ENTRONAP 250MG GASTRO-RESISTANT TABLETS

PL 08553/0228

ENTRONAP 500MG GASTRO-RESISTANT TABLETS

PL 08553/0229

UKPAR

TABLE OF CONTENTS

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 14
Steps taken after authorisation – summary	Page 15
Summary of Product Characteristics	
Product Information Leaflet	
Labelling	

ENTRONAP 250MG GASTRO-RESISTANT TABLETS

PL 08553/0228

ENTRONAP 500MG GASTRO-RESISTANT TABLETS

PL 08553/0229

LAY SUMMARY

The MHRA granted Dr Reddy's Laboratories (UK) Limited licences for the medicinal products Entronap 250mg and 500mg Gastro-resisitant tablets (PL 08553/0228-9) on 30th May 2007. These are prescription-only medicines (POM).

Entronap Gastro-resistant Tablets contain the active ingredient naproxen, which belongs to a group of medicines called non-steroidal anti-inflammatory agents (NSAIDs). This group of medicines help to relieve pain and joint inflammation.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Entronap 250mg and 500mg gastro-resisitant tablets outweigh the risks, hence Marketing Authorisations have been granted.

ENTRONAP 250MG GASTRO-RESISTANT TABLETS

PL 08553/0228

ENTRONAP 500MG GASTRO-RESISTANT TABLETS

PL 08553/0229

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 8
Clinical assessment (including statistical assessment)	Page 9
Overall conclusions and risk benefit assessment	Page 13

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Entronap 250mg and 500mg Gastro-resistant Tablets to Dr Reddy's Laboratories (UK) Ltd (PL 08553/0228-9) on 30th May 2007. The products are prescription-only medicines.

The applications were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Naprosyn EC 250mg Tablets (PL 00031/0467), which have been authorised to Roche Product Ltd on 31st May 1996.

Naproxen is indicated for the treatment of rheumatoid arthritis, osteoarthrosis (degenerative arthritis), ankylosing spondylitis, juvenile rheumatoid arthritis, acute gout, and acute musculoskeletal disorders (such as sprains, strains, direct trauma, lumbosacral pain, cervical spondylitis, tenosynovitis and fibrositis).

Naproxen has analgesic, anti-inflammatory and antipyretic properties. It is an inhibitor of prostaglandin synthetase. Naproxen is used in rheumatic disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis, in mild to moderate pain such as dysmenorrhoea, migraine, and some musculoskeletal disorders, and in acute gout.

PHARMACEUTICAL ASSESSMENT

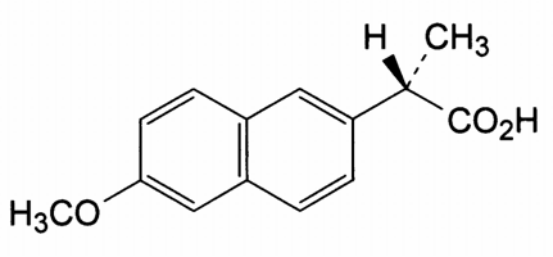
DRUG SUBSTANCE

INN: Naproxen

Chemical Name: (+)-2-(6-Methoxy-2-naphthyl) propionic acid
(S)-2-(6-Methoxynapht-2-yl) propionic acid
(+)-6-Methoxy-□-methyl-2-naphthaleneacetic acid

Molecular Formula: $C_{14}H_{14}O_3$

Chemical Structure:



Molecular Weight: 230.3

Appearance: White or almost white crystalline powder

A valid Certificate of Suitability has been provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

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

Active naproxen is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

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

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 2 years.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of pharmaceutical excipients povidone, colloidal silicon dioxide, microcrystalline cellulose, magnesium state, triethyl citrate, glyceryl monostearate, methacrylic acid copolymer type C, talc, titanium dioxide E171, croscarmellose sodium and water purified.

All excipients have a respective European Pharmacopoeia monograph.

Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph.

Relevant certification on compliance with the requirements in relation to TSE/BSE has been supplied for magnesium stearate and glyceryl monostearate.

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce products with 250mg and 500mg naproxen that are tolerable and can be considered as generic products to the originator products Naprosyn EC tablets.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative *in vitro* dissolution profiles have been generated for the proposed and originator products with satisfactory results. Comparative impurity studies have also been undertaken.

Manufacturing Process

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished Product Specification

The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System

Product is packaged in blisters. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product

Stability studies were performed on pilot-scale batches of all strengths of finished product and all packaging types, in accordance with current guidelines. All results from stability studies on pilot batches were within specified limits. These data support a shelf-life of 4 years, with storage conditions ‘Do not store above 25°C’ and ‘Store in the original package’.

Bioequivalence/bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

CONCLUSION

It is recommended that Marketing Authorisations are granted for these applications.

The proposed products are considered to be generic medicinal products to the reference product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

PRECLINICAL ASSESSMENT

These applications claim to be generic medicinal products of Naprosyn EC 250mg Tablets (Roche Product Ltd).

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

CLINICAL ASSESSMENT

1. INTRODUCTION

These are abridged applications for Marketing Authorisations in the UK submitted under Article 10.1 of Directive 2001/83 (as amended), first paragraph so called generic application.

The original product is Naprocoat 250mg Tablets first authorised on the 14th October 1992 to Roche/Syntex in The Netherlands. The reference medicinal product is listed as Naprosyn EC 250mg Tablets, PL 00031/0467 granted 31st May 1996 which was a change of ownership from PL 00286/0113 granted 12th July 1991. The medicinal product used in bioequivalence was Naprocoat 500 sourced from The Netherlands.

Naproxen is a non-steroidal anti-inflammatory drug (NSAID). It is a non-selective inhibitor of the cyclo-oxygenase enzyme system.

Naproxen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis. It is also used in dysmenorrhoea, headache including migraine, postoperative pain, soft-tissue disorders, acute gout, and to reduce fever. The adverse effects and precautions, for naproxen, are as for any other NSAID in general.

2. INDICATIONS

Naproxen is indicated for the treatment of rheumatoid arthritis, osteoarthrosis (degenerative arthritis), ankylosing spondylitis, juvenile rheumatoid arthritis, acute gout, and acute musculoskeletal disorders (such as sprains, strains, direct trauma, lumbosacral pain, cervical spondylitis, tenosynovitis and fibrositis).

The indications proposed are consistent with that for the originator product and are, therefore, satisfactory.

3. DOSE & DOSE SCHEDULE

Adults:
Rheumatoid arthritis, osteoarthrosis and ankylosing spondylitis: The usual dose is 500 mg to 1 g per day taken in two doses at 12 hour intervals. Where 1 g per day is needed, the suggested regime is 500 mg twice daily.

In the following cases a loading dose of 750 mg or 1 g per day for the acute phase is recommended:
1. In patients reporting severe night-time pain and/or morning stiffness.
2. In patients being switched to naproxen from a high dose of another anti-rheumatic compound.
3. In osteoarthrosis where pain is the predominant symptom.

For the patient who requires 750 mg per day, the size of the morning and evening doses can be adjusted on the basis of the predominant symptoms, i.e. night-time pain or morning stiffness.
Acute gout: The recommended dosage is 750 mg at once, then 250 mg every eight hours until the attack has passed.

Acute musculoskeletal disorders: The recommended dosage is 500 mg initially followed by 250 mg at 6 to 8 hour intervals as needed, with a maximum daily dose after the first day of 1250 mg.

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID (non-steroidal anti-inflammatory drug) is considered necessary, the lowest dose should be used and the patient should be monitored for gastrointestinal bleeding for 4 weeks following initiation of NSAID therapy.

Children: For the treatment of juvenile rheumatoid arthritis in children over five years of age, the usual dosage is 10 mg per kg bodyweight per day taken in two doses at 12 hour intervals.

Method of administration: Oral; the tablets should be swallowed with a drink of water.

The dose and dose schedule proposed are consistent with that for the originator product and are, therefore, satisfactory.

4 CLINICAL PHARMACOLOGY

4.1 PHARMACOKINETICS

Naproxen is fully absorbed when administered orally. The rapidity, but not the extent, of absorption is influenced by the presence of food in the stomach. Peak concentrations in plasma occur within 2 to 4 hours and may be achieved more rapidly after administration of naproxen sodium. Absorption may be accelerated by the concurrent administration of sodium bicarbonate or reduced by magnesium oxide or aluminium hydroxide.

Naproxen and its metabolites are almost entirely excreted in the urine. About 30% of the drug undergoes 6-methylation and most glucuronide or other conjugates. Naproxen is almost completely (99%) bound to plasma protein following normal therapeutic doses. Naproxen crosses the placenta and appears in the milk of lactating women at approximately 1% of the maternal plasma concentration.

4.2 BIOEQUIVALENCE

4.2.1 Study design

Open randomised, two treatments (R and T), two periods, two sequence, crossover steady-state bioavailability study of two 500 mg naproxen gastroresistant formulations in 24 male volunteers. Treatments were separated by a one week washout period.

Results

Results for main pharmacokinetic parameters:

Summary of the bioequivalence analysis for naproxen after single dose administration. Means of log transformed data:

Parent drug: Naproxen

	Test Agent	Reference	Point estimate (90% CI)
C_{max} (ng/mL)	62.8	58.5	1.07 (0.98-1.17)
AUC_t (ng.h/mL)	0.94	0.90	1.04 (1.00-1.08)
$AUC_{\square}$ (ng.h/mL)	1.09	1.06	1.03 (1.00-1.06)
T_{max} (h)	12.0 (5.0-15.0)	12.0 (5.0-24.0)	

Summary of the bioequivalence analysis for naproxen after multiple dose administration. Means of log transformed data:

Parent drug: Naproxen

	Test	Reference	Point estimate (90% CI)
C_{max} (ng/mL)	94.1	94.2	0.99 (0.95-1.04)
AUC_T (ng.h/mL)	0.79	0.81	0.98 (0.94-1.02)
T_{max} (h)	12.0 (0.0-12.0)	5.0 (1.5-12.0)	

The test/reference 90% confidence interval results lay within the acceptance criteria. The acceptance criteria were pre-defined and satisfactory.

PK parameters were in line with published values.

The appearance of individual plasma concentration and time curves are in line with the results.

The validated range of assay is satisfactory.

ASSESSOR'S CONCLUSIONS

Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria and can be approved.

The multiple dose waiver criteria are met and hence this study is accepted as demonstrating bioequivalence for the other product strength.

4.2.2 Assessor's Conclusion on Bioequivalence

The data support bioequivalence for the test drug and the reference. This is consistent with the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98). Since naproxen pharmacokinetics seems to be linear up to 500 mg, this bioequivalence study is acceptable for both strengths: 500 mg and 250 mg.

4.2.3 PHARMACODYNAMICS

Naproxen has analgesic, anti-inflammatory and antipyretic properties. It is an inhibitor of prostaglandin synthetase. Naproxen is used in rheumatic disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis, in mild to moderate pain such as dysmenorrhoea, migraine, and some musculoskeletal disorders, and in acute gout

5. EFFICACY
No new data are submitted and none are required for this type of application.

6. SAFETY
No new data on the safety of entronap are submitted and none are required for this type of application.

7. EXPERT REPORTS
A clinical expert report is provided, written by an appropriately qualified medical doctor. It is satisfactory.

8. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPCs are consistent with the approved SPCs of the reference product and are satisfactory.

9. PATIENT INFORMATION LEAFLET (PIL)
The PIL has been provided and is consistent with the SPC.

10. LABELLING
Labelling has been provided and these are satisfactory.

11. APPLICATION FORM (MAA)
The MAA form is satisfactory.

12. DISCUSSION
Bioequivalence has been satisfactorily demonstrated for the 500mg product in accordance with CPMP criteria. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500mg strength can be extrapolated to the other strength tablet.

The SPC, PIL and Labelling are consistent with those approved in the UK for the originator product and are satisfactory.

13. MEDICAL CONCLUSION
Marketing authorisations may be granted for these products.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Entronap 250mg and 500mg Tablets 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 were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Entronap 500mg tablets and Naprocoat 500mg Tablets. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500mg strength can be extrapolated to the other strength tablet.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with naproxen is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

ENTRONAP 250MG GASTRO-RESISTANT TABLETS

PL 08553/0228

ENTRONAP 500MG GASTRO-RESISTANT TABLETS

PL 08553/0229

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 14th October 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 27th October 2004
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 22nd June 2005, and 25th November 2005 and on clinical dossier 2nd February 2006
4	The applicant responded to the MHRA's requests, providing further information on the quality dossiers on 23rd November 2005, and 22nd October 2006 and on clinical dossier 27th April 2007
5	The applications were determined on 30th May 2007

ENTRONAP 250MG GASTRO-RESISTANT TABLETS

PL 08553/0228

ENTRONAP 500MG GASTRO-RESISTANT TABLETS

PL 08553/0229

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Entronap 250mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 250 mg Naproxen.

For excipients see 6.1

3 PHARMACEUTICAL FORM
Gastro-resistant tablet.

Round, biconvex tablets with a smooth surface.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Naproxen is indicated for the treatment of rheumatoid arthritis, osteoarthrosis (degenerative arthritis), ankylosing spondylitis, juvenile rheumatoid arthritis, acute gout, and acute musculoskeletal disorders (such as sprains, strains, direct trauma, lumbosacral pain, cervical spondylitis, tenosynovitis and fibrositis).

4.2 Posology and method of administration
Adults:

Rheumatoid arthritis, osteoarthrosis and ankylosing spondylitis: The usual dose is 500 mg to 1 g per day taken in two doses at 12 hour intervals. Where 1 g per day is needed, the suggested regime is 500 mg twice daily.

In the following cases a loading dose of 750 mg or 1 g per day for the acute phase is recommended:

1. In patients reporting severe night-time pain and/or morning stiffness.

2. In patients being switched to naproxen from a high dose of another anti-rheumatic compound.

3. In osteoarthrosis where pain is the predominant symptom.

For the patient who requires 750 mg per day, the size of the morning and evening doses can be adjusted on the basis of the predominant symptoms, i.e. night-time pain or morning stiffness.

Acute gout: The recommended dosage is 750 mg at once, then 250 mg every eight hours until the attack has passed.

Acute musculoskeletal disorders: The recommended dosage is 500 mg initially followed by 250 mg at 6 to 8 hour intervals as needed, with a maximum daily dose after the first day of 1250 mg.

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID (non-steroidal anti-inflammatory drug) is considered necessary, the lowest dose should be used and the patient should be monitored for gastrointestinal bleeding for 4 weeks following initiation of NSAID therapy.

Children: For the treatment of juvenile rheumatoid arthritis in children over five years of age, the usual dosage is 10 mg per kg bodyweight per day taken in two doses at 12 hour intervals.

Method of administration: Oral; the tablets should be swallowed with a drink of water.

4.3 Contraindications

A history of, or active, peptic ulceration. Hypersensitivity to naproxen or naproxen sodium formulations. Since the potential exists for cross-sensitivity reactions, naproxen should not be given to patients in whom aspirin or other non-steroidal anti-inflammatory/analgesic drugs induce asthma, rhinitis or urticaria.

4.4 Special warnings and precautions for use

Episodes of gastrointestinal bleeding have been reported in patients on naproxen therapy. Naproxen should be given under close supervision to patients with a history of gastrointestinal disease.

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

Sporadic abnormalities in laboratory tests (e.g. liver function tests) have occurred in patients on naproxen therapy, but no definite trend was seen in any test indicating toxicity.

Naproxen decreases platelet aggregration and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

Mild peripheral oedema has been observed in a few patients receiving naproxen. Although sodium retention has not been reported in metabolic studies, it is possible that patients with questionable or compromised cardiac function may be at a greater risk when taking naproxen.

Caution is required in patients with renal, hepatic or cardiac impairment since the use of NSAIDs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored. NSAIDs should be given with care to patients with a history of heart failure or hypertension.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the high plasma protein binding of naproxen, patients simultaneously receiving hydantoins, anticoagulants or a highly protein-bound sulphonamide should be observed for signs of overdosage of these drugs. No interactions have been observed in clinical studies with naproxen and anticoagulants or sulphonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

The natriuretic effect of frusemide has been reported to be inhibited by some drugs of this class.

Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported.

Naproxen and other non-steroidal anti-inflammatory drugs can reduce the anti-hypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen plasma levels and extends its plasma half-life considerably.

Caution is advised where methotrexate is administered concurrently because of possible enhancement of its toxicity, since naproxen, among other non-steroidal anti-inflammatory drugs, decreases the elimination of methotrexate.

It is suggested that naproxen therapy be temporarily discontinued 48 hours before adrenal function tests are performed because naproxen may artifactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen may interfere with some assays of urinary 5-hydroxy-indoleacetic

acid.

The concomitant use of cyclosporin may lead to an increased risk of nephrotoxicity.

Naproxen should not be used for 8 to 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

There is an increased risk of gastrointestinal bleeding if corticosteroids are used concomitantly.

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking naproxen and quinolones may have an increased risk of developing convulsions.

The concomitant use of two or more NSAIDs should be avoided.

4.6 Pregnancy and lactation

Teratology studies in rats and rabbits, at dose levels equivalent on a human multiple basis to those which have produced foetal abnormality with certain other non-steroidal anti-inflammatory agents, e.g. aspirin, have not produced evidence of foetal damage with naproxen. As with other drugs of this type, naproxen delays parturition in animals (the relevance of this finding to human patients is unknown) and also affects the human foetal cardiovascular system (closure of the ductus arteriosus). Good medical practice indicates minimal drug usage in pregnancy, and use of this class of therapeutic agent requires cautious balancing of possible benefit against potential risk to the mother and foetus especially in the first and third trimesters.

The use of naproxen should be avoided in patients who are breast feeding.

4.7 Effects on ability to drive and use machines

No adverse effects known.

4.8 Undesirable effects

Gastrointestinal: The more frequent reactions are nausea, vomiting, diarrhoea, dyspepsia, abdominal discomfort, melaena, haematemesis, ulcerative stomatitis and gastrointestinal haemorrhage. More serious

reactions which may occur occasionally are gastritis, duodenal ulcer, gastric ulcer and gastrointestinal perforation.

Dermatological/hypersensitivity: Skin rashes, urticaria, pruritis, angio-oedema, purpura, anaphylactic reactions, eosinophilic pneumonitis, alopecia, erythema multiforme. Stevens-Johnson syndrome, epidermal necrolysis and photosensitive dermatitis may occur rarely. Asthma, bronchospasm and dyspnoea have been reported.

CNS: Headache, insomnia, inability to concentrate and cognitive dysfunction have been reported.

Haematological: Thrombocytopenia, neutropenia, granulocytopenia, aplastic anaemia and haemolytic anaemia may occur rarely.

Cardiovascular: Oedema has been reported.

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

Hepatic: Abnormal liver function, hepatitis and jaundice.

Neurlogical and special senses: Visual disturbances, optic neuritis, headaches, paraesthesia, depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Other: Mild peripheral oedema, haematuria and vasculitis and have been reported rarely.

4.9 Overdose

Significant overdosage of the drug may be characterised by drowsiness, heartburn, indigestion, nausea or vomiting. No evidence of toxicity or late sequelae have been reported 5 to 15 months after ingestion, for three to seven days, of doses of up to 3 g per day. One patient ingested a single dose of 25 g of naproxen and experienced mild nausea and indigestion. It is not known what dose of the drug would be life-threatening.

Should a patient ingest a large amount of naproxen accidentally or purposefully, the stomach may be emptied and the usual supportive measures employed. Animal studies indicate that the prompt administration of activated charcoal in adequate amounts would tend to reduce markedly the absorption of the drug.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. However, haemodialysis may still be appropriate in a patient with renal failure who has taken naproxen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: M01A E02

Naproxen has analgesic, anti-inflammatory and antipyretic properties. It is an inhibitor of prostaglandin synthetase. Naproxen is used in rheumatic disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis, in mild to moderate pain such as dysmenorrhoea, migraine, and some musculoskeletal disorders, and in acute gout.

5.2 Pharmacokinetic properties

Naproxen is fully absorbed when administered orally. The rapidity, but not the extent, of absorption is influenced by the presence of food in the stomach. Peak concentrations in plasma occur within 2 to 4 hours and may be achieved more rapidly after administration of naproxen sodium. Absorption may be accelerated by the concurrent administration

of sodium bicarbonate or reduced by magnesium oxide or aluminium hydroxide.

Naproxen and its metabolites are almost entirely excreted in the urine. About 30% of the drug undergoes 6-methylation and most glucuronide or other conjugates. Naproxen is almost completely (99%) bound to plasma protein following normal therapeutic doses. Naproxen crosses the placenta and appears in the milk of lactating women at approximately 1% of the maternal plasma concentration.

5.3 Preclinical safety data
Not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:

Polyvidone

Colloidal Silicon Dioxide

Microcrystalline Cellulose

Croscarmellose sodium

Magnesium stearate

Tablet coating:

Triethyl citrate

Glyceryl monostearate

Methacrylic acid Copolymer

Type C

Talc

Titanium dioxide E171

6.2 Incompatibilities
None known.

6.3 Shelf life
4 years.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Blister packs: 56 tablets

6.6 Special precautions for disposal
None stated.

7 MARKETING AUTHORISATION HOLDER
Dr Reddy's Laboratories (UK) Ltd,

6 Riverview Road,

Beverley,

East Yorkshire,

HU17 0LD, UK.

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0228

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/05/2007

10 DATE OF REVISION OF THE TEXT
30/05/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Entronap 500mg Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg Naproxen.

For excipients see 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

Rectangular, biconvex tablets with a smooth surface.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Naproxen is indicated for the treatment of rheumatoid arthritis, osteoarthrosis (degenerative arthritis), ankylosing spondylitis, juvenile rheumatoid arthritis, acute gout, and acute musculoskeletal disorders (such as sprains, strains, direct trauma, lumbosacral pain, cervical spondylitis, tenosynovitis and fibrositis).

4.2 Posology and method of administration

Adults:

Rheumatoid arthritis, osteoarthrosis and ankylosing spondylitis: The usual dose is 500 mg to 1 g per day taken in two doses at 12 hour intervals. Where 1 g per day is needed, the suggested regime is 500 mg twice daily.

In the following cases a loading dose of 750 mg or 1 g per day for the acute phase is recommended:

1. In patients reporting severe night-time pain and/or morning stiffness.

2. In patients being switched to naproxen from a high dose of another anti-rheumatic compound.

3. In osteoarthrosis where pain is the predominant symptom.

For the patient who requires 750 mg per day, the size of the morning and evening doses can be adjusted on the basis of the predominant symptoms, i.e. night-time pain or morning stiffness.

Acute gout: The recommended dosage is 750 mg at once, then 250 mg every eight hours until the attack has passed.

Acute musculoskeletal disorders: The recommended dosage is 500 mg initially followed by 250 mg at 6 to 8 hour intervals as needed, with a maximum daily dose after the first day of 1250 mg.

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID (non-steroidal anti-inflammatory drug) is considered necessary, the lowest dose should be used and the patient should be monitored for gastrointestinal bleeding for 4 weeks following initiation of NSAID therapy.

Children: For the treatment of juvenile rheumatoid arthritis in children over five years of age, the usual dosage is 10 mg per kg bodyweight per day taken in two doses at 12 hour intervals.

Method of administration: Oral; the tablets should be swallowed with a drink of water.

4.3 Contraindications

A history of or active, peptic ulceration. Hypersensitivity to naproxen or naproxen sodium formulations. Since the potential exists for cross-sensitivity reactions, naproxen should not be given to patients in whom aspirin or other non-steroidal anti-inflammatory/analgesic drugs induce asthma, rhinitis or urticaria.

4.4 Special warnings and precautions for use

Episodes of gastrointestinal bleeding have been reported in patients on naproxen therapy. Naproxen should be given under close supervision to patients with a history of gastrointestinal disease.

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

Sporadic abnormalities in laboratory tests (e.g. liver function tests) have occurred in patients on naproxen therapy, but no definite trend was seen in any test indicating toxicity.

Naproxen decreases platelet aggregration and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

Mild peripheral oedema has been observed in a few patients receiving naproxen. Although sodium retention has not been reported in metabolic studies, it is possible that patients with questionable or compromised cardiac function may be at a greater risk when taking naproxen.

Caution is required in patients with renal, hepatic or cardiac impairment since the use of NSAIDs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored. NSAIDs should be given with care to patients with a history of heart failure or hypertension.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the high plasma protein binding of naproxen, patients simultaneously receiving hydantoins, anticoagulants or a highly protein-bound sulphonamide should be observed for signs of overdosage of these drugs. No interactions have been observed in clinical studies with naproxen and anticoagulants or sulphonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

The natriuretic effect of frusemide has been reported to be inhibited by some drugs of this class.

Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported.

Naproxen and other non-steroidal anti-inflammatory drugs can reduce the anti-hypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen plasma levels and extends its plasma half-life considerably.

Caution is advised where methotrexate is administered concurrently because of possible enhancement of its toxicity, since naproxen, among other non-steroidal anti-inflammatory drugs, decreases the elimination of methotrexate.

It is suggested that naproxen therapy be temporarily discontinued 48 hours before adrenal function tests are performed because naproxen may artifactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen may interfere with some assays of urinary 5-hydroxy-indoleacetic

acid.

The concomitant use of cyclosporin may lead to an increased risk of nephrotoxicity.

Naproxen should not be used for 8 to 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

There is an increased risk of gastrointestinal bleeding if corticosteroids are used concomitantly.

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking naproxen and quinolones may have an increased risk of developing convulsions.

The concomitant use of two or more NSAIDs should be avoided.

4.6 Pregnancy and lactation

Teratology studies in rats and rabbits, at dose levels equivalent on a human multiple basis to those which have produced foetal abnormality with certain other non-steroidal anti-inflammatory agents, e.g. aspirin, have not produced evidence of foetal damage with naproxen. As with other drugs of this type, naproxen delays parturition in animals (the relevance of this finding to human patients is unknown) and also affects the human foetal cardiovascular system (closure of the ductus arteriosus). Good medical practice indicates minimal drug usage in pregnancy, and use of this class of therapeutic agent requires cautious balancing of possible benefit against potential risk to the mother and foetus especially in the first and third trimesters.

The use of naproxen should be avoided in patients who are breast feeding.

4.7 Effects on ability to drive and use machines

No adverse effects known.

4.8 Undesirable effects

Gastrointestinal: The more frequent reactions are nausea, vomiting, diarrhoea, dyspepsia, abdominal discomfort, melaena, haematemesis, ulcerative stomatitis and gastrointestinal haemorrhage. More serious reactions which may occur occasionally are gastritis, duodenal ulcer, gastric ulcer and gastrointestinal perforation.

Dermatological/hypersensitivity: Skin rashes, urticaria, pruritis, angio-oedema, purpura, anaphylactic reactions, eosinophilic pneumonitis, alopecia, erythema multiforme. Stevens-Johnson syndrome, epidermal necrolysis and photosensitive dermatitis may occur rarely. Asthma, bronchospasm and dyspnoea have been reported.

CNS: Headache, insomnia, inability to concentrate and cognitive dysfunction have been reported.

Haematological: Thrombocytopenia, neutropenia, granulocytopenia, aplastic anaemia and haemolytic anaemia may occur rarely.

Cardiovascular: Oedema has been reported.

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

Hepatic: Abnormal liver function, hepatitis and jaundice.

Neurlogical and special senses: Visual disturbances, optic neuritis, headaches, paraesthesia, depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Other: Mild peripheral oedema, haematuria and vasculitis and have been reported rarely.

4.9 Overdose

Significant overdosage of the drug may be characterised by drowsiness, heartburn, indigestion, nausea or vomiting. No evidence of toxicity or late sequelae have been reported 5 to 15 months after ingestion, for three to seven days, of doses of up to 3 g per day. One patient ingested a single dose of 25 g of naproxen and experienced mild nausea and indigestion. It is not known what dose of the drug would be life-threatening.

Should a patient ingest a large amount of naproxen accidentally or purposefully, the stomach may be emptied and the usual supportive measures employed. Animal studies indicate that the prompt administration of activated charcoal in adequate amounts would tend to reduce markedly the absorption of the drug.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. However, haemodialysis may still be appropriate in a patient with renal failure who has taken naproxen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: M01A E02

Naproxen has analgesic, anti-inflammatory and antipyretic properties. It is an inhibitor of prostaglandin synthetase. Naproxen is used in rheumatic disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis, in mild to moderate pain such as dysmenorrhoea, migraine, and some musculoskeletal disorders, and in acute gout.

5.2 Pharmacokinetic properties

Naproxen is fully absorbed when administered orally. The rapidity, but not the extent, of absorption is influenced by the presence of food in the stomach. Peak concentrations in plasma occur within 2 to 4 hours and may be achieved more rapidly after administration of naproxen sodium. Absorption may be accelerated by the concurrent administration of sodium bicarbonate or reduced by magnesium oxide or aluminium hydroxide.

Naproxen and its metabolites are almost entirely excreted in the urine. About 30% of the drug undergoes 6-methylation and most glucuronide or other conjugates. Naproxen is almost completely (99%) bound to plasma protein following normal therapeutic doses. Naproxen crosses the placenta and appears in the milk of lactating women at approximately 1% of the maternal plasma concentration.

5.3 Preclinical safety data
Not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core

Polyvidone

Colloidal Silicon Dioxide

Microcrystalline Cellulose

Croscarmellose sodium

Magnesium stearate.

Tablet coating

Triethyl citrate

Glyceryl monostearate

Methacrylic acid Copolymer Type C

Talc

Titanium dioxide E171.

6.2 Incompatibilities
None known.

6.3 Shelf life
4 years.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Blister packs: 56 tablets6

6.6 Special precautions for disposal
None stated.

7 MARKETING AUTHORISATION HOLDER

Dr Reddy's Laboratories (UK) Ltd,
6 Riverview Road,
Beverley,
East Yorkshire,
HU17 0LD, UK.

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0229

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/05/2007

10 DATE OF REVISION OF THE TEXT
30/05/2007

PATIENT INFORMATION LEAFLET

Entronap 250mg & 500mg Gastro-resistant Tablets
NAPROXEN
Patient Information Leaflet

Please read this leaflet carefully before you start to take your medicine. Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or your pharmacist. This medicine has been prescribed for you personally and you should not pass it onto others. It may harm them, even if their symptoms are the same as yours.

What are Entronap Gastro-resistant Tablets?
Entronap Gastro-resistant Tablets contain the active ingredient Naproxen, which belongs to a group of medicines called non-steroidal anti-inflammatory agents (NSAIDs). This group of medicines help to relieve pain and joint inflammation.

Entronap Gastro-resistant Tablets are available in two strengths. The 250mg tablets contain 250mg of Naproxen and the 500mg tablets contain 500mg of Naproxen. Your tablets also contain the inactive ingredients: Tablet core: polyvidone, collodial silicon dioxide, microcrystalline cellulose, croscarmellose sodium, magnesium stearate. Tablet coating: triethyl citrate, glycerol monostearate, methacrylic acid copolymer type C, talc and titanium dioxide E171

The 250mg tablets are round, biconvex tablets with a smooth surface and the 500mg tablets are rectangular, biconvex tablets also with a smooth surface. Both strengths are available in blister packs of 56 tablets.

The Marketing Authorisation Holder is:
Dr Reddy's Laboratories (UK) Ltd,
6 Riverview Road,
Beverley,
East Yorkshire,
HU17 0LD, UK.

What are Entronap Gastro-resistant Tablets used for?
Entronap Gastro-resistant Tablets can be used to treat the following:
- Rheumatic arthritis,
- osteoarthritis,
- ankylosing spondylitis (causing pain and stiffness in the back),
- back pain,
- neck pain,
- swollen or painful tendons.

When should Entronap Gastro-resistant Tablets not be used?
You should not use Entronap Gastro-resistant Tablets:
- If you are allergic to Entronap Gastro-resistant Tablets or any of the ingredients it contains.
- If you have a stomach ulcer, or bleeding of the stomach or intestine.
- If you have had wheeziness (asthma), hay fever, itchiness or skin rash (urticaria) after taking aspirin or other non-steroidal anti-inflammatory drugs.

When should you be extra careful while taking Entronap Gastro-resistant Tablets?
Make sure your doctor knows if you:
- Suffer from stomach problems, it is known that bleeding in the stomach or gut can occur in patients taking Entronap Gastro-resistant Tablets. If you find you have black, tarry stools while taking this medicine you must stop taking it and tell your doctor at once.
- Have asthma, hay fever or allergies as these tablets can cause breathing difficulties (bronchospasm).
- Have ever suffered any allergic reactions after taking aspirin or other NSAIDs or if you have a history of swelling of the tongue or larynx (angioedema), asthma, inflammation of the nose (rhinitis), or nasal polyps.
- Are having liver or adrenal function tests as taking these tablets can change the results.
- Suffer from any blood clotting disorders or are taking anti-coagulant therapy (blood thinning medicines), e.g. heparin or warfarin, as Entronap Gastro-resistant Tablets decrease the ability of your bloody to clot and will increase the time you bleed if you get a cut.
- Have heart problems. Occasionally patients have reported swollen hands or feet whilst taking this medicine and this is more likely in patients who have heart problems.
- Have kidney problems. Your doctor may wish to check your kidney function before and during treatment and/or use a dose lower than normal.
- Have liver problems, including alcohol-related disease or other forms of cirrhosis of the liver, as you should then take the lowest dose needed.
- Are taking other medicines, including any you have bought without a prescription. This is important because Entronap Gastro-resistant Tablets could alter how other medicines work. These include medicines for epilepsy (hydantoins), blood clots (anti-coagulants), infections (sulphonamides or quinolone antibiotics), heart failure (frusemide or cardiac glycosides such as digoxin), depression (lithium), high blood pressure (propranolol and other beta-blockers, ACE inhibitors e.g. cilazapril), gout (probenecid) and psoriasis (methotrexate), arthritis (steroids), other non-steroidal anti inflammatory drugs (such as aspirin), acute organ rejection (cyclosporin) or a drug, usually prescribed though hospitals, called mifepristone.

Can Entronap Gastro-resistant Tablets be taken throughout pregnancy?
You must tell your doctor if you are pregnant, if you think you might be pregnant or if you intend to become pregnant. Your doctor will then discuss this with you and decide whether you should take this medicine. If you are breast feeding do not take this medicine.

How should Entronap Gastro-resistant Tablets be taken?
Tablets to be taken orally.
- Always take your medicine as your doctor tells you to.
- If you take too much medicine or someone else accidentally takes your medicine, contact your doctor, pharmacist or nearest hospital straight away.

The dosage you should take depends on the type of pain you have. Your doctor will have told you how much medicine to take each day.
Read the following section carefully. It tells you how this medicine is usually taken. If you are not sure, ask your doctor or pharmacist. Do not take more medicine than you are told to, as this increases the possibility of side-effects (especially in the elderly).

For normal use: Take between 500mg and 1g each day in two separate doses, 12 hours apart. Where 1g is needed, you can take 500mg twice each day, or 1g in one single dose (morning or evening).
For gout: Take 750mg as your very first dose, then 250mg every 8 hours until the attack has passed.
For painful periods, acute muscle/joint problems: Take 500mg to start with, then 250mg every 6 to 8 hours as needed, up to a maximum 1250mg per day.
For juvenile rheumatoid arthritis in children over 5 years of age: A dose of 10mg per kg body weight should be given each day. This should be taken in two separate doses, 12 hours apart.
For the Elderly: If you are over 65 years of age, you may be given a lower dose of medicine to start with.

When and how does the treatment with Entronap Gastro-resistant Tablets end?
Your doctor will advise you when to stop taking the medicine.

What are the possible unwanted effects of Entronap Gastro-resistant Tablets?
In addition to the beneficial effects of Entronap Gastro-resistant Tablets, it is possible that unwanted effects will occur during treatment, even when it is used as directed by your doctor.

Tell your doctor if you have any of the following problems which do not go away: nausea, vomiting, stomach discomfort or heartburn.

Some symptoms are more serious. If you have any of the following problems, stop taking your tablets and talk to your doctor urgently: passing of black, tarry stools or blood, mouth or stomach ulcers, severe diarrhoea and lower abdominal pain (colitis).
Other problems include:

Allergies: Symptoms of allergic reactions to Entronap Gastro-resistant Tablets.
Skin: Skin rash, itchiness (urticaria), swelling of the neck and face (angioedema), redness of the skin (erythema multiforme), blistering of hands or feet (Stevens Johnson Syndrome), peeling skin (epidermal necrolysis), rare skin reactions due to exposure to light (pseudoporphyria or epidermolysis bullosa), swelling of the hands and feet (peripheral oedema) or yellow skin (jaundice).
Hair: Loss of hair (alopecia).
Liver: Inflammation of the liver (hepatitis).
Kidney: Inflammation of the kidney (glomerular or interstitial nephritis), protein in the urine (nephrotic syndrome), blood in urine (haematuria), death of part of the tissue of your kidney's (renal papillary necrosis) or kidney failure.
Lungs: Inflammation of the lung (eosinophilic pneumonitis).
Head: Convulsions, headache, inability to sleep (insomnia), inability to concentrate or remember things (cognitive dysfunction), ringing or buzzing in the ears (tinnitus), problems with hearing, dizziness (vertigo) or ulcers or inflammation in the inside of the mouth (ulcerative stomatitis) or non-infectious inflammation of the membranes of the brain (aseptic meningitis).
Blood: A reduction in the number of platelets (clotting blood cells), or white blood cells, a reduction of the oxygen-carrying pigment haemoglobin in the blood (anaemia) caused by decreased production (aplasia) or increased destruction (haemolysis) of red blood cells, high levels of potassium in the blood or inflammation of blood vessels.
Eyes: Visual disturbances or problems with sight. If you do develop any visual disturbances during treatment, then you should talk to your doctor who may arrange for you to have an eye examination.

If you are concerned about these or any other unwanted effects talk to your doctor.

How should Entronap Gastro-resistant Tablets be stored?
- Keep this medicine out of the reach and sight of children.
- Do not store above 25°C. Store in the original package (to protect the product from light)
- This medicine must not be used after the date (EXP) printed on the pack. Return any left over medicine to your pharmacist. Only keep it if your doctor tells you to.

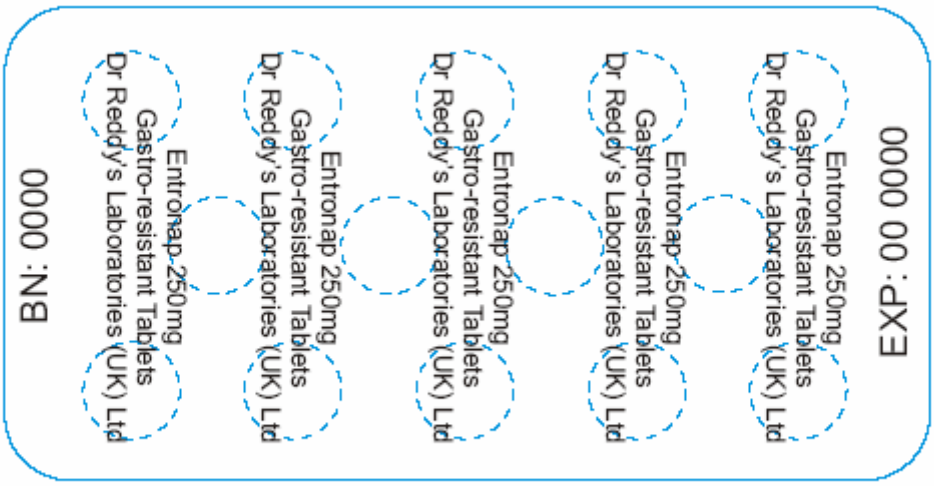
Remember this medicine is for you. Only a doctor can prescribe it for you. Never give it to others. It may harm them even if their symptoms are the same as yours.

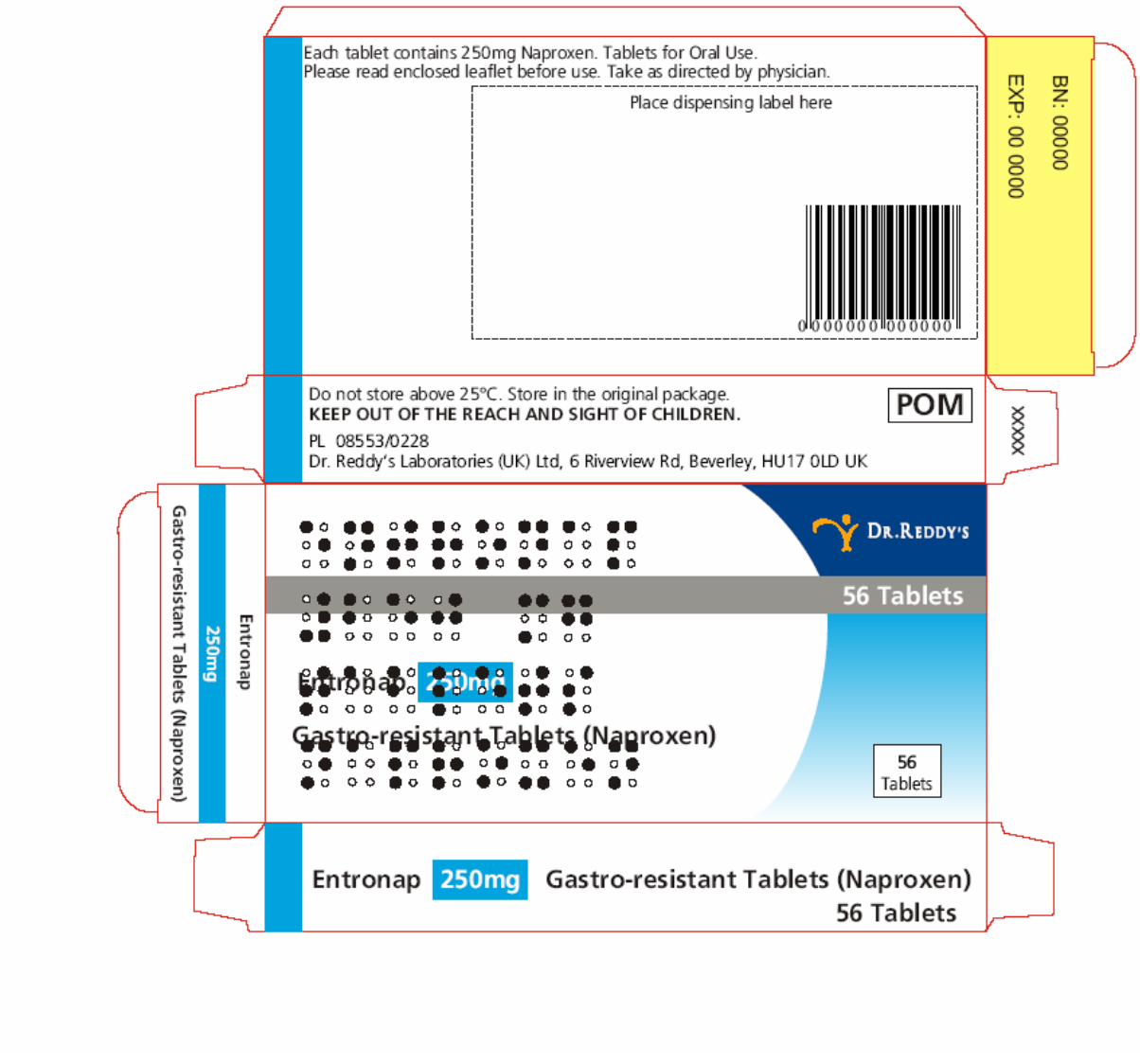
Further information:
You can get more information on Entronap Gastro-resistant Tablets from your doctor or pharmacist.

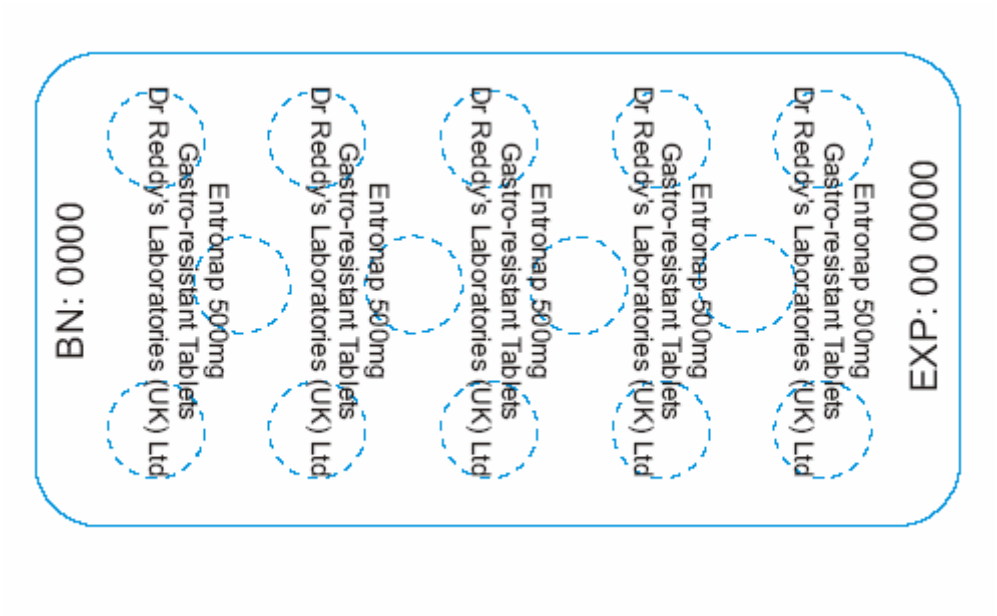
Date of Preparation: 04/10/2006
Entronap 250mg Tablets, PL 08553/0228
Entronap 500mg Tablets, PL 08553/0229

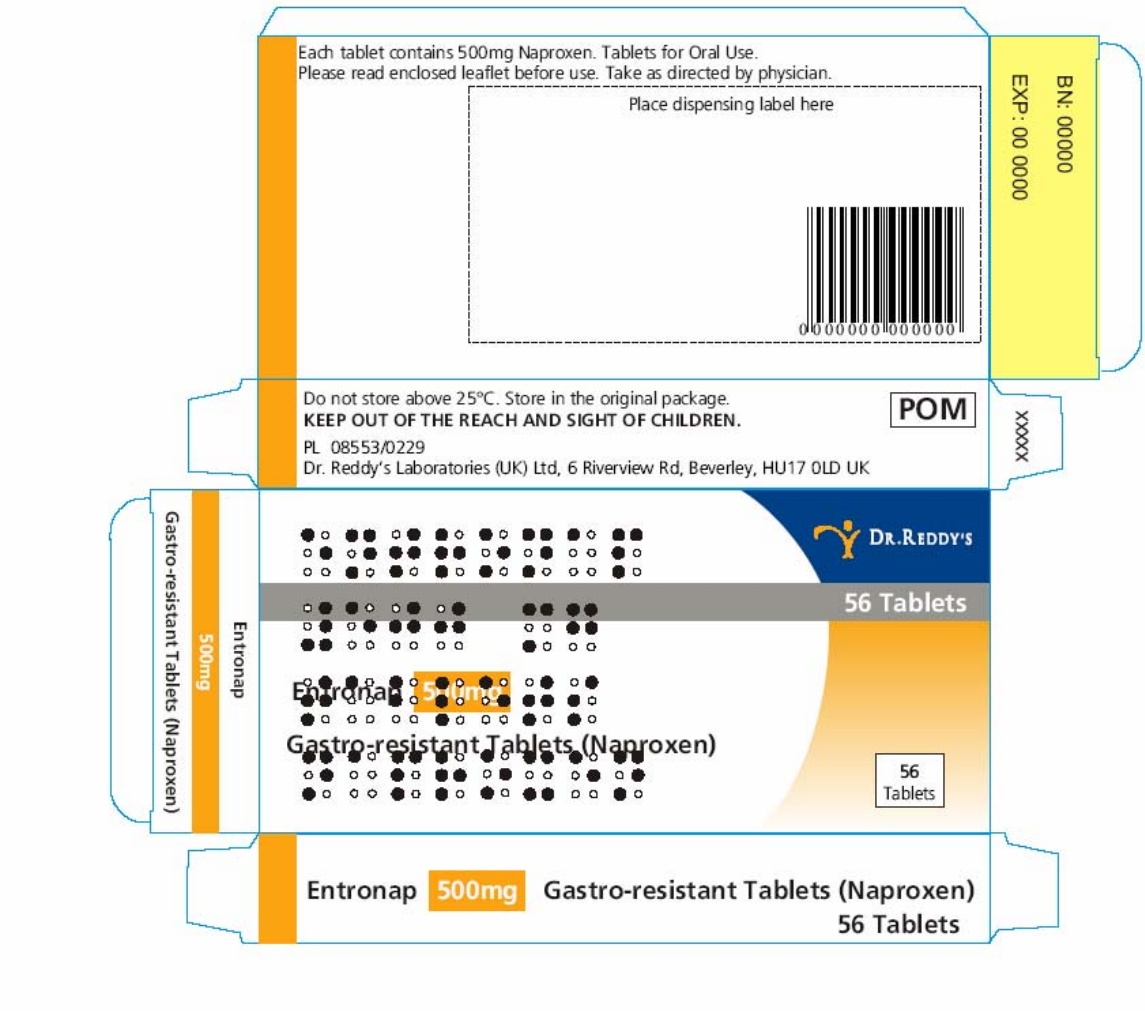
Component code

LABELLING


EXP: 00 0000
Entronap 250mg
Gastro-resistant Tablets
Dr Reddy's Laboratories (UK) Ltd
BN: 0000


Each tablet contains 250mg Naproxen. Tablets for Oral Use.
Please read enclosed leaflet before use. Take as directed by physician.
Place dispensing label here
BN: 00000
EXP: 00 0000
Do not store above 25°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
POM
PL 08553/0228
Dr. Reddy's Laboratories (UK) Ltd, 6 Riverview Rd, Beverley, HU17 0LD UK
XXXXX
Entronap 250mg Gastro-resistant Tablets (Naproxen)
DR.REDDY'S
56 Tablets
Entronap 250mg
Gastro-resistant Tablets (Naproxen)
56 Tablets
Entronap 250mg Gastro-resistant Tablets (Naproxen)
56 Tablets


EXP: 00 0000
Entronap 500mg
Gastro-resistant Tablets
Dr Reddy's Laboratories (UK) Ltd
BN: 0000


Each tablet contains 500mg Naproxen. Tablets for Oral Use.
Please read enclosed leaflet before use. Take as directed by physician.
Place dispensing label here
BN: 00000
EXP: 00 0000
Do not store above 25°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
POM
PL 08553/0229
Dr. Reddy's Laboratories (UK) Ltd, 6 Riverview Rd, Beverley, HU17 0LD UK
XXXX
Entronap 500mg Gastro-resistant Tablets (Naproxen)
DR.REDDY'S
56 Tablets
Entronap 500mg
Gastro-resistant Tablets (Naproxen)
56 Tablets
Entronap 500mg Gastro-resistant Tablets (Naproxen)
56 Tablets