

## **Public Assessment Report**

**Nurofen Ultra Strength 684mg Caplets**

**Ibuprofen lysine**

**PL 00327/0144**

**Crookes Healthcare Ltd**

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## **Lay Summary**

Ibuprofen is one of the most widely used non-steroidal anti-inflammatory drugs. It was first introduced in the UK in 1969 and has been available over-the-counter since 1983. The primary biological action of ibuprofen is to inhibit the enzyme cyclooxygenase which is responsible for the synthesis of prostaglandins and other mediators. This inhibition is responsible for ibuprofen's ant-inflammatory, analgesic and antipyretic effects. These products are intended for the relief of mild to moderate pain, such as headache, migraine, dental pain, dysmenorrhoea, rheumatic and muscular pain, backache, neuralgia, sore throat and the pain of non-serious arthritis. Also, for the symptomatic relief of fever, colds and influenza.

# Scientific Discussion

## Pharmaceutical Assessment

### Introduction

This Public Assessment Report is based on the Assessment Reports for recently granted duplicate National Market Authorisations for Nurofen Maximum Strength Migraine Pain 684mg Caplets and Nurofen Ultra Strength 684mg Caplets. The applications were made under the article 8.3(i), as a line extension of an authorised medicinal product Nurofen Migraine Pain tablets containing 342mg ibuprofen lysine, PL 00327/0125, granted 27 July 2000. The latter formulation is half strength of the duplicate products and in direct proportion. The application relies upon the use of data filed to date, for PL 00327/0125, supplemented by data to meet the extent to which the products are not the same.

### Use

The tablets are used in the treatment of mild to moderate pain, such as headache, migraine, dental pain, dysmenorrhoea, rheumatic and muscular pain, backache, neuralgia, sore throat, and the pain of non-serious arthritis. Also, for the symptomatic relief of fever, colds and influenza.

### TSE

It has been confirmed that none of the ingredients in these products are of animal origin.

### Composition

The qualitative composition of the proposed Medicinal Product (400mg) and comparison of the authorised half-strength 200mg product (PL 00327/0125) is given below.

400mg tablet; Ibuprofen lysine 684mg, povidone, sodium starch glucollate Type A, magnesium stearate, purified water, hypromellose, titanium dioxide, black iron oxide, shellac, soya lecithin, antifoam DC 1510, IMS 660P.

200mg tablet; Ibuprofen lysine 342mg, povidone, sodium starch glucollate Type A, magnesium stearate, purified water, hypromellose, titanium dioxide, black iron oxide, shellac, soya lecithin, antifoam DC 1510, IMS 660P.

### Container

1. A blister pack, consisting of an opaque, white 250um PVC/23um polychlorotrifluoroethylene (Aclar) laminate heat-sealed to 20 um aluminium foil. The blisters are packed in cardboard carton containing 4, 6, 8, 12, 16 and 24 tablets.
2. A blister pack consisting of an opaque, white 250um PVC/40gsm PVDC laminate heat-sealed to 20 um aluminium foil. The blisters are packed in cardboard carton containing 4, 6, 8, 12, 16 and 24 tablets. Both packs are same as in their UK authorised lower strength tablet (PL 00327/0125)

## Clinical Trial Formula(e)

The table below shows two bioavailability studies:

<b>Product used in Volunteer Studies (all strengths are shown as ibuprofen equivalent)</b>	<b>Design of Bioavailability study in human volunteers</b>
Ibuprofen lysine salt 400mg equivalent tablet (test) Nurofen 200mg tablets (Pivotal)	Open, randomised, single-dose, two-way, crossover 1x400mg test v/s 2x200mg Nurofen tablets
Ibuprofen lysine salt 200mg equivalent tablets (test) Dolormin ibuprofen lysine salt 200mg equivalent tablet Nurofen 200mg tablets	Open, randomised, single-dose, three-way, crossover 2x200mg test v/s 2x200mg Nurofen v/s 2x200mg Dolormin tablets

In the first study the Ibuprofen lysine salt 400mg equivalent tablets used are identical to the proposed formulation except the tablets are unprinted. Nurofen tablets are from UK market.

In the second study the Ibuprofen lysine salt 200mg equivalent tablets used were of the same granulation mix as for 400mg equivalent tablets but compressed to a lower weight. The Nurofen tablets were from the UK market and Dolormin tablets were from the German market.

## Development Pharmaceuticals

The objective was to develop tablet with faster release characteristics in vivo than the conventional ibuprofen tablets. The development of the proposed 400mg tablet is based on the earlier development programme for the authorised (PL 00327/0125) ibuprofen lysine salt (200mg ibuprofen equivalent) tablets. The proposed 400mg tablet is directly proportional and is compressed at twice the weight of the 200mg tablet. Therefore, the development pharmaceuticals is accepted. The film-coat formula used for the 200mg tablet was equally applicable to the proposed tablet. The data demonstrated no significant change in the disintegration time from the core tablets.

The tablets were printed with identifying motif using commercially available pharmaceutical grade printing ink.

## Method of Preparation

### GMP Statement and Manufacturing Chain

A satisfactory Manufacture's Licence has been provided by the finished product manufacture.

### Validation

Satisfactory validation data are provided for the batches tested and all batches complied with the Finished Product Specification.

### **Control of Active Substance**

The drug substance is covered by a Drug Master File and a satisfactory Letter of Access has been provided. The AIM specification is the same as that approved for the other UK licenced product (PL 13249/0027) and that provided by the applicant for the proposed product.

### **Control of Excipients and Packaging**

#### **Excipients included in a Pharmacopoeia**

The pharmacopoeial excipients are povidone, sodium starch glycollate type A, hypromellose, magnesium stearate, purified talc, purified water and industrial methylated spirit. Certificates of Analysis were provided for these excipients.

#### **Excipients not included in a Pharmacopoeia**

These are proprietary Opaspray White M-1-711B and Opacode Black S-1-8152HV. All components of the Opaspray White (hypromellose 3.0%, titanium dioxide 30.0%, IMS 10.0% and Purified water 57.0%) are Pharmacopoeial. The components of Opacode Black are IMS 35.075%, shellac 29.925%, Iron oxide black (E172) 25.0%, N-butyl alcohol 8.995%, Soya lecithin 1.000% and Antifoam DC 1510 0.005%. Satisfactory analytical specifications are provided. Certificate of Analysis for Opaspray White and Opacode Black tested by the product manufacturer have been provided.

#### ***Packaging***

The proposed packaging is standard and routinely used in the pharmaceutical industry. Adequate specifications and methods are provided for aluminium, white PVC/Aclar laminate and white PVC/PVdC laminate. Supplier's technical data are also provided and confirm that the materials in contact with the product are food grade and comply with the EU Directive 90/128/EEC.

### **Control Tests on the Finished Product**

#### **Specification**

The following range of test will be performed on the Finished Product: appearance, Infra Red confirmation of Ibuprofen, average mass of tablet, uniformity, disintegration, dissolution, ibuprofen content, impurities and microbiological examination.

#### **Scientific Data**

Satisfactory methodology and validation data are provided for the active and related substances HPLC (same method) and dissolution test UV assay. Satisfactory methodology and validation of microbiological tests are provided.

#### **Batch Data**

Satisfactory batch data has been provided.

**Stability**

Stability testing of the drug substance has been carried out by the drug substance manufacturer and is satisfactory. The finished product was tested under ICH conditions and the following shelf-life and storage conditions accepted.

For PVC/Aclar/Al blister - A shelf life of 36 months and no special storage conditions are proposed.

For PVC/PVdC/Al blister – A shelf life of 36 months. Do not store above 30°C is proposed.

**Bioavailability / Bioequivalence**

The bioequivalence study is reviewed in the Clinical Assessment.

**Product Name and Appearance**

During the procedure the name of the products was changed to Nurofen Maximum Strength Migraine Pain 684mg Caplets (PL 00327/0143) and Nurofen Ultra Strength 684mg Caplets (PL 00327/0144).

**Summary of Product Characteristics**

Minor amendments to the SPC occurred during the application procedure.

**Patient Information leaflet**

The Patient Information is satisfactory and underwent minor changes during the application procedure.

**Labelling**

The Labelling is satisfactory and underwent minor changes during the application procedure.

**Marketing Application Application Form**

Satisfactory

**Conclusion**

All outstanding points were resolved and Market Authorisation was granted on 17<sup>th</sup> January 2006.

# Clinical Assessment

## 1. BACKGROUND

Ibuprofen is one of the most widely used NSAIDs. It was introduced as a prescription drug in 1969 and in 1983 became available as Over the Counter in the UK. The primary biological action of ibuprofen is the inhibition of cyclooxygenase (COX), which is responsible for the synthesis of prostaglandins and other mediators, leading to an antiinflammatory, analgesic and antipyretic effect.

## 2. INDICATIONS

For the relief of mild to moderate pain, such as headache, migraine, dental pain, dysmenorrhoea, rheumatic and muscular pain, backache, neuralgia, sore throat and the pain of non-serious arthritis. For the symptomatic relief of fever, colds and influenza.

## 3. DOSE & DOSE SCHEDULE

For oral administration.

Adults and children over 12 years: Initial dose, one tablet taken with water, then, if necessary, one tablet every four hours. Do not exceed three tablets in any 24 hours. Leave at least 4 hours between doses.

Not recommended for children under 12 years of age.

Elderly: No special dosage modifications are required.

## 4. TOXICOLOGY

No new preclinical data has been submitted or are required for this well established drug.

## 5. CLINICAL PHARMACOLOGY

### 5.1 PHARMACOKINETICS

Ibuprofen is well absorbed from the gastrointestinal tract. Peak plasma concentrations occur 1 - 2 hours after administration of ibuprofen acid. However, ibuprofen is more rapidly absorbed from the gastrointestinal tract following the administration of Ibuprofen Lysine 400 mg Tablets, with peak plasma concentrations occurring approximately 38 minutes after administration.



The drug is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid.

Ibuprofen is metabolised in the liver to two major inactive metabolites and these, together with unchanged ibuprofen, are excreted by the kidney either as such or as conjugates. Excretion by the kidney is both rapid and complete.

The elimination half-life of ibuprofen acid is approximately 2 hours.

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

## 5.2 PHARMACODYNAMICS

Ibuprofen lysine is the lysine salt of ibuprofen, a propionic acid derivative, having analgesic, anti-inflammatory and antipyretic activity. The therapeutic effects of ibuprofen as a non-steroidal anti-inflammatory drug are thought to result from inhibitory activity on prostaglandin synthesis.

Each tablet contains 684 mg of ibuprofen lysine. Following oral administration, ibuprofen lysine dissociates to ibuprofen acid and lysine. Lysine has no recognised pharmacological activity. The pharmacological properties of ibuprofen lysine, therefore, are the same as those of ibuprofen acid.

## 5.3 BIOEQUIVALENCE

### *Study 1*

The pivotal study was conducted in September 1998.

The trial was an open, randomised, single-dose, two-way crossover study in 12 healthy volunteers comparing Ibuprofen lysine 684mg tablets (Lot 86358) and 2x 200mg Nurofen tablets (Lot 31V) marketed in UK.

Blood samples were taken 10, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80 and 90 minutes and 2, 2.5, 3, 4, 6, 8 and 12 hour post-dose. The wash out period of 7 days is accepted (>5x half life of 2h) The sampling span is adequate (Ratio of AUC<sub>0-t</sub> / AUC<sub>0-∞</sub> is 0.96 for both products, i.e. > 0.8%).

The plasma samples were analysed by validated HPLC assay method.

The pharmacokinetic parameters were determined from the log transformed data and are summarised in the table below:

	<b>Ibuprofen 400mg Lysine tablets</b>	<b>Nurofen 2x200mg</b>	<b>Ratio of Ibuprofen Lysine/Nurofen</b>	<b>90% CI</b>
<b>Geometric means</b>				
C <sub>max</sub> (ug/ml)	47.1	38.2	1.23	1.14-1.34
AUC <sub>0-t</sub> (h.ug/ml)	112.6	112.2	1.00	0.96-1.05
AUC <sub>0-∞</sub> (h.ug/ml)	117.0	116.6	1.00	0.96-1.05

Tmax (h)	0.63	1.17	-	-
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The data show that the AUC values are within the EU guideline for bioequivalence (90% confidence interval 80-125% for log transformed data), indicating the extent of absorption from the two products to be equivalent. The rate of absorption is faster for the Ibuprofen 400mg Lysine tablets than from the Nurofen 200mg tablets. The 90% Confidence Interval for Cmax is outside the 80-125% range, indicating non-equivalence for the rate of absorption, with faster Tmax and larger Cmax.

## Study 2

This study was conducted in September 1997.

The trial was an open, randomised, single-dose, three-way crossover study in 24 healthy volunteers comparing 2x200mg Ibuprofen lysine film-coated tablets (Lot 9720B), 2x 200mg Nurofen standard tablets (Lot 9720A) and 2x200mg Dolormin (Ibuprofen lysine) tablets (lot 9720C).

Blood samples were taken 10, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80 and 90 minutes and 2, 2.5, 3, 4, 6, 8 and 12 hour post-dose. The wash out period of 3-7 days is accepted. The sampling span is adequate (Ratio of AUC<sub>0-t</sub> / AUC<sub>0-∞</sub> is 0.96 for both products, i.e. > 0.8%)

The plasma samples were analysed by validated HPLC assay method.

The pharmacokinetic parameters were determined from the log transformed data and are summarised in the table below:

	<b>Dolormin 2x200mg</b>	<b>Ibuprofen Lysine 2X200mg</b>	<b>Nurofen Standard 2x200mg</b>
<b>Geometric means</b>			
Cmax (ug/ml)	48.463	48.483	36.173
AUCT (h.ug/ml)	105.986	104.488	108.56
AUCI (h.ug/ml)	111.188	109.246	114.120
Tmax (h)	0.5	0.583	1.33

Ratio				90% Confidence Interval		
	<b>Dolormin/ Nurofen</b>	<b>Lysine/ Nurofen</b>	<b>Lysine/ Dolormin</b>	<b>Dolormin/ Nurofen</b>	<b>Lysine/ Nurofen</b>	<b>Lysine/ Dolormin</b>
Cmax (ug/ml)	1.33974	1.34028	1.00041	1.24881-1.43728	1.24932-1.43787	0.93251-1.073225
AUCT (h.ug/ml)	0.97629	0.96249	0.98587	0.94116-1.01273	0.92786-0.99842	0.95040-1.02266
AUCI (h.ug/ml)	0.97431	0.95729	0.98253	0.94091-1.00889	0.92448-0.99127	0.94886-1.01741

The data indicate that ibuprofen lysine and Dolormin have similar extents of absorption of ibuprofen as Nurofen, with 90% CI for AUC within the 0.8-1.25 equivalence range defined in the EU guidelines.

The rate of absorption of ibuprofen from ibuprofen lysine and Dolormin was significantly faster than the standard Nurofen, resulting in significantly higher Cmax after ibuprofen Lysine and Dolormin, than the standard Nurofen tablets.

The pharmacokinetic profiles of ibuprofen lysine and Dolormin tablets are similar but different to the standard Nurofen tablets with respect to the rate of absorption. The extent of absorption for all three formulations tested was equivalent.

### **Conclusion**

It is well known that Ibuprofen salts, such as ibuprofen lysine, are more soluble in water and absorption of ibuprofen has been shown to be more rapid following oral administration. The results of the bioequivalence studies are as expected and Ibuprofen Lysine tablets 684 mg were bioequivalent to standard Ibuprofen acid 400mg with regard to extent of absorption. The higher value for C max achieved by Ibuprofen Lysine is still within the therapeutic window for Ibuprofen and is consistent with other formulations of Ibuprofen lysine marketed in the EU, including the UK.

## **6. EFFICACY**

No new efficacy data has been submitted or are required.

## **7. SAFETY**

No new safety data has been submitted or are required.

## **8. SUMMARY OF PRODUCT CHARACTERISTICS**

Amendments to the SPC have been made updating the Administration, Adverse Reactions and other sections. Appropriate changes to reflect the amendments to the SPC were made to the PIL and the labelling.

## **9. MARKETING AUTHORISATION FORM**

This is satisfactory.

## **10. DISCUSSION**

Nurofen Maximum Strength Migraine Pain 684mg Caplets/Nurofen Ultra Strength 684mg Caplets are duplicate standard applications submitted as a line

extension (new strength) of the authorised medicinal product Nurofen Migraine Pain tablets containing 342mg Ibuprofen Lysine.

No new efficacy or safety data have been submitted or are required for these applications. The clinical expert provides a discussion of the results of the bioequivalence data available and considers the applicant's product to be safe and efficacious.

It is well known that Ibuprofen salts, such as ibuprofen lysine, are more soluble in water and absorption of ibuprofen has been shown to be more rapid following oral administration. The results of the bioequivalence studies are as expected and Ibuprofen Lysine tablets 684 mg were bioequivalent to standard Ibuprofen acid 400mg with regard to extent of absorption. The higher value for C max achieved by Ibuprofen Lysine is still within the therapeutic window for Ibuprofen and is consistent with other formulations of Ibuprofen lysine marketed in the EU, including the UK.

## **11 CONCLUSIONS**

Nurofen Maximum Strength Migraine Pain 684mg Caplets/Nurofen Ultra Strength 684mg Caplets were found to have a positive risk/benefit and were granted a Market Authorisation on 17<sup>th</sup> January 2006.

## Steps Taken During Assessment

1	The MHRA received the marketing authorisation applications on 10 <sup>th</sup> March 2003
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 11 <sup>th</sup> April 2003
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 28 <sup>th</sup> May 2004, 7 <sup>th</sup> March 2005 and further information relating to the quality dossiers on 25 <sup>th</sup> June 2003 and 13 <sup>th</sup> December 2004.
4	The applicant responded to the MHRA's requests, providing further information on the clinical dossier on 21 October 2004, 18 <sup>th</sup> April 2005 and 15 <sup>th</sup> June 2005. Additional information on the quality dossier was received on the 14 <sup>th</sup> June 2004, 21 <sup>st</sup> October 2004, 12 <sup>th</sup> December 2004 and again on 15 <sup>th</sup> June 2005.
5	The applications were determined on 17 <sup>th</sup> January 2006.

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE MEDICINAL PRODUCT**

Nurofen Maximum Strength Migraine Pain 684mg Caplets

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Ibuprofen Lysine 684 mg/tablet (equivalent to 400 mg ibuprofen).

For excipients, see 6.1.

### **3. PHARMACEUTICAL FORM**

Coated tablet.

A white, film-coated, capsule-shaped tablet, printed with an identifying logo in black on one face.

## **4. CLINICAL PARTICULARS**

### **4.1. Therapeutic indications**

For the relief of headache and migraine.

### **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 tablet taken with water, then, if necessary, one caplet every four hours. Do not exceed three caplets in any 24 hours. Not for use by children under 12 years of age

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 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 4.6).

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

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

- systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis (see Section 4.8, Unwanted effects)
- gastrointestinal disorders and chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease) (see Section 4.8, Undesirable effects)
- hypertension and/or cardiac impairment as renal function may deteriorate. (see Section 4.3, Contraindications and 4.8, Undesirable effects).
- renal impairment (see Sections 4.3, Contraindications and 4.8, Undesirable effects)
- hepatic dysfunction (see Sections 4.3, Contraindications and 4.8, Undesirable 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.

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.

#### **4.5. Interactions 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. There is limited evidence of enhancement of oral anticoagulant effects.
- 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**

No specific studies have been conducted with ibuprofen lysine.

Whilst no teratogenic effects have been demonstrated with ibuprofen acid in animal experiments, the use of Nurofen Maximum Strength Migraine Pain 684mg Caplets during pregnancy should, if possible, be avoided during the first 6 months of pregnancy. It should not be used for the last trimester of pregnancy 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 duration increased with an increased bleeding tendency in both mother and child. (See Section 4.3 Contraindications).

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 erythema 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 haemorrhage, sometimes fatal, particularly in the elderly (see section 4.4) Exacerbation of ulcerative colitis and Crohn's disease (See section 4.4)
Nervous System	Uncommon:	Headache
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.
Blood	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	Very rare:	severe forms of skin reactions such as erythema multiforme and epidermal necrolysis can occur.
	Uncommon:	Various skin rashes.
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 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 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 lysine is the lysine salt of ibuprofen. 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.

Each tablet contains 684 mg of ibuprofen lysine. Following oral administration, ibuprofen lysine dissociates to ibuprofen acid and lysine. Lysine has no recognised pharmacological activity. The pharmacological properties of ibuprofen lysine, therefore, are the same as those of ibuprofen acid.

#### **5.2. Pharmacokinetic properties**

Most pharmacokinetic data obtained following the administration of ibuprofen acid also apply to ibuprofen lysine.

Ibuprofen is well absorbed from the gastrointestinal tract. Ibuprofen is extensively bound to plasma proteins. Peak serum concentration occurs 1 - 2 hours after administration. However, ibuprofen is more rapidly absorbed from the gastrointestinal tract following the administration of Ibuprofen Lysine 400 mg Tablets, with peak serum concentration occurring approximately 38 minutes after administration.

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 SmPC.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

Povidone, sodium starch glycollate, magnesium stearate, hypromellose, talc, Opaspray White M-1-7111B (contains hypromellose and titanium dioxide (E171)) and Opacode Black S-1-8152HV (contains “black” iron oxide (E172), shellac, soya lecithin and Antifoam DC 1510).

### **6.2. Incompatibilities**

Not applicable.

### **6.3. Shelf life**

36 months.

### **6.4. Special precautions for storage**

Do not store above 30<sup>0</sup>C. Store tablets in the original packaging.

#### **6.5. Nature and contents of container**

Either: -

A blister pack consisting of opaque, white 250 µm polyvinyl chloride (PVC)/23 µm polychlorotrifluoroethylene (Aclar) laminate heat sealed to 20 µm aluminium foil. The blisters are packed in cardboard cartons.

Or: -

**A blister pack consisting of an opaque, white 250 µm polyvinyl chloride (PVC)/40 gsm polyvinylidene chloride (PVdC) laminate heat sealed to 20 µm aluminium foil. The blisters are packed in cardboard cartons.**

Pack sizes: 4, 6, 8,12,16 and 24 tablets.

Not all pack sizes may be marketed.

#### **6.6 Instructions for use and handling and disposal**

Not applicable

#### **7. MARKETING AUTHORISATION HOLDER**

Crookes Healthcare Limited  
1 Thane Road West  
Nottingham NG2 3AA

#### **8. MARKETING AUTHORISATION NUMBER**

PL 00327/0143

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

17/01/2006

**10 DATE OF REVISION OF THE TEXT**

17/01/2006

## **Labeling and Product Information Leaflet**

1) Nurofen Maximum Strength Migraine Pain 684mg Caplets

2) Nurofen Ultra Strength 684mg caplets









N521

