application. If the reclassification is approved, there will be consequential changes made to the abridged licence.

1.2 Letters of Access

A letter of access has been provided, authorising the applicant company to refer to data held by the cross-referral company.

1.3 Cross-referral Product

At the time of publication there were no pending variation applications for the cross-referral product.

1.4 Expert Reports

A Clinical, Non-Clinical and Quality Overview has been provided in CTD Module 2. Information about the Clinical, Non-Clinical and Quality Experts is provided in CTD Module 1.4.3.

2. MAA FORM

2.1 Type of application

The application has been submitted as a simple abridged application, and the appropriate data and fee submitted for applications under Article 10.1c.

2.2 Product Name

The applicant has proposed the name Calprofen 100mg/5ml Oral Suspension Ibuprofen. This name is very similar to an existing name (Calprofen Ibuprofen 100mg/5ml Oral Suspension) but since the composition, strength and intended clinical use of the two products is identical, there are no perceived safety issues. The proposed name is acceptable.

2.3 Pack sizes

The proposed pack sizes are 50ml and 100ml, whilst those approved for the cross-referral are 50ml, 100ml, 150ml and 500ml. Pack sizes are not supposed to differ from the cross-referral licence. The removal of the two larger pack sizes is a change consequential to the reclassification application, and as such, is acceptable.

2.4 Manufacturers and licences

The details of these are as for the cross-referral.

The Ph Eur Certificate of Suitability has been submitted in relation to the manufacture of ibuprofen.

2.5 Qualitative and quantitative composition

As for cross-referral.

3. TSE

The product does not contain any materials of animal and/or human origin. Statements confirming this have been submitted for all ingredients.

4. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Satisfactory

5. PATIENT INFORMATION LEAFLET (PIL)

Satisfactory

6. LABELLING

Satisfactory

7. ADDITIONAL INFORMATION/ ADDITIONAL DATA REQUIREMENTS

7.1 Manufacturing process

As for cross-referral.

7.3 Finished product specification

As for cross-referral.

7.4 Drug substance specification

As for cross-referral.

8. PHARMACEUTICAL CONCLUSION

A marketing authorisation may be granted for this product.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

With respect to the abridged application no new clinical data have been supplied with this application and none are required for an application of this type. With respect to the reclassification application, new data have been submitted to establish the suitability of the product for GSL supply.

APPLICATION FOR RECLASSIFICATION FROM P TO GSL OF IBUPROFEN ORAL SUSPENSION 2% IN MULTIDOSE CONTAINERS

Assessment of Responses to Consultation

PRODUCT LICENCE No:	PL 15513/0147
PRODUCT NAME:	Calprofen 100mg/5ml Oral Suspension Ibuprofen
ACTIVE CONSTITUENT:	Ibuprofen 2%
COMPANY NAME:	Pfizer Consumer Healthcare
LEGAL STATUS:	P to GSL
CONSULTATION LETTER:	ARM 34

1. INTRODUCTION

This is a reclassification application for general sale availability of a multi-dose bottle presentation of Calprofen 100mg/5ml Oral Suspension Ibuprofen, which contains ibuprofen as the sole active ingredient. The reclassification application accompanies an abridged licence application, and both have been submitted by Pfizer Consumer Healthcare.

The effect of this reclassification would be to extend the current conditions for general sale of ibuprofen oral suspension to include supply in multidose containers in addition to sachets.

2. BACKGROUND AND LICENSING HISTORY

Ibuprofen is a well-established analgesic, anti-inflammatory and antipyretic drug. It is available for internal and external use as POM, P and GSL. Pharmacy availability of the solid oral dosage form was introduced in 1983, and GSL availability in 1996. The oral suspension was reclassified to GSL in December 2001.

The current conditions for general sale of ibuprofen for internal use are summarised in Table 1 on the following page. It can be seen from this that 2% (100mg/5ml) ibuprofen oral

suspension can already be supplied on general sale, but only if presented in unit dose packaging (sachets).

This application proposes GSL sale and supply of liquid ibuprofen preparations in multi-dose containers of up to 100ml, under the same conditions of supply that apply to the product in sachets.

Table 1: Current restrictions on GSL supply of ibuprofen for internal use

(Proposed change is given in italics)

	Adults and children over 12 years	**Children under 12 years**
Pharmaceutical form	Tablets or capsules Powder or granules	Oral suspension
Max strength	200mg	2% (100mg in 5ml)
Max dose / max daily dose	400mg / 1200mg	200mg / 800mg
Indications	Rheumatic or muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of cold or influenza	Rheumatic or muscular pain, headache, dental pain, feverishness, symptoms of cold or influenza
Max pack	16 tablets or capsules 12 sachets of powder or granules	Unit doses of not more than 5ml in a pack containing not more than 20 doses ***Multidose containers of not more than 100ml***

In 2005, CSM considered a similar application but in relation to liquid paracetamol preparations of a strength of 2.4% or less. The application proposed GSL supply in multidose containers in addition to the currently permitted unit dose packaging (i.e. sachets). The Committee advised that the product packed in bottles could safely be supplied on general sale, and the application was approved in June 2005.

3. CONSIDERATION BY CSM

CSM advice on this application was <u>not</u> sought prior to consultation. The reasons for this are as follows.

- The product, ibuprofen oral suspension 100mg/5ml, is already available GSL, in sachets.
- The proposed use of the product in bottles is identical to that already approved for the sachet presentation, and the maximum volume to be supplied in bottles is the same as that permitted for sachets (100ml).
- The principle of having sachets and multidose bottles of the same product available GSL has already been accepted, in relation to liquid paracetamol preparations.
- The safety profile of ibuprofen is well established. There does not appear to be any additional risk specific to the bottle presentation.

Members of CSM were given the opportunity to respond to the consultation document.

4. CONSULTATION

Consultation document ARM 34, which summarises the proposals for GSL supply of ibuprofen 2% suspension in multidose containers, was posted on the MHRA website on 21st November 2005. The deadline for comments was 19 December 2005.

Nineteen responses to consultation were received. Of the 19 responses:

- seven supported or did not raise any objections to the proposal
- four supported the proposal but had additional comments
- four were opposed to the reclassification
- four made no comment

Those in support of the reclassification represented a wide range of health professionals. Those opposed to it were primarily pharmaceutical organisations (Royal Pharmaceutical Society of Great Britain, National Pharmacy Association, Association of Independent Multiple Pharmacies) but also included the Royal College of General Practitioners.

The issues raised in the responses are discussed in the following section.

5. DISCUSSION

5.1. Product name

Some respondents considered that the name Calprofen should not be used; they thought that the name was too similar to Calpol and that purchasers may believe that the product contained paracetamol.

Assessor's comment

The 'Calprofen' component of the name has already been approved for other ibuprofen-containing products. Ibuprofen 2% suspension in sachets is currently available on general sale under the trade name Calprofen.

5.2. Risk of asthma

One concern centred on the risk of asthma being precipitated in ibuprofen-sensitive children. It was felt by some respondents that the product should remain as a P medicine so that the pharmacist could provide advice on this issue.

Assessor's comment

This issue was considered in 2001, when liquid ibuprofen preparations for use in children 6 months and over were reclassified as GSL.

5.3. Issues relating to packaging type

One respondent considered that incorrect dosing and overdosing were more likely with a bottle presentation than with a sachet presentation, and that the maximum pack size for the bottle should be 50ml.

Assessor's comment

This issue was considered in 2005, when bottle presentations of liquid paracetamol were switched from P to GSL

5.4. Extending the conditions for GSL supply

A pharmaceutical company was in support of the reclassification and proposed that the lower age limit for use be reduced from 6 months to 3 months.

Assessor's comment

The 6-month age limit is currently included in the MHRA guidance on oral OTC ibuprofen products, and reflects advice given by CSM at the time of switching ibuprofen suspension from P to GSL. A variation to reduce the age limit from 6 months to 3 months was approved by CSM in 2005 in relation to two specific liquid preparations of ibuprofen (one a GSL sachet preparation amd the other a P bottle preparation). Other MA holders are now applying to incorporate this change into their licences.

Although the applicant has not specifically requested it, it seems appropriate to consider the 3-month age limit as part of this reclassification application. For the reasons given in Section 3 above, and since no other new issues have been raised during consultation, there would appear to be no reason why this reclassification application, as submitted, should not be approved. However, if GSL bottles are approved but with a 6-month lower age limit, this could result in confusion: bottles with a 6-month age limit and sachets with a 3-month age limit would both be available GSL.

A parallel may be drawn with liquid paracetamol. In 2005 CSM approved a variation for 2.4% liquid paracetamol, to lower the minimum age for use in infants from 3 months to 2 months. At around the same time a reclassification application for a GSL bottle presentation was ongoing. The final outcome was that CSM considered the lower age limit of 2 months to be applicable to P and GSL products, and bottle and sachet presentations equally.

The main difference between the two situations (ibuprofen and paracetamol) was that the consultation document for liquid paracetamol included a reference to the lower age limit, whereas that for ibuprofen suspension did not. Therefore, although there would appear to be no safety reasons to differentiate between bottle presentations and sachet presentations with respect to this issue, CHM should be advised of the application of a lower minimum age of 3 months to bottle presentations of 2% ibuprofen suspension.

5.5. Product information

Several points were made concerning the patient information leaflet and labelling.

- Parents/carers may not read the leaflet and may therefore administer the product inappropriately.
- Parents/carers may not learn what the precautions and contraindications are until after purchase of the product, when they read the leaflet at home.
- Some parents/carers may not know if their child is sensitive to aspirin.
- A child may not be able to describe symptoms of side effects.

Assessor's comments

These points apply equally to any GSL preparation of ibuprofen intended for use in children. The points have previously been considered.

- The weight of the child should be given in imperial as well as metric units.
- The leaflet should advise the parent/carer to seek rapid action if the there is a deterioration in the child's condition.
- Although the product is intended for use in children, the leaflet gives advice to pregnant women.
- The leaflet and label should include prominent warnings about use by asthma sufferers or those allergic to aspirin or NSAIDs.
- The label should advise the parent/carer to read the leaflet before giving the product.

Assessor's comments

Many of these points have already been addressed. The labelling and leaflet for the bottle presentation will be brought into line with those for the GSL sachet presentation which have already been approved.

6. CONCLUSIONS

6.1 Apart from the proposal to lower the minimum age for use from 6 months to 3 months, no new issues have been identified during consultation, and the objections raised have previously been addressed. In the absence of the age limit proposal, this application would have been processed to approval without referral to CHM.

6.2 The proposal to reduce the minimum age for use from 6 to 3 months has arisen through the consultation process. The consultation document did not include a reference to a 3-month lower age limit and so, although there appears to be no safety reasons to differentiate between bottle presentations and sachet presentations with respect to this issue, CHM should be advised of this.

7. RECOMMENDATIONS

7.1 That the P to GSL reclassification application for 2% ibuprofen suspension in multi-dose containers be approved.

7.2 That a reduction in the lower age limit for use from 6 months to 3 months be included as part of this reclassification application.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application are consistent with those previously assessed for the cross-referenced product and as such have been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No new or unexpected safety concerns arose from this application.

The SPC and combined PIL-labelling are satisfactory and consistent with those of the cross-referenced product, with appropriate amendments to take into account the reclassification of the product..

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-referenced product. Suitable justification has been provided for the reclassification of the product from Pharmacy (P) to General Sale List (GSL). Extensive clinical experience with the active ingredient Ibuprofen is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.

CALPROFEN 100MG/5ML ORAL SUSPENSION IBUPROFEN (IBUPROFEN)

PL 15513/0147

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 25th May 2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 16th August 2005.
3	Pharmaceutical Assessment of this application began on 15 September 2005 and was completed on the 13th July 2006
4	The responses to public consultation were assessed and the results presented to CHM on 16 March 2006
5	The application was determined and the Marketing authorisation granted on 21st July 2006.

CALPROFEN 100MG/5ML ORAL SUSPENSION IBUPROFEN

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

CALPROFEN 100MG/5ML ORAL SUSPENSION IBUPROFEN (IBUPROFEN)
PL 15513/0147

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Calprofen 100mg/5ml Oral Suspension Ibuprofen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Ibuprofen 100 mg/5 ml
For excipients – see section 6.1

3. PHARMACEUTICAL FORM
Oral Suspension
Sugar Free, Colour Free and Strawberry Flavour

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Children aged 3 months to 12 years:
Mild to moderate pain, post-immunisation pyrexia, headache, reduction of fever, sore throat, teething pain, toothache, minor aches and pains, symptoms of cold and influenza.

4.2. Posology and method of administration
To be taken orally. For short term use only.

Children aged 3 months to 12 years:
Not recommended for children weighing less than 5 kg.

For pain and fever – 20mg/kg/day in divided doses.

Infants 3-6 months: 2.5ml three times a day. Do not use for more than 24 hours
Infants 6-12 months: 2.5 ml three times a day Children 1-2 years: 2.5 ml three to four times a day
Children 3-7 years: 5 ml three to four times a day
Children 8-12 years: 10 ml three to four times a day

Doses should be taken every 6-8 hours when required, and at least 4 hours should be left between doses.

Post-immunisation fever:
2.5 ml (50 mg) followed by one further dose of 2.5 ml (50mg) six hours later if necessary. No more than 2 doses in 24 hours. If fever is not reduced, consult a doctor.

Do not give to children under 3 months of age.

For children over 6 months: If the child's symptoms persist for more than 3 days, consult a doctor.

4.3. Contraindications

Hypersensitivity to Ibuprofen or any of the other constituents.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to aspirin or other non-steroidal anti-inflammatory drugs.

Active or previous peptic ulcer.

History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Use with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors. (see section 4.5 Interactions)

Severe hepatic failure, renal failure or heart failure (See section 4.4, Special

warnings and precautions for use)

Last trimester of pregnancy (See section 4.6 Pregnancy and lactation)

4.4. Special warnings and precautions for use

The elderly are at an increased risk of serious consequences of adverse reactions.

Systemic lupus erythematosus and mixed connective tissue disease - increased risk of aseptic meningitis (see Section 4.8 Undersirable effects)

Chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease) - as these conditions may be exacerbated (see section 4.8 Undesirable Effects).

Undesirable effects may be minimized by using the minimum effective dose for the shortest possible duration.

There is some evidence that drugs which inhibit cyclooxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment. The use of Ibuprofen is therefore not recommended in women attempting to conceive.

GI bleeding, ulceration or perfusion, 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 GI events.

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 gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin (see section 4.5).

Where GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Administration of NSAID's such as Ibuprofen may cause dose dependent renal toxicity in patients with reduced renal blood flow or blood volume where renal prostaglandins support the maintenance of renal perfusion.
Patients at risk of this reaction include those with impaired renal function, heart failure or liver dysfunction. This is of particular importance in hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur. Caution is therefore required in the use of Ibuprofen in such patients.

Ibuprofen should be used with caution in patients with bronchial asthma or allergic disease, since such patients may have NSAID-sensitive asthma which has been associated with severe bronchospasm.

Not recommended for children under 3 months.

<u>The Label will include:</u>
"Read the enclosed leaflet before taking this product.
Do not give this product if your baby or child

- Has or has ever had stomach ulcer, perforation or bleeding
- Is allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers
- Is taking other NSAID painkillers, or aspirin with a daily dose above 75mg

Speak to a pharmacist or your doctor before giving this product if your baby or child

- Has asthma, liver, heart, kidney or bowel problems

If you are an adult taking this product you should not take Calprofen in the last 3 months of pregnancy and you should contact your doctor or pharmacist before taking it in the first 6 months of pregnancy or if trying to get pregnant.

Do not give to babies aged 3-6 months for more than 24 hours.

Do not give to children aged 6 months or older for more than 3 days.

If symptoms persist or worsen, consult your doctor promptly.

Do not exceed the stated dose.

Not recommended for children under 3 months."

4.5. Interactions with other medicinal products and other forms of interaction

Ibuprofen should not be used in combination with: Aspirin: 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 4.3 Contraindications)

Other NSAIDs: As these may increase the risk of adverse effects (See section 4.3 Contraindications.)

Ibuprofen should be used with caution in combination with:
Anticoagulants: NSAIDS may enhance the effects of anti-coagulants, such as warfarin (see section 4.4)

Antihypertensives and diuretics: NSAIDs may diminish the effect of these drugs.

Corticosteroids: May increase the risk of adverse reactions in the gastrointestinal tract (see section 4.4 Special Warnings)

Lithium: There is evidence for potential increases in plasma levels of lithium.

Methotrexate: There is potential for an increase in plasma methotrexate

Zidovudine: There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6. Pregnancy and lactation

While no teratogenic effects have been demonstrated in animal experiments, the use of ibuprofen should, if possible, be avoided during the first 6 months of pregnancy.

During the 3rd trimester, ibuprofen is contraindicated as there is a risk of premature closure of foetal ductus arteriosus with possible persistent pulmonary hypertension. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child. (see section 4.3 Contraindications).

In limited studies, ibuprofen appears in breast milk in very low concentration and is unlikely to affect breast-fed infant adversely.
See section 4.4 regarding female fertility.

4.7. Effects on ability to drive and use machines

It is not expected that Calprofen 100mg/5ml Oral Suspension would interfere with the ability to drive or operate machinery at the recommended dose and duration of therapy.

4.8. Undesirable effects

Hypersensitivity reactions 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 or dyspnoea,
c) various skin reactions, e.g. pruritis, urticaria, purpurea, angioedema and more rarely exfoliative dermatitis and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The following list of adverse effects relates to those experienced with ibuprofen at OTC doses, for short term use. In the treatment of chronic conditions, under long term treatment, additional adverse effects may occur.

Hypersensitivity reactions:
Uncommon: hypersensitivity reactions with urticaria and pruritus.

Very rare: severe hypersensitivity reactions. Symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema and severe shock)

Exacerbation of asthma and bronchospasm

Gastrointestinal:
Uncommon: abdominal pain, nausea and dyspepsia.

Rare: diarrhoea, flatulence, constipation and vomiting.

Very rare: peptic ulcer, perforation or gastrointestinal haemorrhage, sometimes fatal, particularly in the elderly. Exacerbation of ulcerative colitis and Crohn's disease (see section 4.4).

Nervous System:
Uncommon: headache

Renal:
Very rare: acute renal failure, papillary necrosis Especially in long term use, associated with increased serum urea and oedema.

Hepatic:
Very rare; liver disorders

Haematological:
Very rare: haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

Skin:
Uncommon: various skin rashes
Very rare: severe forms of skin reactions such as erythema multiforme and epidermal necrosis can occur.

Immune System:
In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see section 4.4).

4.9. Overdose

In children ingestion of more than 400mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life at overdose is 1.5 –3 hours.

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, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma.

Occasionally patients develop convulsions. In serious poisoning 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 is the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Ibuprofen is a Phenylpropionic Acid derivative, which has analgesic, anti-inflammatory and antipyretic actions. These actions are thought to be from its inhibitory effect on the enzyme cyclo-oxygenase which results in a reduction/inhibition of prostaglandin synthesis.

5.2. Pharmacokinetic properties

Ibuprofen is rapidly absorbed from the gastro-intestinal tract and rapidly distributed throughout the whole body. Peak plasma concentrations occur about 1 to 2 hours after ingestion with food or in 45 minutes if taken on an empty stomach. These times may vary with different dosage forms.

The excretion is rapid and complete via the kidneys.

The elimination half-life is about 2 hours.

It is metabolized to two inactive metabolites and these are rapidly excreted in urine. About 1 percent is excreted in urine as unchanged Ibuprofen and about 14 percent as conjugated Ibuprofen.

Ibuprofen is extensively bound to plasma proteins.

In limited studies, ibuprofen appears in breast milk in very low concentrations.

5.3. Preclinical safety data

No relevant information additional to that contained elsewhere in the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glycerol (E422), xanthan gum, maltitol syrup (Lycasin 80/55 (E965)), polysorbate 80, saccharin sodium (E954), citric acid monohydrate, sodium methylhydroxybenzoate, sodium propylhydroxybenzoate, purified water and strawberry flavour.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Do not store above 25ºC.
Keep out of reach and sight of children.

6.5. Nature and contents of container

6.6 Special precautions for disposal

Amber glass bottle sealed with a child resistant, tamper evident cap. Pack sizes: 50ml and 100ml
Shake well before use. Return any left over medicine to the Pharmacist.

7. MARKETING AUTHORISATION HOLDER

Pfizer Consumer Healthcare
Walton Oaks
Dorking Road
Walton-on-the-Hill
Surrey KT20 7NS
UK

8. MARKETING AUTHORISATION NUMBER

PL 15513/0147

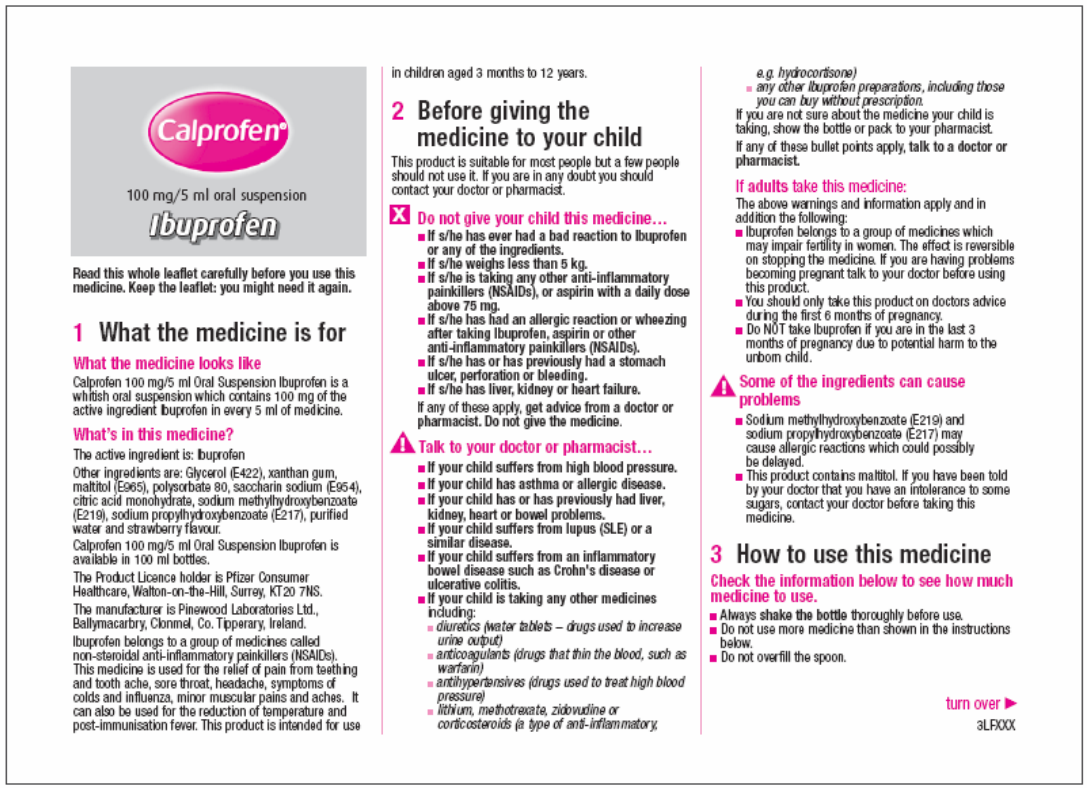
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/07/2006

10 DATE OF REVISION OF THE TEXT

21/07/2006

CALPROFEN 100MG/5ML ORAL SUSPENSION IBUPROFEN (IBUPROFEN)
PL 15513/0147
PAITENT INFORMATION LEAFLET



Calprofen®

100 mg/5 ml oral suspension

Ibuprofen

Read this whole leaflet carefully before you use this medicine. Keep the leaflet: you might need it again.

1 What the medicine is for

What the medicine looks like

Calprofen 100 mg/5 ml Oral Suspension Ibuprofen is a whitish oral suspension which contains 100 mg of the active ingredient Ibuprofen in every 5 ml of medicine.

What's in this medicine?

The active ingredient is: Ibuprofen

Other ingredients are: Glycerol (E422), xanthan gum, maltitol (E965), polysorbate 80, saccharin sodium (E954), citric acid monohydrate, sodium methylhydroxybenzoate (E219), sodium propylhydroxybenzoate (E217), purified water and strawberry flavour.

Calprofen 100 mg/5 ml Oral Suspension Ibuprofen is available in 100 ml bottles.

The Product Licence holder is Pfizer Consumer Healthcare, Walton-on-the-Hill, Surrey, KT20 7NS.

The manufacturer is Pinewood Laboratories Ltd., Ballymacarbry, Clonmel, Co. Tipperary, Ireland.

Ibuprofen belongs to a group of medicines called non-steroidal anti-inflammatory painkillers (NSAIDs). This medicine is used for the relief of pain from teething and tooth ache, sore throat, headache, symptoms of colds and influenza, minor muscular pains and aches. It can also be used for the reduction of temperature and post-immunisation fever. This product is intended for use in children aged 3 months to 12 years.

2 Before giving the medicine to your child

This product is suitable for most people but a few people should not use it. If you are in any doubt you should contact your doctor or pharmacist.

X Do not give your child this medicine...

- **If s/he has ever had a bad reaction to Ibuprofen or any of the ingredients.**
- **If s/he weighs less than 5 kg.**
- **If s/he is taking any other anti-inflammatory painkillers (NSAIDs), or aspirin with a daily dose above 75 mg.**
- **If s/he has had an allergic reaction or wheezing after taking Ibuprofen, aspirin or other anti-inflammatory painkillers (NSAIDs).**
- **If s/he has or has previously had a stomach ulcer, perforation or bleeding.**
- **If s/he has liver, kidney or heart failure.**

If any of these apply, get advice from a doctor or pharmacist. Do not give the medicine.

⚠ Talk to your doctor or pharmacist...

- **If your child suffers from high blood pressure.**
- **If your child has asthma or allergic disease.**
- **If your child has or has previously had liver, kidney, heart or bowel problems.**
- **If your child suffers from lupus (SLE) or a similar disease.**
- **If your child suffers from an inflammatory bowel disease such as Crohn's disease or ulcerative colitis.**
- **If your child is taking any other medicines including:**
  - *diuretics (water tablets – drugs used to increase urine output)*
  - *anticoagulants (drugs that thin the blood, such as warfarin)*
  - *antihypertensives (drugs used to treat high blood pressure)*
  - *lithium, methotrexate, zidovudine or corticosteroids (a type of anti-inflammatory e.g. hydrocortisone)*
  - *any other Ibuprofen preparations, including those you can buy without prescription.*

If you are not sure about the medicine your child is taking, show the bottle or pack to your pharmacist.

If any of these bullet points apply, talk to a doctor or pharmacist.

If adults take this medicine:

The above warnings and information apply and in addition the following:

- Ibuprofen belongs to a group of medicines which may impair fertility in women. The effect is reversible on stopping the medicine. If you are having problems becoming pregnant talk to your doctor before using this product.
- You should only take this product on doctors advice during the first 6 months of pregnancy.
- Do NOT take Ibuprofen if you are in the last 3 months of pregnancy due to potential harm to the unborn child.

⚠ Some of the ingredients can cause problems

- Sodium methylhydroxybenzoate (E219) and sodium propylhydroxybenzoate (E217) may cause allergic reactions which could possibly be delayed.
- This product contains maltitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3 How to use this medicine

Check the information below to see how much medicine to use.

- Always **shake the bottle** thoroughly before use.
- Do not use more medicine than shown in the instructions below.
- Do not overfill the spoon.

turn over ►

3LFXXX

COLOURS: Magenta Black Cutter

SIZE: 210 x 148 mm

VERSION 9

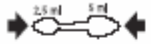
05-1062 Pil Calprofen GSL 100 ml UK

DATE:6/6/06

Pfizer Consumer Healthcare

A print out of this image should not be used for exact colour matching but to check if the layout, spelling, text and colour references are correct. Please check thoroughly.

There is a double ended measuring spoon in the pack, which is to be used to measure doses of 2.5 ml and 5 mls.



For Post-Immunisation Fever:

One small (2.5 ml) spoonful, followed by another small (2.5 ml) spoonful 6 hours later if necessary.

- Do not give more than 2 doses in 24 hours.
- If the fever is not reduced you should consult your doctor.
- For babies and children older than 3 months.
- Do not give to your baby / child if they weigh less than 5 kg.

For Pain and Fever Relief:

Age	Dose
Babies under 3 months	Not recommended
3 months - 6 months weighing over 5 kg	One small (2.5 ml) spoonful 3 times a day. Do not use for more than 24 hours
6 months - 1 year	One small (2.5 ml) spoonful 3 times a day
1 year - 2 years	One small (2.5 ml) spoonful 3 or 4 times a day
3 years - 7 years	One large (5 ml) spoonful 3 or 4 times a day
8 years - 12 years	Two large (5 ml) spoonfuls 3 or 4 times a day

- Doses should usually be given every 6 - 8 hours. Leave at least 4 hours between doses.
- Short term use only:
  - Do not give to babies aged 3 – 6 months for more than 24 hours.
  - Do not give to children aged 6 months or over for more than 3 days.
- If symptoms persist or worsen consult your doctor.

If you forget to give the medicine

Give the next dose when needed. Do not give a double dose.

If anyone has taken too much

In the event of an overdose, you should contact a doctor immediately or go to the nearest hospital accident and emergency department.

4 Possible side effects

Calprofen 100 mg/5 ml Oral Suspension Ibuprofen can have side effects, like all medicines, although these don't affect everyone and are usually mild. The most common side effect is irritation of the stomach which can cause problems (e.g. indigestion, heartburn) in some people. Stop giving the medicine and seek immediate medical help if your child starts to suffer from any of the following:

- blood in the faeces (stools/motions)
- black tarry stools
- vomiting blood or dark particles that look like ground coffee

If your child experiences any of the following, stop giving the medicine and tell your doctor

- unexplained stomach pain, feeling sick and/or vomiting
- unexplained wheezing, shortness of breath, skin rash, itching or bruising, lightheadedness, racing heart or fluid retention, e.g. swollen ankles
- yellowing of the eyes and/or skin
- severe sore throat with high fever, unexplained bruising or tiredness.

Other effects which may occur are listed below.

- Other unusual effects may include headache, diarrhoea, wind or constipation. If any of these become troublesome or last more than a few days, tell you doctor.
- Very rarely kidney problems may occur with Ibuprofen.

If your child experiences any other unusual symptoms while taking this medicine, tell your doctor or pharmacist.

5 Storing this medicine

Do not take your medicine after the expiry date shown on the bottle.

Do not store above 25°C.

Keep all medicines out of the reach and sight of children.

This leaflet was revised June 2006.

For further information please contact:
Pfizer Consumer Healthcare,
Walton-on-the-Hill, Surrey, KT20 7NS.

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Pfizer Consumer Healthcare

05-1062
3LFXXX

COLOURS:
Magenta
Black
Cutter

SIZE:
210 x 148 mm

VERSION 9
05-1062 Pil Calprofen GSL 100 ml UK
DATE 5/5/06

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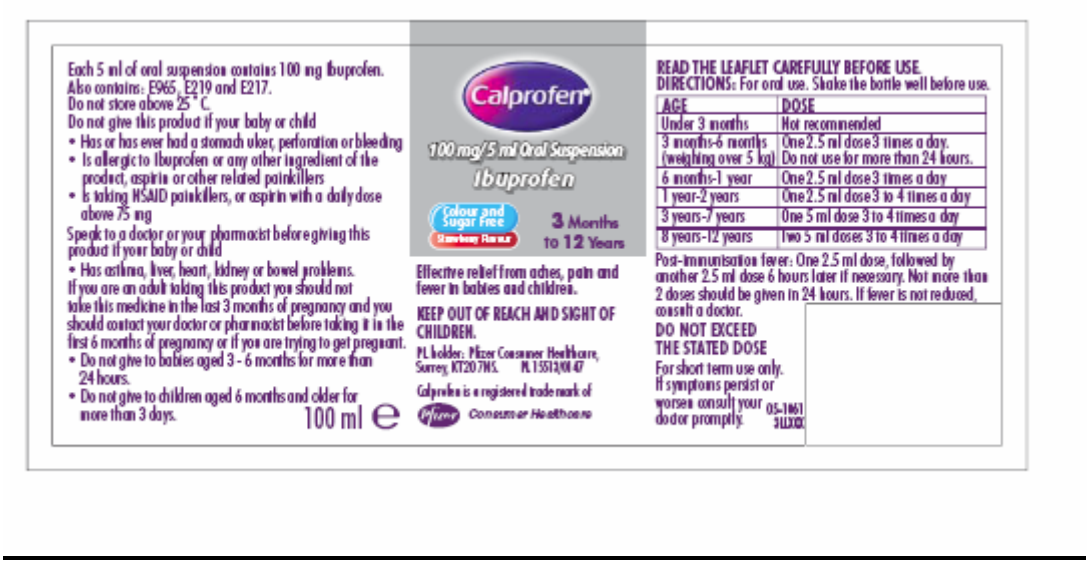
CALPROFEN 100MG/5ML ORAL SUSPENSION IBUPROFEN (IBUPROFEN)

PL 15513/0147

CARTON LABELLING

BOTTLE LABELLING



Each 5 ml of oral suspension contains 100 mg Ibuprofen.
Also contains: E965, E219 and E217.
Do not store above 25° C.
Do not give this product if your baby or child
- Has or has ever had a stomach ulcer, perforation or bleeding
- Is allergic to Ibuprofen or any other ingredient of the product, aspirin or other related painkillers
- Is taking NSAID painkillers, or aspirin with a daily dose above 75 mg

Speak to a doctor or your pharmacist before giving this product if your baby or child
- Has asthma, liver, heart, kidney or bowel problems.

If you are an adult taking this product you should not take this medicine in the last 3 months of pregnancy and you should contact your doctor or pharmacist before taking it in the first 6 months of pregnancy or if you are trying to get pregnant.
- Do not give to babies aged 3 - 6 months for more than 24 hours.
- Do not give to children aged 6 months and older for more than 3 days.

100 ml e

Calprofen
100 mg/5 ml Oral Suspension
Ibuprofen
Colour and Sugar Free
Strawberry Flavour
3 Months to 12 Years

Effective relief from aches, pain and fever in babies and children.

KEEP OUT OF REACH AND SIGHT OF CHILDREN.

PL holder: Pfizer Consumer Healthcare, Surrey, KT20 7NS. PL 15513/0147

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READ THE LEAFLET CAREFULLY BEFORE USE.
DIRECTIONS: For oral use. Shake the bottle well before use.

AGE	DOSE
Under 3 months	Not recommended
3 months-6 months (weighing over 5 kg)	One 2.5 ml dose 3 times a day. Do not use for more than 24 hours.
6 months-1 year	One 2.5 ml dose 3 times a day
1 year-2 years	One 2.5 ml dose 3 to 4 times a day
3 years-7 years	One 5 ml dose 3 to 4 times a day
8 years-12 years	Two 5 ml doses 3 to 4 times a day

Post-immunisation fever: One 2.5 ml dose, followed by another 2.5 ml dose 6 hours later if necessary. Not more than 2 doses should be given in 24 hours. If fever is not reduced, consult a doctor.

DO NOT EXCEED THE STATED DOSE

For short term use only.
If symptoms persist or worsen consult your doctor promptly.

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