Public Assessment Report

Galprofen Ibuprofen 300mg Long Lasting Capsules

PL 16028/0109

Galpharm Healthcare Limited

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Lay Summary

The MHRA granted Galpharm Healthcare Limited a Marketing Authorisation (Licence) for the medicinal products Galprofen Ibuprofen 300mg Long Lasting Capsules (PL 16028/0109) on 22nd August 2006.

Galprofen Ibuprofen 300mg Long Lasting Capsules contains the active ingredient ibuprofen which is indicated for rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea (period pain), feverishness, symptoms of colds and influenza.

No new or unexpected safety concerns arose from this simple application and it was judged, therefore that the benefits of Galprofen Ibuprofen 300mg Long Lasting Capsules outweigh the risks, hence a Marketing Authorisation was granted.

SCIENTIFIC DISCUSSION

1. INTRODUCTION

This Public Assessment Report is based on the National Assessment Report for the recently granted Market Authorisations for Galprofen Ibuprofen 300mg Long Lasting Capsules (PL 16028/0109). The applicant claims essential similarity, under article 10.1(a)(i), to PL 16028/0092 Galprofen Extra Strength Long Lasting Ibuprofen Capsules, held by the applicant, granted 15th September 2004.

Galprofen Ibuprofen 300mg Long Lasting Capsules contains the active ingredient ibuprofen which is indicated for rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea (period pain), feverishness, symptoms of colds and influenza.

The reference product underwent a COA on 15th September 2004 from PL 10887/0023 Galprofen Ibuprofen Long Lasting Extra Strength Capsules 300mg, owned by Healthy Ideas Ltd (cancelled 15th September 2004). The product's legal status is Pharmacy Only.

The applicant is the same MAH as that for the reference products. Therefore, the applicant will have access to clinical and quality dossiers and no further authorisation was required. Satisfactory expert statements from pre-clinical, clinical and pharmaceutical experts were provided.

2 DRUG SUBSTANCE

The proposed drug substance specification is identical to that approved for the cross reference products. The active substance manufacturers are the same as previously authorised for the cross-referenced product. Certificates of Suitability were included for the different sources of the drug substance.

3. DOSAGE FORM

The qualitative composition of the dosage form is shown in the Table below.

IBUPROFEN
MICROCRYSTALLINE CELLULOSE
EUDRAGIT NE-30D
HYPROMELLOSE
TALC IT EXTRA
COLLOIDAL SILICON DIOXIDE
GELATIN
TITANIUM DIOXIDE E171
PATENT BLUE E131
ERYTHROSINE E127
WATER PURIFIED

The formula, reference to standards and modifiers are in line with reference product. Only gelatine is of animal origin and a satisfactory current TSE certificate is provided. None of the ingredients comes from a genetically modified organism.

3.2 Manufacture

A brief description of the manufacturing method was provided. A statement from the pharmaceutical expert indicates that an identical manufacturing process to that for the cross-reference product is used. Applicant has provided the details for the manufacturing approvals previously granted.

3.3 Container Closure System

The product is in blister packs made of aluminium, polyvinylidene chloride and polyvyinylchloride and comes in pack sizes of 6,12, 18, 24, 28, 36, 48 and 96 capsules.

4.4 Storage Details

Galprofen Ibuprofen 300mg Long Lasting Capsules have a shelf life on 24 months.

5. DATA

5.1 Summary of Product Characteristics

The SPC is essentially similar to the cross reference product with minor changes in line with a recent renewal of the reference product.

5.2 Patient Information Leaflet

Patient information leaflet is near identical to that approved for the cross-reference product with minor changes in line with a recent renewal of the reference product.

5.3 Labels

Labelling is satisfactory.

PRE-CLINICAL ASSESSMENT

No new data were submitted and none are required for an application of this type.

CLINICAL ASSESSMENT

No new data were submitted and none are required for an application of this type.

CONCLUSION

A Marketing Authorisation was granted.

OVERALL CONCLUSION AND RISK/BENEFIT ANALYSIS

Quality

The data for these applications are consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

Preclinical

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

Efficacy

No new efficacy data for were submitted and none are required for this type of application.

Risk Benefit Assessment

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products which, in turn, have been shown to be interchangeable with the innovator products. Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

STEPS TAKEN DURING ASSESSMENT

1	The MHRA received the application on 24th June 2005.
2	Following initial assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 30th September 2005, 30th November 2005, 17th January 2006 and 29th June 2006.
3	The applicant provided further information in regard to the quality assessment on 11th October 2005, 17th January 2006, 13th February 2006 and 21st August 2006.
4	The application was determined on 22nd August 2006.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Galprofen Ibuprofen 300mg Long Lasting Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ibuprofen 300mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Prolonged Release Capsule, Hard.

Blue/Clear capsules containing white coated beads.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea (period pain), feverishness, symptoms of colds and influenza.

4.2. Posology and method of administration

For oral administration and short term use only:

Adults, the elderly and children over 12 years:
The minimum effective dose should be used for the shortest time necessary to relieve symptoms. The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 10 days.

Swallow 300mg – 600mg (1-2 capsules), preferably with water, each morning and evening, as required. Do not take more than 1200mg (4 capsules) in any 24 hour period.

Not to be given to children under 12 years.

4.3. Contraindications

Hypersensitivity to ibuprofen or any of the constituents in the product.

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

Active or previous peptic ulcer.

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

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

Severe hepatic failure, renal failure or heart failure (see section 4.4 Special warnings and precautions for use).

Last trimester of pregnancy (see section 4.6 Pregnancy and lactation).

4.4. Special warnings and precautions for use

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

Undesirable effects may be minimized 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 on 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 corticosteroid, or anticoagulants such as warfarin or anti-platelet agents such as aspirin (see section 4.5 Interactions).

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

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 in the last three months of pregnancy

Talk to a pharmacist or your doctor before taking this product if you
- are aged 75 years or over
- have asthma, liver, heart or kidney problems
- have stomach or bowel disorders
- are in the first 6 months of pregnancy

Do not exceed the stated dose. Keep all medicines out of the reach and sight of children.

If symptoms persist or worsen, consult your doctor or pharmacist.

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

Ibuprofen should not be used in combination with:

Aspirin: Unless low-dose aspirin (not above 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see section 4.3 contraindications).

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

Ibuprofen should be used with caution in combination with:

Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4 special warnings and precautions for use).

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

Corticosteroids: May increase the risk of adverse reactions in the gastrointestinal tract (see section 4.4 special warnings and precautions for use).

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

Methotrexate: There is a potential for an increase in plasma methotrexate.

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

4.6. Pregnancy and lactation

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

During the 3rd trimester, 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).

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

Gastrointestinal Disorders	Uncommon	Abdominal pain, nausea and dyspepsia
	Rare	Diarrhoea, flatulence, constipation and vomiting
	Very rare	Peptic ulcer, perforation or gastrointestinal haemorrhage, sometimes fatal, particularly in the elderly. Exacerbation of ulcerative colitis and Crohn's disease (see section 4.4 special warnings and precautions for use)
Nervous System	Uncommon	Headache
Kidney	Very rare	Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema
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	Uncommon	Various skin rashes.
	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 (see section 4.4 special warnings and precautions for use).
Hypersensitivity reactions	Uncommon	Hypersensitivity reactions with urticaria and pruritus.
	Very rare	Severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock). Exacerbation of asthma and bronchospasm.

4.9. Overdose

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

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, non-steroids, propionic acid derivatives.
ATC code: M01A E01

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.

5.2. Pharmacokinetic properties

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys.

With immediate release formulations of ibuprofen, maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, high peak levels are observed after 1 to 2 hours. These times may vary with different dosage forms. The sustained release product releases drug more slowly, with a lower peak level being reached in plasma about 4 hours after dosage.

The half life of ibuprofen is about 2 hours. For sustained release formulations, the drug concentration in plasma decays more slowly and remains at significant levels 12 hours after dosing. With continuous dosing the peak/trough ratio is markedly less than with immediate release formulations of ibuprofen.

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

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsule contents
Microcrystalline Cellulose
Eudragit NE30D
Hypromellose
Talc
Collodial Anhydrous Silica

Shell
Gelatin
Titanium Dioxide (E171)
Patent Blue V (E13l)
Erythrosine (El27)

6.2. Incompatibilities

None.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5. Nature and contents of container

Blister packs comprised of Al/PVC strips enclosed in an outer carton containing 6, 10, 12, 18, 24, 28, 36, 48, 96 capsules

Blister strips comprising aluminium foil/PVC/PVDC enclosed in a cardboard outer containing 6, 12, 18, 24, 28, 36, 48, 96 capsules.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Galpharm Healthcare Limited
Hugh House
Upper Cliffe Road
Dodworth Business Park
Dodworth
South Yorkshire
S75 3SP

8. MARKETING AUTHORISATION NUMBER(S)

PL 16028/0109

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/08/2006

10 DATE OF REVISION OF THE TEXT

22/08/2006

LABELS AND LEAFLETS

GALPROFEN® IBUPROFEN 300MG LONG LASTING CAPSULES

Read this leaflet carefully because it contains important information for you.
This medicine is available without prescription for you to treat a mild illness without a doctor's help. Nevertheless, you still need to use Galprofen® Ibuprofen 300mg Long Lasting Capsules carefully to get the best results from them.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must see your doctor if your symptoms worsen or do not improve.

In this leaflet:

1. What your medicine is and what it's used for
2. Before you take your medicine
3. How to take your medicine
4. While taking your medicine
5. Storing your medicine

1. WHAT YOUR MEDICINE IS AND WHAT IT'S USED FOR

This pack contains 12 pale blue and clear coloured prolonged release capsules containing 300mg of ibuprofen as the active ingredient. Also contains: microcrystalline cellulose, Eudragit NE 30D, hypromellose, talc and colloidal anhydrous silica. The capsule shell contains gelatin, titanium dioxide (E171), patent blue (E131) and erythrosine (E127).

Product Licence Holder	Manufacturer
Galpharm Healthcare Ltd Upper Cliffe Road Dodworth Business Park Dodworth South Yorkshire S75 3SP	Galpharm International Ltd Upper Cliffe Road Dodworth Business Park Dodworth South Yorkshire S75 3SP

How does your medicine work?
Galprofen® Ibuprofen 300mg Long Lasting Capsules contain ibuprofen, which belongs to a group of medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), which work by changing the body's response to pain, swelling and high temperature. The ibuprofen is released slowly over a 12 hour period from these prolonged release capsules.

What is your medicine for?
For the relief of pain of non-serious arthritic conditions, rheumatic and muscular pain, backache, neuralgia, headache, migraine, dental pain, period pain, feverishness and for relief of the symptoms of colds and flu.

2. BEFORE YOU TAKE YOUR MEDICINE

Do not take Galprofen® Ibuprofen 300mg Long Lasting Capsules 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 (an allergic reaction may be recognised as shortness of breath, runny nose, skin rash or itching)
- are taking other NSAID painkillers, or aspirin with a daily dose above 75mg
- are in the last 3 months of pregnancy

Talk to your doctor or pharmacist before taking if you:
- are aged 75 years or over
- have asthma or have suffered from asthma
- have liver, kidney or heart problems
- have stomach or bowel disorders
- have Systemic Lupus Erythematosus (SLE) – a condition of the immune system affecting connective tissue resulting in joint pains, skin changes and disorders of other organs
- are taking any regular medication, especially:
    - aspirin at low dose (i.e. below 75mg daily)
    - medicines for high blood pressure and water tablets (diuretics)
    - medicines for thinning the blood (anti-coagulants)
    - corticosteroids
    - Methotrexate (an anti-cancer agent)
    - Lithium (used to treat depression)
    - Zidovudine (an anti-viral drug)
- are in the first 6 months of pregnancy or are breastfeeding

Galprofen® Ibuprofen 300mg Long Lasting Capsules belong to a group of medicines, which may impair fertility in women. This is reversible on stopping the medicine. It is unlikely that the capsules, used occasionally, will affect your chances of becoming pregnant. However, tell your doctor before taking this medicine if you have problems becoming pregnant.

3. HOW TO TAKE YOUR MEDICINE

Swallow whole, do not chew. Capsules should be swallowed with a glass of water.

Adults, the elderly and children over 12 years:
1 to 2 capsules to be taken each morning and evening, as required.
Do not exceed 4 capsules in 24 hours.

Do not give to children under 12 years.

4. WHILE TAKING YOUR MEDICINE

The capsules are intended for short-term use only. The lowest effective dose should be used for the shortest time necessary to relieve symptoms. You should consult a doctor or pharmacist if symptoms persist or worsen, or if new symptoms occur. You should not take Galprofen® Ibuprofen 300mg Long Lasting Capsules for longer than 10 days unless your doctor tells you to.

If you take too many capsules by mistake, talk to your doctor or pharmacist as soon as possible. Take with you any remaining capsules and container so that the medicine can be identified.

Possible Side Effects

Galprofen® Ibuprofen 300mg Long Lasting Capsules are generally well tolerated but can have side effects, like all medicines.

Side effects do not occur very often with ibuprofen, but if anything unusual happens talk to your doctor or pharmacist straight away. To reduce the possibility of side effects, especially if you are elderly, you should use the lowest effective dose for the shortest possible time.

Side effects that may occur include:

Stomach and intestine disorders including abdominal discomfort or pain, nausea, indigestion or heartburn, stomach ulcer, vomiting containing blood or dark particles (like coffee grounds), black tarry stools or blood passed in your stools, worsening of existing bowel diseases (ulcerative colitis or Crohn's disease)

Blood disorders which cause unexplained or unusual bruising or bleeding, sore throat, mouth ulcers, fever, extreme pallor/paleness or weakness/exhaustion

Allergic reactions including asthma, worsening of asthma, unexplained wheezing or shortness of breath, swelling of the face, lips, tongue and throat (causing difficulty in swallowing or breathing), rapid heart rate, low blood pressure, collapse. Also, there may be skin reaction (including hives, rash and itching) – very rarely these can be severe with blistering and peeling skin

If you develop any of the symptoms above, at any time while taking your medicine, STOP TAKING and contact your doctor immediately.

Other stomach and intestine effects including diarrhoea, flatulence, constipation and vomiting

Liver disorders that might be indicated by yellowing of the skin and eyes (jaundice) and/or pale coloured stools and dark urine

Kidney disorders that might 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) – very rarely kidney failure

Nervous system disorders including aseptic meningitis, which can include symptoms such as headache, and severe headache, stiff neck, disorientation, fever and eye sensitivity to light in those with existing auto-immune disorders

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

5. STORING YOUR MEDICINE

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

Do not store above 25°C. Store in the original container.

KEEP ALL MEDICINES OUT OF THE REACH & SIGHT OF CHILDREN.

Text prepared: July 2006.


GALPROFEN®
Ibuprofen 300mg Long Lasting Capsules
12 Capsules
Pain relief for up to 12 hours
galpharm
BN:
Exp:
F.P.O: BAR CODE
0000000000000
Prints PMS 2597
PL Holder: Galpharm Healthcare Ltd., South Yorkshire S75 3SP.
PL16028/0109
South Yorkshire S75 3SP
European Patent Number: 0 255 404
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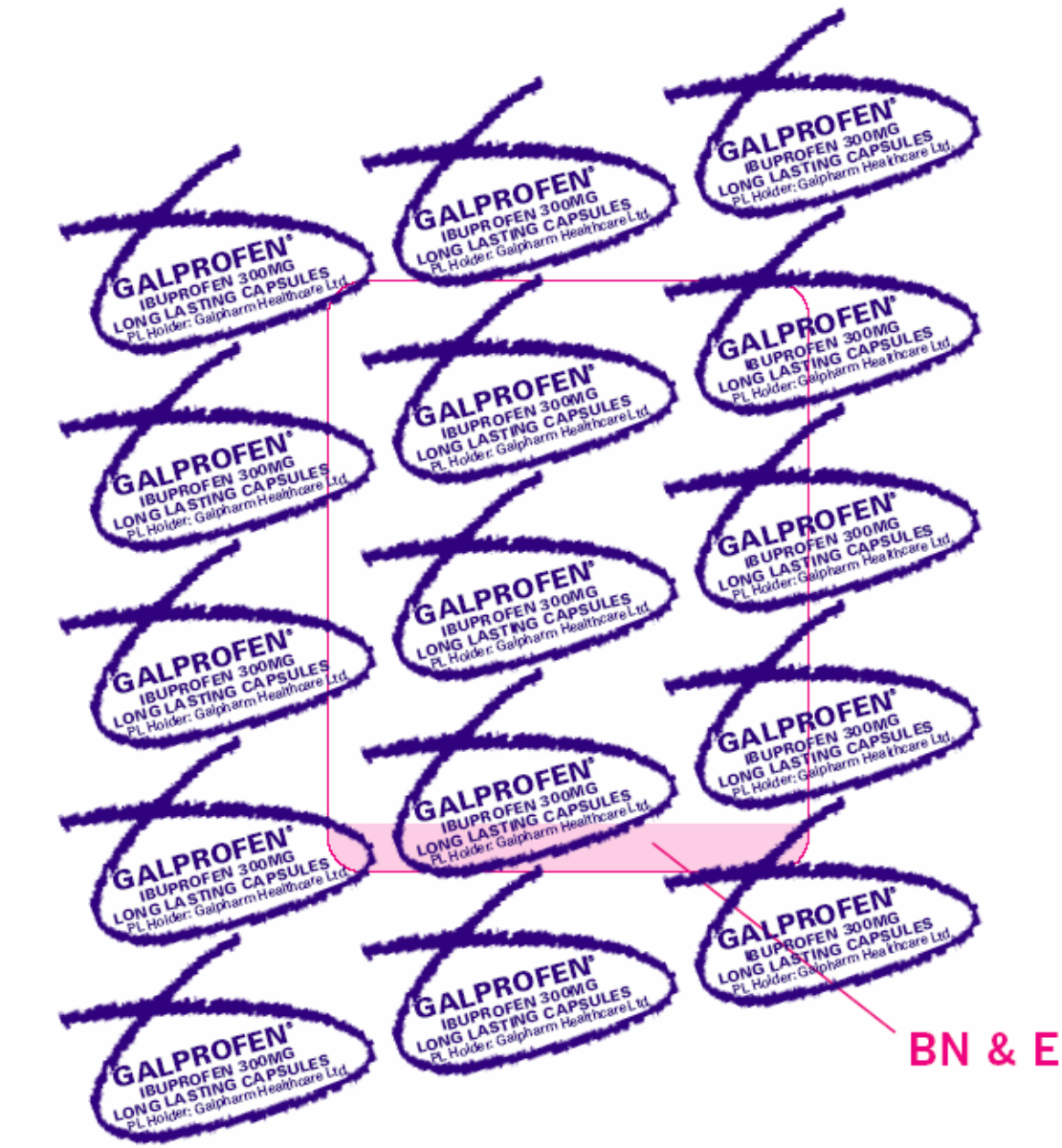
GALPROFEN®
IBUPROFEN 300MG
LONG LASTING CAPSULES
PL Holder: Galpharm Healthcare Ltd.
BN & E