NUROFEN EXTRA STRENGTH 400 MG LIQUID CAPSULES
PL 00327/0198

UKPAR

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NUROFEN EXTRA STRENGTH 400 MG LIQUID CAPSULES
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LAY SUMMARY

The MHRA granted Crookes Healthcare Ltd a Marketing Authorisation (licence) for the medicinal product Nurofen Extra Strength 400 mg Liquid Capsules (PL 00327/0198), on the 21st July 2006. This pharmacy medicine (P) is used for the symptomatic relief of non-serious arthritic conditions, rheumatic or muscular pain, backache, neuralgia, migraine, headaches, dental pain, dysmenorrhoea, feverishness, colds and influenza.

Nurofen Extra Strength 400 mg Liquid Capsules contain the active ingredient ibuprofen, which is a nonsteroidal anti-inflammatory agent that possesses analgesic and antipyretic activities. It has been in clinical use for well over three decades world-wide for arthritis and various other conditions characterised by inflammation. Its mode of action, like that of other nonsteroidal anti-inflammatory agents, is not completely understood, but appears to be related to prostaglandin synthetase inhibition.

No new or unexpected safety concerns arose from these applications. It was, therefore, judged that the benefits of taking Nurofen Extra Strength 400 mg Liquid Capsules outweigh the risks. Hence a Marketing Authorisation has been granted.

NUROFEN EXTRA STRENGTH 400 MG LIQUID CAPSULES
PL 00327/0198

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Nurofen Extra Strength 400 mg Liquid Capsules (PL 00327/0198) to Crookes Healthcare Ltd on 21st July 2006. The product is a pharmacy medicine.

This is a complete application for a Marketing Authorisation in the UK submitted under Article 8.3 [formerly Article 8.3(i) of Directive 2001/83 (as amended)]. This is a line extension with the change listed as addition of a new strength or a quantitative change to the active substance.

This product contains the active ingredient ibuprofen and is indicated for the symptomatic relief of non-serious arthritic conditions, rheumatic or muscular pain, backache, neuralgia, migraine, headaches, dental pain, dysmenorrhoea, feverishness, colds and influenza.

Ibuprofen is a nonsteroidal anti-inflammatory agent that possesses analgesic and antipyretic activities. It has been in clinical use for well over three decades world-wide for arthritis and various other conditions characterised by inflammation. Its mode of action, like that of other nonsteroidal anti-inflammatory agents, is not completely understood, but appears to be related to prostaglandin synthetase inhibition.

PHARMACEUTICAL ASSESSMENT

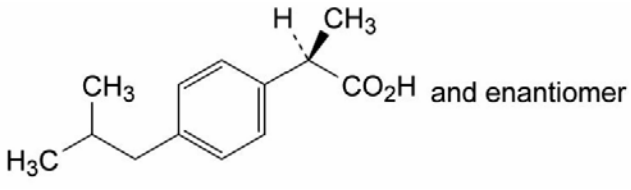
I. INTRODUCTION

This is a complete application for a Marketing Authorisation in the UK submitted under Article 8.3 [formerly Article 8.3(i) of Directive 2001/83 (as amended)]. This application is a line extension with the change listed as addition of a new strength or a quantitative change to the active substance.

II. DRUG SUBSTANCE

The suitability of the drug substance has been confirmed by appropriate Certificates of Suitability which are the most recent versions supplied by the Drug Substance Manufacturers.

1.1 General information

Structure: 

Description: White crystalline powder or colourless crystals

Chemical name: (2RS)-2-[4-(2-Methylpropyl)phenyl]propanoic acid

Molecular formula: $C_{13}H_{18}O_2$

Relative molecular mass: 206.3

Chirality: (±) mixture

2.2.1 Manufacturing process

The manufacturing process is referenced to the certificate of suitability.

2.2.2 Impurities

Details regarding all impurities have been provided and are satisfactory.

2.3 Control of active substance

2.3.1 Specification

The finished product manufacturer specification provided for ibuprofen is detailed. This covers the requirements of the European Pharmacopoeia.

2.3.2 Analytical test methods

The test methods used by the finished product manufacturer are those described in the pharmacopoeia.
Data has been presented from two sites using the proposed methods for different batches covering the suppliers demonstrating comparable results between sites which is considered to be suitable in demonstrating the validity of the method.

2.3.3 Batch analyses

Assessment of batches by the finished product manufacturers, demonstrate compliance to the specifications and inter-batch conformity. Certificates of analysis have been provided.

2.3.4 Reference standards

Relevant information on the reference standards has been supplied.

2.3.5 Container closure system

Details of the container closure systems used by the different drug substance manufacturers have been provided.

2.3.6 Stability

A certificate of suitability including a retest date has been provided for one manufacturer.

Stability data has been presented for the other manufacturer at 25°C/60%RH and at 40°C/75%RH. Batches were assessed on appearance, melting point, moisture content, assay, 4-isobutylacetophenone and other related substances.

All parameters remained in specification for all batches under both conditions, with no apparent increases in any of the parameters. The results justify the absence of any specific storage conditions.

III. DRUG PRODUCT

3.1 Composition

The composition of the products are summarised below.

Name of ingredient	Reference Standards
Composition of fill contents	
Ibuprofen	Ph. Eur.
Macrogol 600	Ph. Eur.
Potassium hydroxide 50% solution	Internal*
Shell base materials	
Gelatin	Ph. Eur.
Sorbitol liquid, partially dehydrated	Internal
Purified water	Ph. Eur.
Ponceau 4R	Internal
Lecithin	Internal
Fractionated coconut oil	Ph. Eur.
Total	
Printing ink	
White printing ink Opacode	Internal
Ribbon print solvent	Internal

The product is a clear red soft gelatin capsule containing a clear, colourless liquid solution of ibuprofen. The capsule is printed on one side with white ink.

The product is packed in thermoform blister strips.

Four alternative blister materials are proposed, clear PVC/PVdC, opaque PVC/PVdC, clear PVC/PE/PVdC and opaque PVC/PE/PVdC. All types are sealed with hard tempered aluminium lidding foil. These blister strips are packed in to cartons.

3.2 Pharmaceutical Development

3.2.1 Formulation development

The development of the product was based on the formulation of the existing licensed product (Nurofen Liquid Capsules 200mg PL 00327/0118), with the intention of producing a smaller size capsule.

The same formulation and dye has been used as in the existing product. Consequently compatibility has been assumed, which has been supported by the stability studies.

3.2.2 Clinical trial formula

A pharmacokinetic study has been completed with the ibuprofen 400mg soft gelatin capsules Individual capsule data has been provided.

3.2.3 Overages

No overages have been included in the formulation.

3.2.4 Physicochemical and biological properties

The validation results demonstrate a suitable homogeneous solution.

3.2.5 Manufacturing development

Relevant details on the sampling for the validation of batches has been provided, explaining where the samples were taken and the quantities of sample.

3.2.6 Container closure system

The packaging materials are standard commercial presentations and have been used for a wide range of products.

3.3 Manufacture

3.3.1 Manufacturer(s)

All the manufacturers have been listed and are acceptable.

3.3.2 Batch formula

The batch formula has been presented. The proposed commercial routine batch size has also been stated.

3.3.3 Manufacturing process and process controls

A flow diagram detailing the manufacturing process and in-process control testing has been provided. A written summary of the process has been included.

3.3.4 Reprocessing

No reprocessing is performed.

3.3.5 Control of critical steps (in-process controls)

The in-process controls seem reasonable for this type of product with suitable limits and test points.

3.3.6 Process validation or evaluation

Validation will be performed on the production scale batches of the product. Details of the parameters to be evaluated has been supplied and considered acceptable. Supporting validation has been described in the manufacturing process development section.

An acceptable sampling plan for the validation of the production scale batches has been provided covering the location, timing and quantity of the samples.

3.4 Control of excipients

3.4.1 Specification

All the excipients used in the product are acceptable and suitable specifications have been provided for them.

3.5 Control of drug product

3.5.1 Specification

The finished product specification of the products is acceptable.

3.5.2 Analytical procedures

The assay, related substances and degradation product method has an acceptable system suitability check. Relevant chromatograms have been provided.

3.5.3 Validation

Validation of the microbiological methods has been provided.

3.5.4 Reference standards

Suitable information on the reference standards has been provided.

3.5.5 Batch analyses

Batch analyses have been provided for the validation batches of the product. These are all within specification and show a reasonable degree of comparability. The impurity level in all batches is non-existent.

3.6 Container closure system

Clear, polyvinylchloride (PVC) coated with polvinylidene chloride (PVdC) laminate heat sealed to aluminium foil.
Opaque, white PVC polyethylene (PE), coated with PVdC laminate heat sealed to aluminium foil.
Clear, PVC /polyethylene (PE), coated with PVdC laminate heat sealed to aluminium foil.

The blister pack will be packed into a carton.

The materials are from approved suppliers and tested for identification. Suitable certificates of analysis have been supplied.

Certification of compliance to the EU directives on contact materials have been provided from the suppliers and manufacturers.

Certification has been supplied for the blister laminates demonstrating compliance to the relevant European Pharmacopoeia monograph.

The alternative sites are not intended to be used on a routine basis consequently no packaging materials have been sourced for these sites. It has been confirmed that the specifications for the packaging materials will be the same for the listed packaging sites. Relevant certificates of analysis will be supplied from the other sites when relevant.

3.7 Stability

Stability data has been presented for the validation batches of the 400mg product. The storage conditions are 25°C/60%RH, 30°C/65%RH and 40°C/75%RH.

Stability is assessed using the appropriate criteria. Stability testing is performed according to the relevant ICH guidelines.

The applicant is proposing a shelf life of 24 months when stored below 25°C. This is considered reasonable on the basis of the data presented.

Dissolution method
Full details of the dissolution method have been supplied.

A validation report has been supplied. The validation is sufficient for the purpose and the relevance of the data presented.

3.8 Other information

3.8.1 Bioanalytical method

The validation report has been provided demonstrating the method to be sufficiently accurate, precise, sensitive, specific, linear and selective for ibuprofen over a suitable range.

3.8.2 Clinical work

An open-label, crossover, randomised, single centre pharmacokinetic study in healthy volunteers to compare the bioavailability of ibuprofen from one 400mg liquid capsule with two 200mg Nurofen tablets was conducted.

The batch of ibuprofen 400mg liquid capsules used in the clinical study is at least 10% of the final intended batch size and is the proposed commercial formulation, with the exception of the inclusion of titanium dioxide in the capsule shell. The presence of titanium dioxide would not be expected to influence performance of the product. Rupture times and disintegration times have been shown to be comparable with and without titanium dioxide in the capsule shell. This deviation to the commercial formulation is acceptable.

Following oral administration ibuprofen was absorbed more quickly from the liquid filled soft gelatin capsule than from the tablets, with the overall extent of absorption being the same for both formulations. For further discussion see the medical assessment report.

4. PRODUCT LITERATURE

4.1 SPC

4.1.1 The summary of product characteristics is acceptable.

4.2 PIL

4.2.1 The PIL is acceptable.

4.3 LABEL

4.3.1 The proposed labels are acceptable.

5. ADMINISTRATIVE

5.1 MAA form

The MAA is in line with the quality section and SPC.

5.2 Quality Overall Summary

The summary has been done by a suitably qualified expert. The report is a summary of the module.

6. CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

Pharmaceutical Assessor
May 2006

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

PRODUCT

Nurofen 400mg Liquid Capsules PL 00327/0198
A pharmacy only medicine (P)

MARKETING AUTHORISATION HOLDER

Crookes Healthcare Limited
1 Thane Road West, Nottingham, NG2 3AA

These are national applications for the UK marketing authorisation which are not intended for subsequent mutual recognition by other Member States.

The applications are line extensions, representing a fundamental change to existing marketing authorisations as referred to in Annex II of Regulations (EC) No 541/95 or 542/95 as amended.

This product is a line extension to the existing Nurofen Liquid Capsules (PL 00327/0147).

The change involves addition of a new strength / quantitative change to the active substance. The applications are submitted under Article 8.3 of Directive 2001/83/EC [formerly Article 8.3(i) of Directive 2001/83/EC].

1. INTRODUCTION

Ibuprofen is (±)-2-(*p*-isobutylphenyl) propionic acid.

Ibuprofen is a nonsteroidal anti-inflammatory agent that possesses analgesic and antipyretic activities. It has been in clinical use for well over three decades world-wide for arthritis and various other conditions characterised by inflammation. Its mode of action, like that of other nonsteroidal anti-inflammatory agents, is not completely understood, but appears to be related to prostaglandin synthetase inhibition.

Ibuprofen is rapidly absorbed when administered orally. Peak serum ibuprofen levels are generally attained one to two hours after administration. With single doses up to 800mg, a linear relationship exists between the amount of drug administered and the integrated area under the serum drug concentration vs. time curve. Above 800mg, however, the area under the curve increases less than proportional to increases in dose. There is no evidence of drug accumulation.

The administration of ibuprofen tablets either under fasting conditions or immediately before meals yields quite similar serum ibuprofen concentration-time profiles. When ibuprofen is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption. The bioavailability of ibuprofen is minimally altered by the presence of food.

A bioavailability study has shown that there was no interference with the absorption of ibuprofen when given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide.

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. The serum half-life is 1.8 to 2.0 hours.

2. ASSESSMENT

The following sections review the proposed Summary of the Product Characterisitcs for Nurofen 400mg Extra Strength Liquid Capsules.

2.1. Therapeutic indications

Satisfactory and acceptable

2.2. Posology and method of administration

Satisfactory and acceptable

2.3. Contraindications

Satisfactory and acceptable

2.4. Special warnings and precautions for use

Satisfactory and acceptable

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

Satisfactory and acceptable

2.6. Pregnancy and lactation

Satisfactory and acceptable

2.7. Effects on ability to drive and use machines

Satisfactory and acceptable

2.8. Undesirable effects

Satisfactory and acceptable

2.9. Overdose

Satisfactory and acceptable

2.10. Pharmacodynamic properties

Satisfactory and acceptable

2.11 Pharmacokinetic properties

Satisfactory and acceptable

3. BIOEQUIVALENCE

The applicant has submitted a single bioequivalence study

The 400 mg application is a line extension to Nurofen 400 mg Tablets for the registration of a new pharmaceutical form, Ibuprofen 400 mg clear Soft Gelatin Capsules. It is based on the bioavailability of the Ibuprofen 400 mg Soft Gelatin Capsules and the currently available formulation, Nurofen 2 x 200 mg Tablets. No biopharmaceutic studies were conducted using the 400 mg Soft Gelatin Capsules but this application refers to the bioavailability study using the 400 mg Soft Gelatin Capsules and Nurofen 2 x 200 mg (i.e., 400 mg) Tablets.

Reference and test product used in the clinical trial:
Standard Nurofen 200mg x 2 Tablets = 400mg
Ibupofen soft gelatin 400mg x 1 capsule, the applicant confirmed that this is the same as the 400mg products applied for.

Study design:
Open randomised two-way crossover, single dose study in healthy volunteers

Results of clinical trial

Arithmetic mean ± SD (range)

Parameter	Test	Reference	Ratio (T/R)
Cmax µg/mL	39.51 ± 8.91 (24.16-52.48)	30.07 ± 5.90 (20.23-45.14)	1.31
Tmax h	0.82 ± 0.64	1.53 ± 0.95	0.54
AUC(o-t) µg.h/mL	101.66 ± 19.98 (68.17-136.56)	101.29 ± 19.29 (78.62-143.31)	1.00
AUC(o-α) µg.h/mL	104.53 ± 20.40 (70.73-142.77)	104.40 ± 19.38 (81.08-148.67)	1.00
t1/2 h	1.91 ± 0.36	1.88 ± 0.33	1.02

Geometric mean

Parameter	Test	Reference	Ratio (T/R)	95% CI (%)
Cmax µg/mL	38.44	29.56	1.30	115.27 – 146.74
Tmax h	0.67	1.28	0.52	
AUC(o-t) µg.h/mL	99.76	99.62	1.00	95.89 – 104.59
AUC(o-α) µg.h/mL	102.61	102.77	0.998	95.78 – 104.08
t1/2 h	1.88	1.85	1.02	

As anticipated by virtue of its formulation, the C_{max} is higher and earlier following the test product. However, in terms of exposure (AUC), the test product is bioequivalent to the reference product.

At 12 hours post-dose, the plasma concentrations were below quantifiable limits in 11 of the 24 volunteers on test product and in 9 of the 24 volunteers on reference product.

4. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is identical to the SPC of the reference product.

5. PATIENT INFORMATION LEAFLET

The patient information leaflet is satisfactory and acceptable.

6. LABELLING

The labels are satisfactory.

7. DISCUSSION

Ibuprofen is a nonsteroidal anti-inflammatory agent that possesses analgesic and antipyretic activities. It has been in clinical use for well over three decades world-wide for arthritis and various other conditions characterised by inflammation. The SPC is identical to the SPC of the reference product. Furthermore the results of the bioequivalence study show that in terms of exposure (AUC), the test product is bioequivalent to the reference product.

8. CONCLUSIONS

There are no clinical objections to the grant of a marketing authorisation for this product.

Senior Clinical Assessor
24 June 2005

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Nurofen Extra Strength 400 mg Liquid Capsules are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's Nurofen Extra Strength 400 mg Liquid Capsules and the originator product.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the originator product.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is therefore considered to be positive.

NUROFEN EXTRA STRENGTH 400 MG LIQUID CAPSULES
PL 00327/0198

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 28/09/2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 06/10/2004
3	Following assessment of the application the MHRA requested further information relating to the dossier on 03/06/2005, 24/06/2005, 28/06/2005, 16/08/2005, 08/12/2005 and 31/01/2005.
4	The applicant responded to the MHRA's requests, providing further information relating to the dossier on 15/07/2005, 16/10/2005, 07/03/2005, 08/05/2006 and.
5	The application was determined on 21/07/2006

NUROFEN EXTRA STRENGTH 400 MG LIQUID CAPSULES
PL 00327/0198

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

NUROFEN EXTRA STRENGTH 400 MG LIQUID CAPSULES
PL 00327/0198

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nurofen Extra Strength 400 mg Liquid Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule, soft contains Ibuprofen 400 mg

Excipients

Potassium hydroxide
Sorbitol

For a full list of excipients see 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft
A clear red oval soft gelatin capsule printed with an identifying logo in white.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults, elderly and Children over 12 years:
Nurofen Extra Strength 400 mg Liquid Capsules are indicated for symptomatic relief of non-serious arthritic conditions, rheumatic or muscular pain, backache, neuralgia , migraine, headaches, dental pain, dysmenorrhoea, feverishness, colds and influenza.

4.2 Posology and method of administration

For oral administration and short-term use only

During short-term use, if symptoms persist or worsen the patient should be advised to consult a doctor

Adults and children over 12 years: Initial dose one capsule taken with water, then if necessary, one capsule every four hours. Do not exceed three capsules in any 24 hours. Not for use by children under 12 years of age without medical advice.

Elderly: No special dosage modifications are required. (See Section 4.4)

The minimum effective dose should be used for the shortest time necessary to relieve symptoms. If the product is required for more than 10 days, or if the symptoms worsen the patient should consult a doctor.

4.3 Contraindications

Patients with a known hypersensitivity to ibuprofen or any other constituent of the medicinal product.

Patients with a history of bronchospasm, asthma, rhinitis, or urticaria associated with aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs).

Patients with a history of, or existing gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs. (See Section 4.4)

Patients with severe hepatic failure, severe renal failure or severe heart failure. See also Section 4.4

Use with concomitant NSAIDs, including cyclo-oxygenase-2 specific inhibitors – increased risk of adverse reactions (see section 4.5)"

During the last trimester of pregnancy as there is a risk of premature closure of the fetal 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 4.6).

4.4 Special warnings and precautions for use

Caution is required in patients with certain conditions, which may be made worse:

- systemic lupus erythematosus as well as those with mixed connective tissue disease (see Section 4.8, Unwanted effects)
- gastrointestinal disorders and chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease) (see Section 4.8, Unwanted effects)
- hypertension and/or cardiac impairment (see Section 4.5, Interactions)
- renal impairment (see Sections 4.3, Contraindications and 4.8, Unwanted effects)
- hepatic dysfunction (see Sections 4.3, Contraindications and 4.8, Unwanted effects)

Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

The elderly are at increased risk of the consequence of adverse reactions.

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration.
GI bleeding, ulceration or perforation, which can be fatal has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of GI events.

Patients with a history of GI toxicity, particularly the 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).

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

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.

The label will include:
Read the enclosed leaflet before taking this product
Do not take if you:

- have or have ever had a stomach ulcer, perforation or bleeding
- are allergic to ibuprofen, to any of the ingredients, or to aspirin or other painkillers
- are taking other NSAID pain killers or aspirin with a daily dose above 75mg
- are in the last 3 months of pregnancy
- or the patient is under 12 years of age.

This medicine contains 28 mg of potassium per dose. To be taken into consideration by patients on a controlled potassium diet.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Contains 79.8 mg of sorbitol per dose, a source of 19.9 mg of fructose per dose.

Speak to your doctor or pharmacist before use if you

- Have asthma , heart, liver, kidney or bowel problems,
- are in the first 6 months of pregnancy.

If symptoms persist or worsen, or if new symptoms occur, consult your doctor or pharmacist.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen (like other NSAIDs) 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).
- Other NSAIDs as these may increase the risk of adverse effects (see Section 4.3)

Ibuprofen should be used with caution in combination with:

- Corticosteroids as these may increase the risk of adverse reactions, especially of the gastrointestinal tract. (see Section 4.3)
- Antihypertensives and diuretics since NSAIDs may diminish the effects of these drugs.
- Anticoagulants. NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4).
- Lithium. There is evidence for potential increase in plasma levels of lithium.
- Methotrexate. There is evidence for the potential increase in plasma levels of 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

Whilst no teratogenic effects have been demonstrated in animal experiments, the use of Nurofen Extra Strength 400 mg Liquid Capsules should, if possible, be avoided during the first 6 months of pregnancy.

During the 3rd trimester, ibuprofen is contra-indicated as there is a risk of premature closure of the 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). It should not be used for the last trimester of pregnancy. The onset of labour may be delayed and duration of labour increased. (See Section 4.3)

In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

None expected at 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, dyspnoea
c. various skin reactions e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erthema multiforme)

The list of the following 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.

Gastrointestinal Disorders	Uncommon:	abdominal pain, dyspepsia and nausea.
	Rare:	diarrhoea, flatulence, constipation and vomiting
	Very rare:	Peptic ulcer, perforation or gastrointestinal haemorrage, sometimes fatal, particularly in the elderly (see section 4.4) Exacerbation of ulcerative colitis and Chrohn's disease (See section 4.4)
Nervous System	Uncommon:	Headache
	Very rare:	Aseptic meningitis – single cases have been reported very rarely
Kidney	Very rare:	Decrease of urea excretion and oedema can occur. Also, acute renal failure. Papillary necrosis, especially in long-term use, and increased serum urea concentrations have been reported.
Liver	Very rare:	liver disorders, especially in long-term treatment.
Blood	Very rare:	haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding.
Skin	Very rare:	severe forms of skin reactions such as erythema multiforme and epidermal necrolysis can occur.

Immune System	Very rare:	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
Hypersensitivity Reactions	Uncommon:	Hypersensitivity reactions with urticaria and pruritus.
	Very rare:	Severe hypersensitivity reactions. Symptoms could be: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).

4.9 Overdose

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in 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 maore 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 cloting 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 maintainance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if 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 propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

ATC Code: M01A E01 Propionic acid derivative

5.2 Pharmacokinetic properties

Ibuprofen is well absorbed from the gastrointestinal tract. Ibuprofen is extensively bound to plasma proteins.

Nurofen Extra Strength 400 mg Liquid Capsules consist of ibuprofen 400 mg dissolved in a hydrophilic solvent inside a gelatin shell. On ingestion, the gelatin shell disintegrates in the gastric juice releasing the solubilised ibuprofen immediately for absorption. The median peak plasma concentration is achieved in approximately 30 minutes after administration.
The median peak plasma concentration for Nurofen tablets is achieved approximately 1-2 hours after administration. A direct comparison of the 400 mg ibuprofen capsule with 2x200 mg Nurofen tablets showed that the median peak plasma concentration was achieved more than twice as fast for the liquid capsule (32.5 min) compared to the tablets (90 min). When taken with food, peak plasma levels may be delayed.

Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete.

Elimination half-life is approximately 2 hours.

No significant differences in pharmacokinetic profile are observed in the elderly.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill
Macrogol 600
Potassium hydroxide 50% solution (E525)

Capsule shell
Gelatin
Sorbitol Liquid, Partially Dehydrated (420)
Purified Water
Ponceau 4R (E124)
Lecithin (E322)
Triglycerides , medium chain

Capsule printing
Ethanol
White ink *

The ink contains the following residual materials after application: Titanium Dioxide (E171), Polyvinyl Acetate Phthalate, Macrogol 400, ammonium hydroxide (E527).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Blisters formed from

Opaque Duplex PVC/PVdC 250µm/60gsm heat sealed to 20µm aluminium foil

or

opaque Tristar (Triplex) PVC/PE/PVdC 250µm/25µm/90gsm heat sealed to 20µm aluminium foil

packed into cartons

Each carton may contain 10, 12, 16, 18, 20, 24, 28, 30, 32, 36, 48, 96 in blister strips

Not all packs will be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Crookes Healthcare Limited
1 Thane Road West
Nottingham
NG2 3AA

8 MARKETING AUTHORISATION NUMBER(S)

PL 00327/0198

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/07/2006

10 DATE OF REVISION OF THE TEXT

21/07/2006

NUROFEN EXTRA STRENGTH 400 MG LIQUID CAPSULES
PL 00327/0198

PRODUCT INFORMATION LEAFLET

NUROFEN

contains ibuprofen

EXTRA STRENGTH
400mg Liquid Capsules

PLEASE READ THIS LEAFLET CAREFULLY BEFORE YOU START TO TAKE YOUR MEDICINE.
Keep this leaflet. You may want to read it again.

NUROFEN EXTRA STRENGTH 400mg LIQUID CAPSULES

WHAT IS IN NUROFEN EXTRA STRENGTH 400mg LIQUID CAPSULES ?
Each Nurofen Extra Strength 400mg Liquid Capsule contains the active ingredient ibuprofen 400mg.
Also contains : Macrogol 600, Potassium Hydroxide Solution, Sorbitol Liquid, partially dehydrated, Gelatin, Glycerol 85 (E422), Lecithin, Medium Chain Triglycerides, Titanium Dioxide (E171), Propylene Glycol, Polyvinyl Acetate Phthalate, Ammonium Hydroxide (E527), Macrogol 400, Purified Water.

Nurofen Extra Strength 400mg Liquid Capsules are available in packs of 10 and 20 capsules.
Licence Holder & Manufacturer: Crookes Healthcare Ltd, Nottingham, NG2 3AA
PL 00327/0198

HOW DO NUROFEN EXTRA STRENGTH 400mg LIQUID CAPSULES WORK ?
Nurofen Extra Strength 400mg Liquid Capsules contain ibuprofen which belongs to a group of medicines known as nonsteroidal anti-inflammatory drugs (NSAIDs).
NSAIDs provide relief by disrupting the body's response to pain, swelling and high temperature.
Nurofen Extra Strength 400mg Liquid Capsules are designed to provide effective relief to pain.
Nurofen Extra Strength 400mg Liquid Capsules break down easily in the body and the liquid, which is released from the capsule, is easily absorbed into the body to get to the site of pain quickly.
Nurofen Extra Strength 400mg Liquid Capsules are for the relief of **headaches, migraine, backache, period pain, dental pain, neuralgia, muscular pain, rheumatic pain, cold and flu symptoms, feverishness and pain of non-serious arthritis.**

BEFORE YOU TAKE NUROFEN EXTRA STRENGTH 400mg LIQUID CAPSULES:
Do Not take Nurofen Extra Strength 400mg Liquid Capsules if you:
- have rare hereditary problems of fructose intolerance. Contains 79.8 mg of sorbitol per dose, a source of 19.9 mg of fructose per dose.
- have or have ever had a stomach ulcer, perforation or bleeding
- are allergic to ibuprofen, to any of the ingredients, or to aspirin or other painkillers
- are taking other NSAIDs painkillers or aspirin with a daily dose above 75mg
- are in the last 3 months of pregnancy
- are under 12 years of age.
- Has a very low potassium (<2mg of potassium per dose. To be taken into consideration if you have reduced kidney function or are on a controlled potassium diet.

Ask your doctor before taking Nurofen Extra Strength 400mg Liquid Capsules if:
- you have asthma or have suffered from asthma
- you have kidney, heart, or liver or bowel problems
- have Systemic Lupus Erythematosus (SLE) - a condition of the immune system affecting connective tissue resulting in joint pains, skin changes and disorder of other organs
- you are taking any regular medication, especially:
  - aspirin at low dose (ie below 75 mg daily)
  - medicines for high blood pressure and water tablets (diuretics)
  - medicines for thinning the blood (anticoagulants)
  - corticosteroids
  - Methotrexate (an anti-cancer agent)
  - Lithium (used to treat depression)
  - Zidovudine (an anti-viral drug)
- you are in the first 6 months of pregnancy or breastfeeding.
- Nurofen belongs to a group of medicines which may impair fertility in women. This is reversible on stopping the medicine. It is unlikely that Nurofen, used occasionally, will affect your chances of becoming pregnant. However, tell your doctor before taking this medicine if you have problems becoming pregnant.

HOW TO TAKE NUROFEN EXTRA STRENGTH 400mg LIQUID CAPSULES:
Adults and children of 12 years and older:
Initial dose: Take 1 Nurofen Extra Strength 400mg Liquid Capsule with water, then if necessary 1 Capsule every 4 hours. **Do not chew the Capsules.** For oral use.
Do not exceed 3 Capsules in 24 hours.
Not suitable for children under 12 years
WARNING: DO NOT EXCEED THE STATED DOSE

This product is intended for short-term use only. You should take the lowest dose for the shortest time necessary to relieve your symptoms. You should not take Nurofen Extra Strength 400mg Liquid Capsules for longer than 10 days. If symptoms persist or if the pain or fever worsens, or if new symptoms occur, talk to your doctor or pharmacist.

WHILST TAKING NUROFEN EXTRA STRENGTH 400mg LIQUID CAPSULES:
If you take too many capsules by mistake, talk to your doctor or pharmacist as soon as possible.
Side Effects
Nurofen Extra Strength 400mg Liquid Capsules are generally well tolerated by the majority of people, however, elderly patients are at increased risk of developing problems associated with side effects.
Disorders of the stomach & intestines including abdominal discomfort or pain, nausea, stomach ulcer, vomiting containing either blood or brown grit (like coffee grounds), black tarry stools, worsening of existing bowel diseases (ulcerative colitis or Crohn's disease).
Blood disorders resulting in unexplained or unusual bruising or bleeding, fever, sore throat, mouth ulcers, extreme pallor or weakness.
Allergic reactions including worsening of asthma, unexplained wheezing or shortness of breath, swelling of the face and tongue, collapse. In addition, there may be skin reaction (including hives and itching); these can sometimes be severe with blistering and peeling of skin.
If you develop any of these symptoms above, stop the capsules and contact your doctor immediately.
Liver disorders that may be indicated by yellowing of the skin and eyes and/or pale stools and dark urine.
Kidney disorders that may be indicated by passing less or more urine than normal, cloudy urine, blood in the urine, pain in the back and/or swelling (particularly of the legs).
Nervous system disorders indicated by severe headache, neck stiffness, disorientation, and light hurting the eyes.
If you experience any of these, or have any other unusual symptoms or concerns, stop taking the product and see your doctor.

HOW SHOULD THIS PRODUCT BE STORED ?
Use by' date. Do not use after the expiry date given on the carton or the blister packaging.
Store below 25°C.

Remember: Keep all medicines out of the reach and sight of children.
Date of revision: December 2005.

CROOKES HEALTHCARE
Crookes Healthcare Ltd., Nottingham NG2 3AA

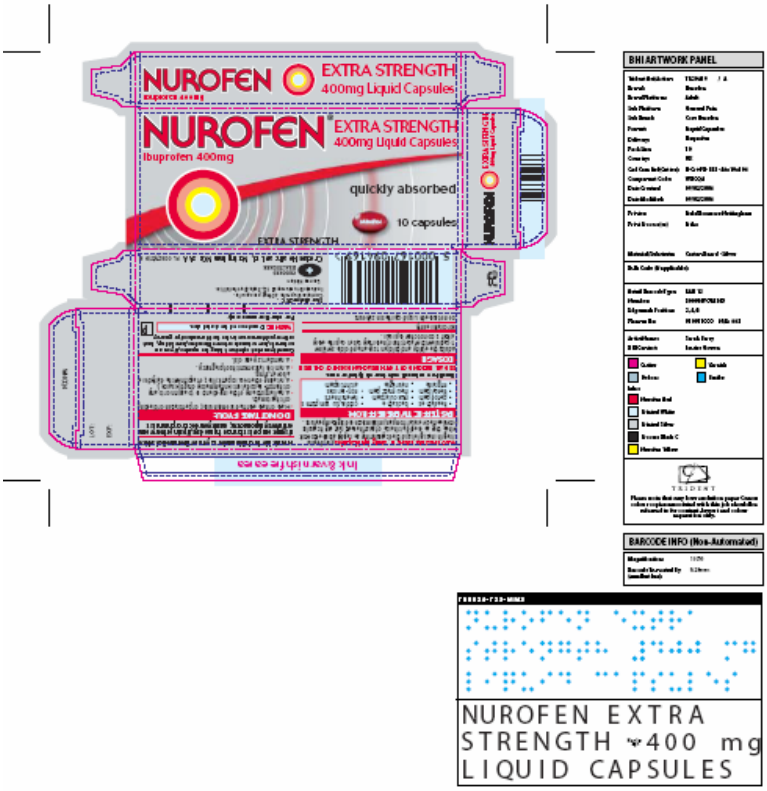
BMI ARTWORK PANEL

BARCODE INFO (Non-Automated)

MHRA PAR – Nurofen Extra Strength Liquid Capsules PL 00327/0198

NUROFEN EXTRA STRENGTH 400 MG LIQUID CAPSULES
PL 00327/0198

LABELLING



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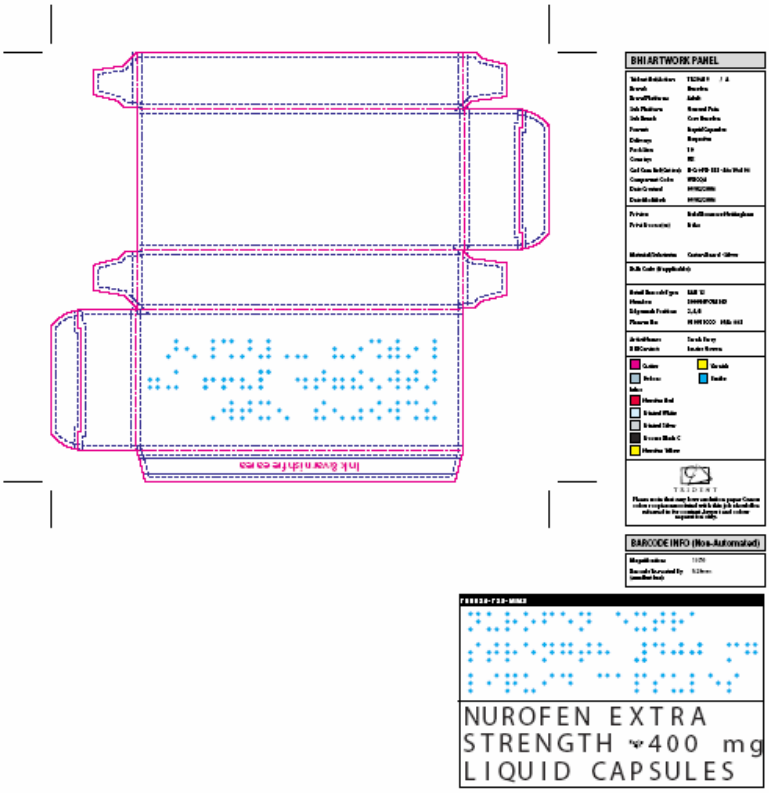

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LABELLING