

NUROFEN COLD & FLU LIQUID CAPSULES

PL 00327/0209

UKPAR

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NUROFEN COLD & FLU LIQUID CAPSULES

PL 00327/0209

LAY SUMMARY

The MHRA today granted Crookes Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Nurofen Cold & Flu Liquid Capsules (PL 00327/0209). This pharmacy-only medicine (P) is used for relief of cold and influenza.

Nurofen Cold & Flu Liquid Capsules are effective in helping clear a blocked nose and sinuses, relieving aches, pains, headache and feverishness, and easing the discomfort of a sore throat.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Nurofen Cold & Flu Liquid Capsules outweigh the risks, hence a marketing authorisation has been granted.

NUROFEN COLD & FLU LIQUID CAPSULES

PL 00327/0209

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisation for the medicinal product Nurofen Cold & Flu Liquid Capsules (PL 00327/0209) to Crookes Healthcare Limited on 2nd February 2007. This product is a pharmacy-only medicine.

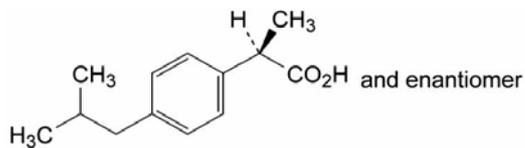
This application is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, last paragraph, claiming essential similarity to the original product Nurofen Cold and Flu tablets (PL 00327/0060, granted 24th of October 1993).

Nurofen Cold & Flu Liquid Capsules contain ibuprofen which belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs provide relief by changing the body's response to pain, swelling and high temperature. Pseudoephedrine belongs to a group of drugs called vasoconstrictors which act on the blood vessels in the nose to relieve nasal congestion.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Ibuprofen



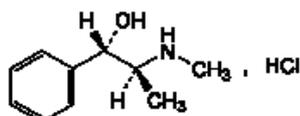
Description: White odourless crystalline powder or colourless crystals

Molecular formula: C₁₃H₁₈O₂

RMS: 206.3

Chirality: racemic

Pseudoephedrine Hydrochloride



Description: White odourless crystalline powder or colourless crystals

Molecular formula: C₁₀H₁₅NO.HCl

RMS: 201.69

Chirality: (+) enantiomer

There are two active manufacturers for the active substances. A valid certificate of suitability have been supplied for both manufacturers.

The manufacturing processes for both suppliers are referenced to their certificates of suitability.

The impurities are controlled by the levels in the European Pharmacopoeia monograph and certificate of suitability. Details regarding all impurities have been provided and are satisfactory.

The finished product manufacturer specification provided for the active substances are in compliance with the European Pharmacopoeia monograph.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

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

A certificate of suitability for one manufacturer of active including a retest period of 3 years has been supplied.

Stability data has been presented for other manufacturer at 25°C/60%RH a retest period of 5 years is considered acceptable and at 40°C/75%RH which show no change justify the absence of any specific storage conditions. Batches were assessed on appearance, melting point, specific rotation, pH, loss on drying, assay and related substances.

The impurities are controlled by the levels in the European Pharmacopoeia monograph and certificate of suitability.

DRUG PRODUCT

Description and Composition of the Drug product

The product is a soft gelatin capsule for oral administration. It is a 12 oval, clear capsule with an orange shell containing a hydrophilic solution of ibuprofen 200mg and pseudoephedrine hydrochloride 30mg. The capsule is printed in black ink with a logo. The primary packaging is a thermoform opaque blister strip. Each blister strip is formed from Triplex laminate aluminium lidding foil.

The composition of the products are summarised below.

Name of ingredient	Reference Standards
Composition of fill contents	
Ibuprofen	Ph. Eur.
Pseudoephedrine HCl	Ph. Eur.
Other excipients	
Macrogol 600	Ph. Eur.
Macrogol 600	Ph. Eur.
Purified Water	USP NF
Potassium hydroxide 43% w/w solution	Internal
Total fill weight	
Shell base materials	
Gelatin	Ph. Eur.
Sorbitol liquid, partially dehydrated	Ph. Eur.
FD&C Yellow #6 (Sunset yellow E110)	FD&C Codex
Lecithin	USP NF
Medium chain triglycerides	Ph. Eur.
Total	
Printing ink	
White printing ink Opacode NSP-78-18022	Internal
Ribbon print solvent	Internal
SDA 35A alcohol	USPNF

Propylene glycol	Ph. Eur.
Titanium dioxide (E171)	Ph. Eur.
Polyvinyl acetate phthalate	USP
Purified water	Ph. Eur.
Isopropyl alcohol	Ph. Eur.
Macrogol 400	Ph. Eur.
Iron oxide, black (E172)	JP
Ammonium hydroxide 28%	Reagent grade

The development of the product was based on the formulation of the existing licensed product with intention of producing a capsule with desired drug loading, a stable fill formulation and of an appropriate size.

A pharmacokinetic study has been completed which was identical to the reference product.

Dissolution comparison study was carried out and both formulations achieved adequate dissolution of each drug substance with no difference between the release rates of the actives.

No overages were applied to the formulation.

A flow diagram detailing the manufacturing process and in-process control testing has been provided. This is satisfactory.

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

Microbiological quality testing is included in the finished product specification. The proposed manufacturing process contributes low microbiological count.

All the details have been provided for the pharmacopoeia and non-pharmacopoeia methods and are acceptable.

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

The analytical methods used to test the excipients are those provided in the European Pharmacopoeia.

The capsules will be packed in a blister pack consisting of a clear PVC/PE, coated with PVdC laminate heat seal coated aluminium foil.

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

The finished product specification of the product is acceptable.

The method used for the assay, related substances and degradation products have been validated. Specificity, robustness, accuracy and precision have been demonstrated with the analytical procedures.

The microbiological methods used are valid.

Certificates of analysis on the reference standards are provided.

Batch analyses provided for the batches are within specification and show a reasonable degree of comparability. A valid certificates of analysis have been supplied.

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

The manufacturers certificates of conformity/analysis that accompany the packaging materials for the blister laminates and the aluminium foil have been supplied.

Stability data has been presented for the validation batches of the 200mg and 400mg products. The storage conditions are 25°C/60%RH, 30°C/65%RH and 40°C/75%RH.

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.

PRECLINICAL ASSESSMENT

This application for generic product claims essential similarity to Nurofen Cold and Flu tablets, which has been licensed in the EEA for over 10 years.

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

CLINICAL ASSESSMENT

1. INTRODUCTION

This is a national application concerning a new formulation called Nurofen Cold and Flu Capsules. The originator product is Nurofen Cold and Flu tablets were first approved in November 1993 in the UK.

Ibuprofen [2-(4-isobutylphenyl) propionic acid] is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activity, and is used for the symptomatic treatment of mild to moderate pain and fever.

Pseudoephedrine HCl is an established sympathomimetic amine with direct and indirect effects on alpha- adrenergic receptors of the respiratory tract mucosa, producing vasoconstriction, reducing swollen nasal mucous membranes, tissue hyperaemia, oedema and nasal congestion whilst increasing nasal airway patency and drainage of sinus secretions.

2. NON-CLINICAL ASSESSMENT

Pharmacodynamic, pharmacokinetic and toxicological properties of Ibuprofen and pseudoephedrine HCl are well known. As Ibuprofen and pseudoephedrine HCl are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. The overview based on a literature review is appropriate.

The non-clinical overview has been written by a Consultant Toxicologist.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

There are no non-clinical objections to approval of ibuprofen and pseudoephedrine HCl.

3. CLINICAL ASSESSMENT

3.1 INTRODUCTION

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The clinical overview was reviewed and approved by Medical Director.

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

3.2 CLINICAL STUDY REPORTS

To support the application, the applicant has submitted a report on one bioequivalence study.

Pharmacokinetic study NL0407

A bioavailability study has been carried out to demonstrate the bioequivalence of ibuprofen and pseudoephedrine from two liquid capsules (each containing 200 mg

ibuprofen and 30 mg pseudoephedrine) with that from two Nurofen Cold & Flu reference tablets (each containing 200 mg ibuprofen and 30 mg pseudoephedrine) produced by the same manufacturer.

Study NL0407

An open-label, two-way crossover, randomised, single centre pharmacokinetic study in 24 healthy volunteers to compare the bioavailability of ibuprofen and pseudoephedrine from two liquid capsules (200 mg ibuprofen; 30 mg pseudoephedrine) with that from two Nurofen Cold & Flu reference tablets (200 mg ibuprofen; 30 mg pseudoephedrine)

Population studied

Twenty-four healthy subjects were enrolled into the study, and following a screening visit were randomised (immediately prior to administration of the first dose) to receive the two study treatments. One subject was withdrawn after the second dosing period and replaced by a further subject who completed both treatment periods.

Results

This was a bioavailability study and no efficacy parameters were assessed. The bioavailability results are summarised here.

Ibuprofen

Administration of the soft gelatin capsule (test) product resulted in a shorter ibuprofen t^x (45 min) than for standard Nurofen Cold & Flu tablets (reference, 70 min) this difference was not statistically significant ($p=0.09$, Wilcoxon matched pairs test). The ibuprofen C_{max} values for the soft gelatin capsule (test) product and standard Nurofen Cold & Flu (reference) formulation were 39.82 and 33.89 $\mu\text{g/mL}$, respectively (geometric LSmeans).

The ratio of test / reference was 117.52% with 90% confidence intervals of 104.92-131.64%. AUC_{0-t} was 125.28 and 128.96 pg.h/mL for the soft gelatin capsules (test) and standard Nurofen Cold & Flu tablets (reference), respectively (geometric LSmeans). The ratio of test / reference was 97.15% with 90% confidence intervals of 92.34-102.21%. $AtI C^t$ was 126.09 and 129.86 ug.h/mL for the soft gelatin capsules (test) and standard Nurofen Cold & Flu tablets (reference), respectively (geometric LSmeans). The ratio of test / reference was 97.10% with 90% confidence intervals of 92.33-102.12%. Data are summarised in the table and figure below

Pharmacokinetic parameters for ibuprofen

	Test (Soft Gelatin Capsules)	Reference (Nurofen Cold & Flu® Tablets)	Ratio (%) Test / Reference	90% Confidence Interval
Geometric LSmeans				
C _{max} (µg/mL)	39.82	33.89	117.52	104.92 – 131.64
AUC _{0-t} (µg.h/mL)	125.28	128.96	97.15	92.34 – 102.21
AUC _{0-inf} (µg.h/mL)	126.09	129.86	97.10	92.33 – 102.12
	Median		Median Difference	95% CI for Difference
T _{max} (min)	45	70	-22.5	-50.0 – 0.0
			(p=0.0910) *	

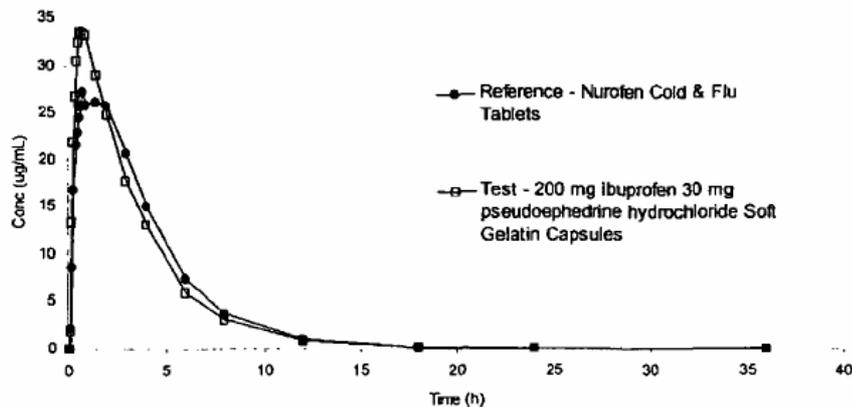
* Wilcoxon Matched Pairs Test

Pharmacokinetic parameters for ibuprofen

	Test (Soft Gelatin Capsules)	Reference (Nurofen Cold & Flu® Tablets)	Ratio (%) Test / Reference	90% Confidence Interval
Geometric LSmeans				
C _{max} (µg/mL)	39.82	33.89	117.52	104.92 – 131.64
AUC _{0-t} (µg.h/mL)	125.28	128.96	97.15	92.34 – 102.21
AUC _{0-inf} (µg.h/mL)	126.09	129.86	97.10	92.33 – 102.12
	Median		Median Difference	95% CI for Difference
T _{max} (min)	45	70	-22.5	-50.0 – 0.0
			(p=0.0910) *	

* Wilcoxon Matched Pairs Test

Mean plasma ibuprofen concentrations (µg/mL) after administration of the reference and test formulations to 24 healthy volunteers in trial NL0407



Pseudoephedrine

Administration of the soft gelatin capsule (test) product resulted in a slightly longer Pseudoephedrine t_{max} (105min) than for standard Nurofen Cold & Flu tablets (reference 90 min) ($p=0.0187$, Wilcoxon matched pairs test, see Table 11.4.9).

The pseudoephedrine C_{max} values obtained for the soft gelatin capsule (test) product and standard Nurofen Cold & Flu (reference) formulation were 289.15 and 329.33 ng/mL, respectively (geometric LSmeans). The ratio of test / reference was 87.80% with 90% confidence intervals of 81.83-94.21%.

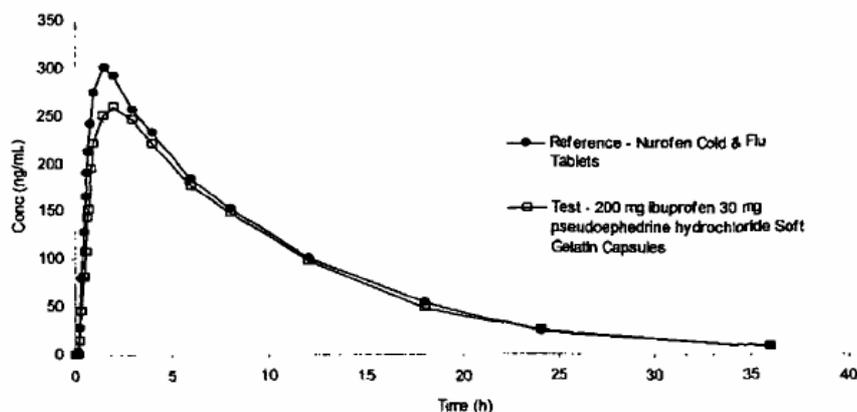
AUC was 2774.45 and 2931.04ng.h/mL for the soft gelatin capsules (test) and standard Nurofen Cold & Flu tablets (reference), respectively (geometric LSmeans). The ratio of test reference was 94.66% with 90% confidence intervals of 87.48-102.43%. AUC_{WnI} was 2838.39 and 3002.11 ng.h/mL for the soft gelatin capsules (test) and standard Nurofen Cold & Flu tablets (reference), respectively (geometric LSmeans). The ratio of test / reference was 94.55% with 90% confidence intervals of 87.22-102.49%. Data are summarised in the table and figure below.

Pharmacokinetic parameters for pseudoephedrine

	Test (Soft Gelatin Capsules)	Reference (Nurofen Cold & Flu® Tablets)	Ratio (%) Test / Reference	90% Confidence Interval
Geometric LSmeans				
C_{max} (ng/mL)	289.15	329.33	87.8	81.83 – 94.21
AUC _{0-t} (ng.h/mL)	2774.45	2931.04	94.66	87.48 – 102.43
AUC _{0-inf} (ng.h/mL)	2838.39	3002.11	94.55	87.22 – 102.49
Median				
T_{max} (min)	105	90	30.5	12.5 – 57.5
			($p=0.0187$) *	

* Wilcoxon Matched Pairs Test

Mean plasma pseudoephedrine concentrations (ng/mL) after administration of the reference and test formulations to 24 healthy volunteers in trial NL0407.



3.3 Pharmacokinetic conclusions

The applicant has shown acceptable bioequivalence for pseudoephedrine for the dose of 30mg in the liquid gelatine capsule formulation within the acceptance levels of 80-125% of the NfG on Bioequivalence. The pseudoephedrine component of the 200 mg ibuprofen 30 mg pseudoephedrine HCl soft gelatin capsules is bioequivalent to standard Nurofen Cold & Flu tablets (CPMP/EWP/QWP/1401/98).

The applicant has not shown bioequivalence for the 200mg dose of ibuprofen in the liquid gelatine capsule formulation within the acceptance levels of 80-125% of the NfG. The range found for C_{max} is 104.92 -131.64. The ibuprofen component is absorbed slightly more quickly from the soft gelatin capsules resulting in a higher C_{max} than from standard Nurofen Cold & Flu tablets (reference formulation). A previous study (NL9712) using a similar formulation discussed by the company in the Clinical Expert Report describes this faster absorption rate. The study was not used in the submission. The statistical analysis plan for the current study NL0407 did not account for this and did not prespecify it as indicated in CPMP/EWP/QWP/1401/98. The applicant has presented the counter argument that ibuprofen has a wide therapeutic window and that the therapeutic implications associated with the small increases in C_{max} for the ibuprofen component of the soft gelatine capsules are at least comparable regarding analgesic, anti-inflammatory and antipyretic effects without an increase in adverse events.

Both treatments are well tolerated, no serious or severe adverse events related to therapy being reported.

3.4 Pharmacodynamic studies.

None

3.5 Post marketing experience

This product is not available in any other country in the European Union. A similar product is currently registered in the US (FDA, NDA 21-374) under the name of Advil Cold and Sinus Liquigels and it contains 200mg of ibuprofen and 30mg of pseudoephedrine HCl. The applicant has submitted numerous PSURs for the reference product Nurofen Cold and Flu tablets, which indicate that this product is well-tolerated since it has been commercialised as a non-prescription medicine 12 years ago.

Trial NL0407 presented here did not show any significant difference with respect to adverse events between the two formulation studies. It is therefore concluded that the adverse events expected with Nurofen Cold and Flu Soft Gelatine Capsules would be the same as the reference product which is currently marketed Nurofen Cold and Flu Tablets.

3.6 Risk Benefit Assessment

The application contains an adequate review of published clinical data and clearly links the findings of trial NL0407 in context with other bioequivalence work done with a similar formulation in the US. In this early study similar findings for C_{max} for Ibuprofen were found. Approval however is not recommended since the applicant did not prospectively define the expanded Confidence Intervals in the statistical analysis plan as indicated in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98 Section 3.6.2 "Acceptance range for

Pharmacokinetic Parameters”. This was not done even though the applicant was aware of the risk of obtaining confidence intervals outside of the standard range accepted.

The applicant has based their SmPC on that of Nurofen Cold and Flu Tablets used in the UK.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Nurofen Cold & Flu 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 submitted and none are required for application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Nurofen Cold & Flu Liquid Capsules and the originator product.

No new or unexpected safety concerns arise from this application.

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

RISK BENEFIT ASSESSMENT

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

NUROFEN COLD & FLU LIQUID CAPSULES**PL 00327/0209****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the marketing authorisation application on 2 nd June 2005
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 14 th July 2005
3	Following assessment of the application the MHRA requested further information relating to the quality dossiers on 18 th November 2005.
4	The applicant responded to the MHRA's request, providing further information for the quality section on 7 th March 2006.
5	The application was determined on 2 nd February 2007

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nurofen Cold and Flu® Liquid Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg ibuprofen and 30 mg pseudoephedrine hydrochloride

For excipients see 6.1

3. PHARMACEUTICAL FORM

Orange soft gelatin capsule with an identifying mark

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the relief of cold and influenza symptoms with associated congestion, including aches and pains, headache, fever, sore throat, blocked nose and sinuses

4.2. Posology and method of administration

For oral administration and short-term use only

Swallow whole with a glass of water. Do not chew.

Adults and children 12 years of age and over: Initial dose, 2 capsules. Then, if necessary, 1 or 2 capsules every 4 hours. Do not exceed 6 capsules in any 24-hour period.

Not to be given to children under 12 years.

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, the patient should consult a doctor.

Should not be administered to elderly patients or patients with impaired renal or hepatic function (see section 4.3 and 4.4).

4.3. Contraindications

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)

Cardiovascular disease such as ischaemic heart disease, tachycardia and (severe) hypertension

Narrow angle glaucoma

Urinary retention

Hyperthyroidism

Patients with a history of haemorrhagic stroke or patients with risk factors that may increase the risk of haemorrhagic stroke, for example patients taking vasoconstrictors or any other oral or nasal decongestants (see section 4.5)

Nurofen Cold & Flu Liquid Capsules must not be used during pregnancy (See section 4.6 Pregnancy and lactation).

4.4. **Special warnings and precautions for use**

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

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

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

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

Chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease) – as these conditions may be exacerbated (See section 4.8 Undesirable effects)

Hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur

Renal impairment as renal function may further deteriorate (See section 4.3 Contraindications and Section 4.8 Undesirable effects)

Hepatic dysfunction (See section 4.3 Contraindications and Section 4.8 Undesirable effects)

There is limited evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

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 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 Interactions).

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

Cardiac arrhythmias, hypertension, a history of myocardial infarction or cardiac impairment

Diabetes mellitus

Bladder neck obstruction

Pyloroduodenal obstruction

Prostate enlargement

Glaucoma

The treatment should be discontinued if the patient experiences hypertension, tachycardia, palpitations or cardiac arrhythmias, nausea or any other neurologic sign (such as headache or increased headache).

As with other CNS stimulants, Pseudoephedrine has a risk of abuse. Increased doses may ultimately produce toxicity. Continuous use can lead to tolerance resulting in an increased risk of overdosing. Depression may follow rapid withdrawal.

Athletes should be informed that treatment with Pseudoephedrine could lead to positive dope tests.

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

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 or any other ingredient of the product, aspirin or other related painkillers
- are taking other NSAID painkillers, or aspirin with a daily dose above 75mg
- are pregnant or breast feeding
- are taking medicines known as Mono-amine Oxidase Inhibitors (MAOIs), or took them less than 2 weeks previously
- have an eye-condition called narrow-angle glaucoma
- have urinary retention
- have high blood pressure (hypertension), or a heart disorder, including angina, or very rapid, irregular heart beat
- have had a stroke in the past
- have an over-active thyroid (hyperthyroidism)

Speak to a pharmacist or your doctor before taking this product if you

- have asthma, liver, heart, kidney or bowel problems.

If symptoms persist or worsen, consult your doctor.

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

Nurofen Cold & Flu must not be used in combination with:

- Monoamine Oxidase Inhibitor (MAOI) therapy or within 14 days of ceasing such treatment. Concurrent administration of MAOI and sympathomimetic drugs can cause critical hypertension reactions.
- The following combinations are not recommended because of increased risk of vasoconstriction and increase in blood pressure when combined with pseudoephedrine:
 - Ergot derived dopamine receptor agonists - bromocriptine, cabergoline, lisuride, pergolide
 - Dopaminergic vasoconstrictors - dihydroergotamine, ergotamine, methylgometrine
 - Linezolid
 - Nasal decongestants (oral and nasal) - phenylephrine, ephedrine, phenylpropanolamine.

Nurofen Cold & Flu Liquid capsules should be used with caution in combination with:

- Aspirin or other NSAIDs or glucocorticoids. In combination with Ibuprofen (like other NSAIDs), these may increase the risk of adverse reactions in the gastrointestinal tract.
- Antihypertensives and diuretics since ibuprofen (like other NSAIDs) may diminish the effects of these drugs.
- Lithium. There is evidence that concurrent administration with ibuprofen (like other NSAIDs) may increase the plasma levels of lithium.
- Methotrexate. There is evidence that concurrent administration with ibuprofen (like other NSAIDs) may increase the 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.
- The following combinations with pseudoephedrine are not recommended:
 - appetite suppressants, as it may potentiate their effects
 - amphetamine-type psycho-stimulants, as it may potentiate their effects
 - antihypertensive agents, alpha methyl dopa, mecamylamine, reserpine, veratrum alkaloids and guanethidine, as it may reduce their antihypertensive effects
 - tricyclic antidepressants, as theoretically it may increase the potential of the patient experiencing hypertension and arrhythmias.
- Antacids increase the rate of pseudoephedrine absorption, kaolin decreases it.
- Volatile halogenated anaesthetics, as perioperative acute hypertension can occur if they are used during treatment with indirect sympathomimetic agents. Therefore, if surgery is scheduled, it is preferable to discontinue treatment 24 hours before anaesthesia.

4.6. Pregnancy and lactation

The use of this product is contra-indicated during pregnancy and breastfeeding.

There is a possible association between the development of foetal abnormalities and first trimester exposure to pseudoephedrine. The use of pseudoephedrine decreases the maternal uterine blood flow.

In the first six months of pregnancy there is insufficient experience about the safety of use of ibuprofen in humans. In the last trimester, ibuprofen must be avoided as it may inhibit uterine contractions, cause the premature closure of ductus arteriosus, cause pulmonary hypertension in the neonate, increase the bleeding tendency in mother and child and increase the formation of oedema in the mother. The use of pseudoephedrine decreases the maternal uterine blood flow.

Ibuprofen and its metabolites can pass in very small concentrations (0.0008% of the maternal dose) into the breast milk, whereas, significant amounts of pseudoephedrine are excreted into breast milk, and therefore this product should be avoided during lactation.

See Section on Special Warnings and Precautions for use regarding female fertility.

4.7. Effects on ability to drive and use machines

For short-term use of this product, no special precautions are necessary.

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 erythema multiforme).

The list of the following adverse effects relate to those experienced with the product at non-prescription doses, for short term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Blood and Lymphatic System Disorders	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.
Immune Systems Disorders	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). Exacerbation of asthma and bronchospasm.
Psychiatric Disorders	Uncommon: Anxiety, insomnia, restlessness, hallucinations
Nervous System Disorders	Common: Somnolence, dizziness Uncommon: Headache, syncope, dysguesia (change in sense of taste) Very rare: Paraesthesia, Myasthenia
Eye Disorders	Very Rare: Blurred vision, lacrimal disorder
Cardiac Disorders	Uncommon: Palpitations Very rare: Hypertension, tachycardia
Vascular Disorders	Very rare: Vasodilatation
Gastrointestinal Disorders	Uncommon: Abdominal pain, dyspepsia and nausea. Rare: Diarrhoea, flatulence, constipation and vomiting Very Rare: Gastro-intestinal ulcers, sometimes with bleeding and perforation
Hepato-biliary Disorders	Very Rare: Liver disorders, especially in long-term treatment.
Skin and Subcutaneous Tissue Disorders	Very Rare: Severe forms of skin reactions such as erythema multiforme and epidermal necrolysis can occur.
Renal and Urinary Disorders	Very Rare: Dysuria. 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.

Very Common (>1/10); Common ($\geq 1/100$ - <1/10); Uncommon ($\geq 1/1000$ - <1/100); Rare ($\geq 1/10000$ - <1/1000); Very Rare (<1/10000)

4.9. Overdose

a).Symptoms of Overdosing

Pseudoephedrine toxicity does not correlate well with the dose taken, as some individuals are sensitive to its sympathomimetic properties. The clinical effects are more likely to be due to the pseudoephedrine rather than ibuprofen in this product.

The sympathomimetic symptoms can vary from CNS depression (sedation, apnoea, diminished mental alertness, cyanosis, coma, CV collapse) to CNS stimulation (insomnia, hallucinations, tremors, convulsions) with possible fatal outcome. The following symptoms

could also be experienced: headache, anxiety, difficulty in micturition, muscle weakness and tenseness, euphoria, excitement, tachycardia, palpitations, thirst, sweating, nausea, vomiting, chest pain, dizziness, tinnitus, ataxia, blurred vision and hypertension or hypotension. CNS stimulation is more likely in children (dry mouth, fixed-dilated pupils, flushing, fever and gastrointestinal symptoms).

In addition, the following ibuprofen related symptoms could be experienced when doses of >400 mg/kg have been taken: nausea, vomiting, abdominal pain, headache, dizziness, drowsiness, nystagmus, blurred vision, tinnitus and, rarely, hypotension, metabolic acidosis, renal failure and loss of consciousness.

b) Therapeutic Measures in Overdosing

No specific antidote is available.

Observation in hospital for a minimum of 4 hours is recommended for ingestion of greater than the maximum daily dose of pseudoephedrine (adult > 240 mg, children: 6-12 years > 120 mg, 2-5 years > 60 mg and < 2 years any amount).

Gastric lavage is not recommended, as the risk of serious toxicity is low. Activated charcoal (adult 50 g and child 1 g/kg) if the patient presents within one hour of ingestion.

Patients should receive mainly symptomatic and supportive care. In all symptomatic cases, electrolytes should be checked and an ECG performed. If there are ECG changes, cardiovascular instability or severe clinical effects (e.g. coma, convulsions) then cardiac monitoring should be performed for 12-24 hours. Seizures may be managed with diazepam. Severe hypertension may be treated using an alpha-blocker.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group (ATC Code): R05X Other Cold Combination Preparations

Ibuprofen is a propionic acid derivative, having analgesic, anti-inflammatory and antipyretic activity. The drug's therapeutic effects as a non-steroidal anti-inflammatory drug, is thought to result from its inhibitory activity on prostaglandin synthesis.

Pseudoephedrine is a sympathomimetic agent with direct and indirect effects on alpha-adrenergic receptors. It has alpha and beta stimulant adrenergic activity and a weak stimulant effect on the central nervous system. The sympathomimetic effect of pseudoephedrine produces vasoconstriction which in turn relieves nasal congestion.

5.2. Pharmacokinetic properties

Ibuprofen is well absorbed from the gastrointestinal tract. The maximum plasma concentration of ibuprofen is usually achieved in approximately 1-2 hours after administration. Ibuprofen is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid.

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.

Pseudoephedrine is readily and completely absorbed from the gastrointestinal tract following oral administration, with no presystemic metabolism.

The peak plasma concentrations of pseudoephedrine are usually achieved within 1-3 hours after oral dosing.

Pseudoephedrine is eliminated largely unchanged in the urine (55-90%), together with small amounts (<1%) of a hepatic metabolite. It has a plasma half-life of 5-8 hours but its urinary

elimination, and hence half-life, is pH dependent. Elimination is increased in subjects with acidic urine and decreased in subjects with alkaline urine.

5.3. Preclinical safety data

The toxicity of ibuprofen in animal experiments was observed as lesions and ulcerations in the gastro-intestinal tract. Ibuprofen did not show mutagenic potential *in vitro* and was not carcinogenic in rats and mice. Experimental studies have demonstrated that ibuprofen passes the placenta, but there is no evidence of any teratogenic action.

Preclinical data on pseudoephedrine are limited but do not show any special hazard for humans based on studies of acute and repeat dose toxicity. The effects seen are generally exaggerated pharmacological effects related to its sympathomimetic activity.

In acute and multiple dose studies, the combination of ibuprofen and pseudoephedrine exhibited a low order of toxicity. The combination was not more toxic than the individual components and the effects seen were those of the individual drugs. In a reproductive toxicity study in rats, the combination of ibuprofen and pseudoephedrine was not teratogenic.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Macrogol 600
Potassium Hydroxide 43% solution
Gelatin
Sorbitol liquid, partially dehydrated

Purified water
Sunset yellow E110
Lecithin
Triglycerides
Black ink

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2 years

6.4. Special precautions for storage

Do not store above 25°C.

6.5. Nature and contents of container

PVC/PE/PVDC blister/aluminium foil
Pack sizes: 4, 10, 20 or 30
Not all pack sizes may be marketed.

6.6. Instruction for use and handling

None

7. MARKETING AUTHORISATION HOLDER

Crookes Healthcare Limited
1 Thane Road West
Nottingham NG2 3AA
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00327/0209

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/02/2007

10 **DATE OF REVISION OF THE TEXT**
02/02/2007

NEZP

NUROFEN[®]

COLD & FLU liquid capsules



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

WHAT IS IN NUROFEN COLD & FLU LIQUID CAPSULES?

Each capsule contains the active ingredients Ibuprofen PL Eur 200mg and Pseudoephedrine Hydrochloride PL Eur 30mg

They also contain Microgel, Potassium Hydroxide, Gelatin, Sorbitol, Purified Water, Sunset Yellow (E110), Triglycerides, Black Printing Ink.

Nurofen Cold & Flu Liquid Capsules are available in packs of 10, 20 and 30 capsules.

License holder and manufacturer:
Cresles Healthcare Limited
Holdingham NG22 3AA

Product Licence No: PL 00327/0209

HOW DO NUROFEN COLD & FLU LIQUID CAPSULES WORK?

Nurofen Cold & Flu Liquid Capsules contain Ibuprofen which belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs provide relief by changing the body's response to pain, swelling and high temperatures. Pseudoephedrine belongs to a group of drugs called vasoconstrictors which act on the blood vessels in the nose to relieve nasal congestion.

Nurofen Cold & Flu Liquid Capsules are effective in helping clear a blocked nose and sinuses, relieving aches, pains, headache and feverishness, and easing the discomfort of a sore throat.

BEFORE YOU TAKE NUROFEN COLD & FLU LIQUID CAPSULES:

DO NOT TAKE IF YOU:

- have or have ever had a stomach ulcer, or perforation or bleeding of the stomach
- are allergic to ibuprofen, any of the ingredients or to aspirin or to other pain killers
- are taking other NSAID pain killers, or aspirin with a daily dose above 75mg daily
- are taking medicines known as Monoamine Oxidase Inhibitors (MAOIs), or took them less than 2 weeks ago
- suffer from severe liver, kidney or heart problems
- suffer from an eye condition called narrow angle glaucoma
- suffer from high blood pressure (hypertension), or a heart disorder, including angina, or rapid, irregular heart beat
- have an over-active thyroid
- have urinary retention
- have suffered from a stroke
- are pregnant or breast-feeding
- are under 12 years old

Ask your doctor before taking Nurofen Cold & Flu Liquid Capsules if:

- you have asthma or have suffered from asthma
- you have kidney, liver, or liver or bowel problems
- have Systemic Lupus Erythematosus (SLE) - a condition of the immune system affecting connective tissues resulting in joint pains, skin changes and disorder of other organs
- you have been told by your doctor that you have an intolerance to some sugars.
- you are taking any regular medication, especially:
 - if you are on low dose aspirin (up to 75mg daily)
 - medicines for high blood pressure and water tablets (diuretics)
 - medicines for thinning the blood (anticoagulants)
 - corticosteroids
 - Methotrexate
 - Lithium (used to treat depression)
 - Zidovudine (an antiviral drug)
 - Dopamine
 - Other nasal decongestant products
 - Appetite suppressants
 - Digestive medicines (antacids)
 - Stimulants and antidepressant drugs
- 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 COLD & FLU LIQUID CAPSULES:

Adults, the elderly and children 12 years and older.

Swallow 2 capsules with water, then if necessary take 1 or 2 capsules every 4 hours.

Do not exceed 8 capsules in 24 hours.

Not for use in children under 12 years.

If symptoms persist or worsen consult your doctor or pharmacist.

WHILST TAKING NUROFEN COLD & FLU LIQUID CAPSULES:

If you take too many capsules by mistake, talk to your doctor or pharmacist as soon as possible.

If symptoms persist or worsen, or if new symptoms occur, talk to your doctor or pharmacist. 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 Cold & Flu Liquid Capsules for longer than 10 days unless your doctor tells you to.

Side effects: Nurofen Cold & Flu 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 and bowel (including abdominal discomfort or pain, nausea, dyspepsia, diarrhoea, flatulence (wind), constipation, stomach ulcer, vomiting containing either blood or brown/gut (like coffee grounds), black tarry stools, worsening of existing bowel diseases (ulcerative colitis or Crohn's disease).

Blood disorders resulting in a bruised 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, rapid irregular heart beat. 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 the symptoms above, stop taking 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 (puffiness) of the legs

Nervous system disorders indicated by severe headaches, neck stiffness, disorientation, light hurting the eyes and muscle weakness.

Also, anxiety, restlessness and sleep difficulties, mood changes, disorientation, headaches, blurred and or watery eyes, hearing problems.

If you experience any of these, or have any other unusual symptoms or concerns, stop taking the product and see your doctor.

HOW SHOULD NUROFEN COLD & FLU LIQUID CAPSULES BE STORED?

Do not use after the expiry date shown on the pack.

Do not store above 25°C

Store in the original packaging.

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

HOW CAN YOU OBTAIN MORE INFORMATION ABOUT NUROFEN COLD & FLU LIQUID CAPSULES?

This leaflet gives you the most important patient information about Nurofen Cold & Flu Liquid Capsules. If you have any questions after you have read it, ask your doctor or pharmacist, who will give you further information.

Date: December 2005



**CROCKET'S
HEALTHCARE**

Crocket's Healthcare Ltd, Nottingham, NG2 3AA.

UPL 0216



BHI ARTWORK PANEL

Trident Ref/Action:	TRI 8916 / B
Brand:	Nurofen
Brand Platform:	Adult
Sub Platform:	Brand Stretch
Sub Brand:	Cold & Flu
Format:	Capsule
Delivery:	Ibuprofen & Pseudoephedrine
Pack Size:	10
Country:	UK
Cad Cam Ref (Cutter):	N Foil 101 x 40 L
Component Code:	TASV4
Date Created:	19/12/2005
Date Modified:	27/01/2006

Printer:	G&A Healthcare Packaging Ltd
Print Processes:	Gravure
	N/A
	N/A
Material/Substrate:	Aluminium Foil

Bulk Code (if applicable):	N/A
Updated:	N/A

Retail Barcode Type:	Not Known
Number:	N/A
Edgemark Position:	N/A
Pharma No:	N/A N/E: N/A

Artist Name:	Jennifer Smith
BH Contact:	Louise Gowen

Cutter

Inks:

Process Black C



TRIDENT

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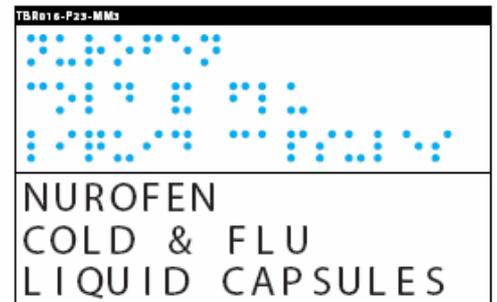
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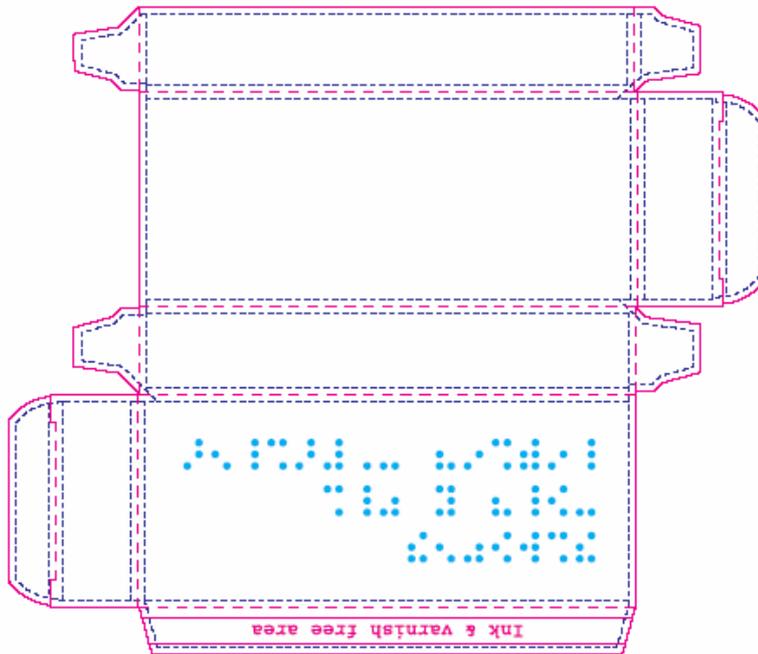
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BHI ARTWORK PANEL	
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Brand:	Nurofen
Brand Platform:	Adult
Sub Platform:	Cold & Flu
Sub Brand:	Cold & Flu
Format:	Capsules
Delivery:	10 capsules 6 Pseudoephedrine
Pack Size:	10
Country:	UK
Cell Can File (Country):	P23
Compass Code:	38492
Date Created:	21/02/2005
Date Modified:	10/02/2006
Printer:	Field Economics Marketing
Print Processed:	UK N.A. N.A.
Material/Substrate:	Carton Board - Silver
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Updated:	UK
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RM Contact:	Leslie Owen
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BARCODE INFO (Non-Automated)	
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BHIARTWORK PANEL							
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Brand Platform:	Adult						
Sub-Platform:	Brand Stretch						
Sub-Brand:	Cold & Flu						
Format:	Capsule						
Delivery:	10mg x 10 Pseudoephedrine						
Pack Size:	10						
Country:	UK						
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Component Code:	384402						
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 Process Black/C	 Printed Silver						
 Printed White	 Nurofen CAP Blue						
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