

**PARACETAMOL TABLETS 500MG
PL 02000/0056**

UKPAR

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**PARACETAMOL TABLETS 500MG
PL 02000/0056**

LAY SUMMARY

The MHRA granted Norbrook Laboratories a Marketing Authorisation for the medicinal product Paracetamol Tablets 500mg (PL 02000/0056) on 17th December 2007. This is a general sales list (GSL) medicine, available to the general public without prescription. Paracetamol Tablets 500mg is used in the treatment of mild to moderate pain.

The active ingredient, paracetamol is a centrally acting analgesic (a pain killer that acts on pain centres in the brain), which is used to relieve pain in the body.

This application is identical to a previously granted application for Paracets-Paracetamol Tablets 500mg (PL 22959/0001), granted to Line Range Ltd on 5th May 2005 and, as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Paracetamol Tablets 500mg outweigh the risks; hence a Marketing Authorisation has been granted.

**PARACETAMOL TABLETS 500MG
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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Paracetamol Tablets 500mg (PL 02000/0056) to Norbrook Laboratories, on 17th December 2007. The product is a general sales list (GSL) medicine.

The application was submitted as a simple abridged application according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Paracets-Paracetamol Tablets 500mg currently authorised to Line Range Ltd, PL 22959/0001, approved on 5th May 2005 following a change of ownership. The product was previously authorised by UAC International Ltd and was granted a licence on 25th June 1982.

No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) has been generated for it.

The product contains the active ingredient paracetamol which is a centrally acting analgesic used for the treatment of mild to moderate pain, including headache, toothache, period pains, symptomatic relief of influenza, feverish colds and rheumatic aches and pains.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 02000/0056

PROPRIETARY NAME: Paracetamol Tablets 500mg

ACTIVE(S): Paracetamol

COMPANY NAME: Norbrook Laboratories

E.C. ARTICLE: Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC

LEGAL STATUS: GSL

1. INTRODUCTION

This is a simple, informed consent application for Paracetamol Tablets 500mg submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Norbrook Laboratories, Station Works, Camlough Road, Newry Co. Down, BT 35 6JP, UK.

The application cross-refers to Paracets-Paracetamol Tablets 500mg, approved on 5th May 2005 to the marketing authorisation holder Line Range Ltd which had previously been owned by UAC International Ltd., and granted 25th June 1982. The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the product is Paracetamol Tablets 500mg. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains paracetamol, equivalent to 500mg. It is to be stored in blisters composed of aluminium and polyvinyl chloride (PVC). The proposed shelf-life (5 years) and storage conditions ("Do not store above 25°C. Store in the original package") are consistent with the details registered for the cross-reference product. Paracetamol Tablets 500mg are available in pack sizes of 2, 4, 8 and 16 tablets.

2.3 Legal status

On approval, the product will be available as a general sales list medicine (GSL).

2.4 Marketing authorisation holder/Contact Persons/Company

Norbrook Laboratories, Station Works, Camlough Road, Newry Co. Down, BT 35 6JP, UK.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification

The proposed finished product specification is in line with the details registered for the cross-reference product.

2.9 Drug substance specification

The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance

None of the excipients used are derived from animal or human origin.

3. EXPERT REPORTS

The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The proposed summary is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON

PIL

The patient information leaflet has been prepared in-line with the details registered for the cross-reference product. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Carton and blister

The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS

The data submitted with the application are acceptable. A Marketing Authorisation should be granted.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

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

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is 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 an application of this type.

EFFICACY

Paracetamol is a well known drug and has been used as an analgesic for many years. This application is identical to previously granted application for Paracets-Paracetamol Tablets 500mg (PL 22959/0001). No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. Extensive clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

**PARACETAMOL TABLETS 500MG
PL 02000/0056**

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 24/03/2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 19/04/2004.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 27 th January 2005, 25 th October 2005 and 17 th November 2006
4	The applicant responded to the MHRA's requests, providing further information on 9 th June 2005, 14 th November 2006 and 3 rd December 2006.
5	The application was determined on 11 th July 2007

**PARACETAMOL TABLETS 500MG
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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

PARACETAMOL TABLETS 500MG
PL 02000/0056

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Tablets 500mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of paracetamol. Each tablet also contains sodium metabisulphite 0.56 mg.

For a list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, flat bevelled edge tablets with breakline on one face.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of mild to moderate pain, including headache, neuralgia, toothache, period pains, aches and pains.

Symptomatic relief of rheumatic aches and pains.

Symptomatic relief of influenza, feverishness, feverish colds.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

These tablets are for oral administration.

Adults, the elderly and children over 12 years:

Single dose: 0.5 g to 1 g (1 to 2 tablets).

Maximum daily dose: 4 g (8 tablets) in divided doses.

Children:

Age 6 years to under 12 years: half tablet to one tablet.

Not for use in under 6 year olds.

Dosage instruction:

Take every 4 to 6 hours, as required. Do not take more frequently than every 4 hours. Not more than 4 doses should be administered in any 24 hour period. Dosage should not be continued for more than three days without consulting a doctor.

4.3 CONTRAINDICATIONS

Hypersensitivity to paracetamol or any other ingredients. Alcoholics could be at risk in taking paracetamol.

Contains sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- i) Do not exceed the stated dose.
- ii) Consult a doctor if symptoms persist. Do not continue to use for longer than 3 days without consulting your doctor or pharmacist.
- iii) Ask the doctor or pharmacist about taking the capsules if pregnant or already on a course of medication.

- iv) This product contains paracetamol.
- v) *The label shall say:* “Do not take with any other paracetamol-containing products” and “Immediate medical advice should be sought in the event of an overdose, even if you feel well”.
- vi) *The leaflet shall say:* “Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage”.
- vii) Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
- viii) Keep out of the reach and sight of children.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Alcohol reduces liver capacity to deal with paracetamol. Chronic use of paracetamol enhances effect of warfarin and other coumarins with increased risk of bleeding; occasional doses have no significant effect. Cholestyramine reduces absorption of paracetamol. Metoclopramide and Domperidone accelerate absorption of paracetamol.

May interact with Chloramphenicol causing increased plasma levels.

4.6 PREGNANCY AND LACTATION

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol being used in the recommended dosage, but patients should follow the advice of their doctor regarding its use. Paracetamol is excreted in breast milk but not in clinically significant quantities. Available published data do not contraindicate breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None.

4.8 UNDESIRABLE EFFECTS

Adverse effects of paracetamol are rare but hypersensitivity including skin rash can occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis and/or acute pancreatitis, but these were not necessarily causally related to paracetamol.

4.9 OVERDOSE

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage in the patient has risk factors (see below).

Risk Factors:

If the patient

a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John’s Wort or other drugs that induce liver enzymes.

Or

b, Regularly consumes ethanol in excess of recommended amounts.

Or

c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms:

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may

develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management:

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are employed) become irreversibly bound to liver tissue.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: N02BE01

Paracetamol is an effective analgesic and antipyretic agent but has only weak antiinflammatory properties. Its mechanism of action is not fully understood, as it is only a weak inhibitor of prostaglandin bio-synthesis, but it has been suggested that it is more effective against enzymes in the CNS than those in the periphery. The drug has no effect on the cardiovascular and respiratory systems, and it does not cause gastric irritation or bleeding like salicylates.

5.2 PHARMACOKINETIC PROPERTIES

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1-4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentration.

A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

5.3 PRECLINICAL SAFETY DATA

There is no pre-clinical data of relevance to a prescriber, which is additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Pregelatinised starch (maize)
Sodium metabisulphite
Stearic acid (E570)
Magnesium stearate (E572)

6.2 INCOMPATIBILITIES

None stated.

6.3 SHELF LIFE

5 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

Paracetamol Tablets 500mg are available in child-resistant packs of 2, 4, 8 and 16 tablets.

Specification details of blister packs:

- PVC (white, rigid, opaque): 250 microns
- PVC/Aluminium foil (hard tempered): 15/20 microns
- Primer (nitrocellulose): 1.5 to 2.5 gsm
- Heat seal lacquer: 6.5 to 8.5 gsm

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special precautions required.

7 MARKETING AUTHORISATION HOLDER

Norbrook Laboratories Limited
Station Works
Camlough Road
Newry Co. Down
BT35 6JP
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 02000/0056

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/12/2007

10 DATE OF REVISION OF THE TEXT

17/12/2007

PARACETAMOL TABLETS 500MG PL 02000/0056

PATIENT INFORMATION LEAFLET

Patient Information Leaflet Paracetamol Tablets 500 mg

GSL

Read all of 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 Paracetamol Tablets 500 mg carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must see a doctor if your symptoms worsen or do not improve after 3 days.
- If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Paracetamol Tablets are and what they are used for
2. Before you take Paracetamol Tablets
3. How to take Paracetamol Tablets
4. Possible side effects
5. How to store Paracetamol Tablets
6. Further information

1. WHAT PARACETAMOL TABLETS ARE AND WHAT THEY ARE USED FOR

Each tablet contains 500 mg of the active ingredient paracetamol.

Paracetamol Tablets 500 mg are analgesics (pain relievers) which may be used for the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, period pains and the symptomatic relief of rheumatic aches and pains. They also reduce temperature and can be used for the symptomatic relief of feverishness, feverish colds and influenza.

2. BEFORE YOU TAKE PARACETAMOL TABLETS

Do not take Paracetamol Tablets:

- If you are allergic to paracetamol or any of the other ingredients listed.
- If you suffer from any kidney or liver impairment or alcoholic liver disease.

Taking Paracetamol Tablets with food and drink

You are advised NOT to drink alcohol whilst taking Paracetamol Tablets.

Pregnancy and breastfeeding:

There is no evidence that Paracetamol Tablets will harm your baby if you are pregnant. Paracetamol is excreted in breastmilk but in insignificant amounts. However, if you are pregnant or breast-feeding, if you think you may be pregnant or if you are trying for a baby, you should let your doctor know. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Paracetamol is not expected to impair your ability to drive or to operate machinery.

Taking/using other medicines:

You should always make sure that you are not taking any other paracetamol-containing preparations. If you have been prescribed chloramphenicol, or are taking cholestyramine or anti-coagulants (blood thinning preparations), or preparations to counteract nausea or vomiting, particularly after radiotherapy or other anti-cancer treatment, you should consult your doctor. Please note that these statements may also apply to products used some time ago or at some time in the future. Please inform your doctor or pharmacist if you are taking, or have recently taken any other medicine – even those not prescribed.

Important information about some of the ingredients of Paracetamol Tablets

Sodium Metabisulphite can cause allergic type reactions including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma or allergy.

3. HOW TO TAKE PARACETAMOL TABLETS

The normal dose for adults, the elderly and children over 12 years of age, is one or two tablets to be swallowed with a drink of water. The dose may be taken every 4 - 6 hours, as required. Do not exceed 8 tablets in one day. For children between 6 and 12 years, a half to one tablet can be given up to 4 times a day. Do not exceed 4 tablets in one day. Not for use in under 6 year olds. Do not take more frequently than every 4 hours. If symptoms persist for more than three days, consult your doctor.

If you forget to take Paracetamol Tablets:

If you forget to take one dose, you should never make up for the missing dose by doubling the dose next time. Instead you should simply continue with the next dose when it is due.

Do not exceed the stated dose. Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, paracetamol can have side effects. Adverse effects of paracetamol are rare but hypersensitivity including skin rash can occur. There are usually no ill effects due to paracetamol being used in the recommended dosage during pregnancy, but patients should follow the advice of their doctor regarding its use.

If you are concerned about these or if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. HOW TO STORE PARACETAMOL TABLETS

The tablets should be stored below 25°C in the original package.

This medicine must not be used after the expiry date printed on the pack. Return any left over medicine to your pharmacist.

Do not use Paracetamol Tablets if you notice any changes in the colour or the appearance of the tablets.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Keep this medicine out of the reach and sight of children.

6. FURTHER INFORMATION

What Paracetamol Tablets contains

These tablets contain 500 mg of Paracetamol BP as the active ingredient.

They also contain Maize Starch, Magnesium Stearate (E572), Stearic Acid (E570) and Sodium Metabisulphite (E223).

What Paracetamol Tablets look like and contents of the pack

Paracetamol Tablets are flat, white bevelled edge tablets with a breakline on one face, containing 500 mg of the active ingredient paracetamol. Paracetamol Tablets are available in blister packs of 2, 4, 8 and 16 tablets.

Marketing Authorisation Holder and Manufacturer

The manufacturer and licence holder is: Norbrook Laboratories Limited, Newry, Co. Down, Northern Ireland
Product Licence number PL 02000/0056

You can get more information on Paracetamol Tablets 500 mg from your doctor or pharmacist.

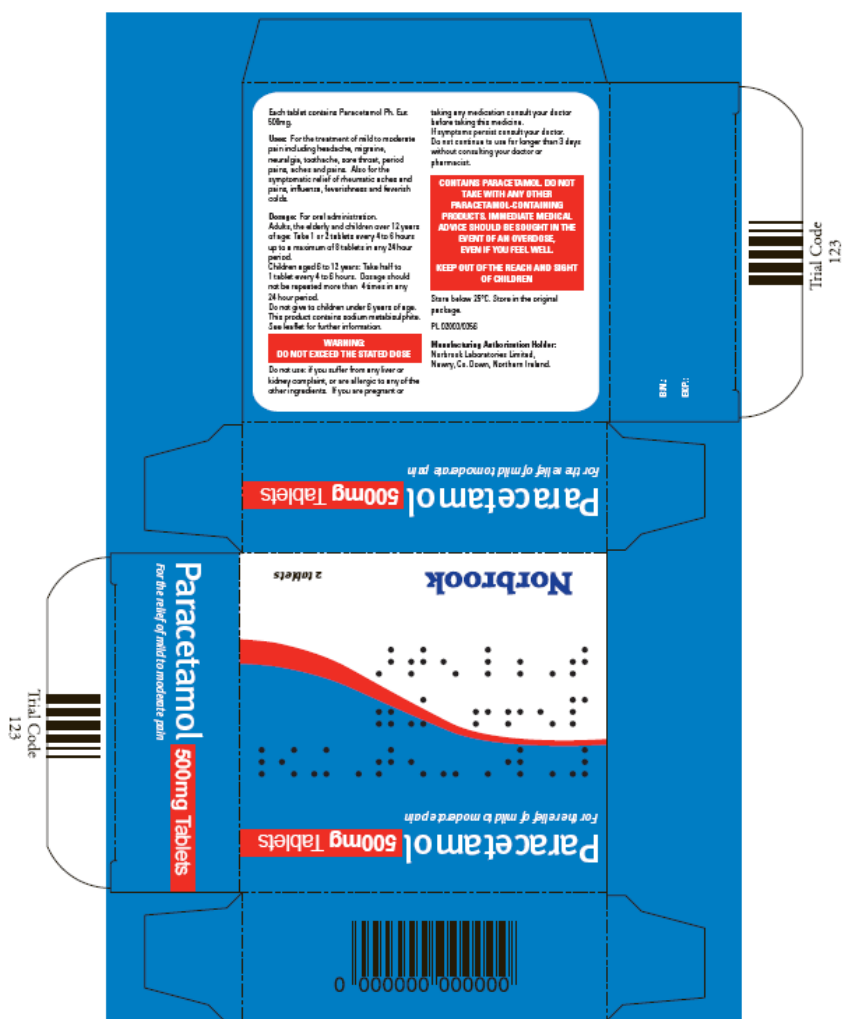
DATE OF PREPARATION: September 2007

Norbrook
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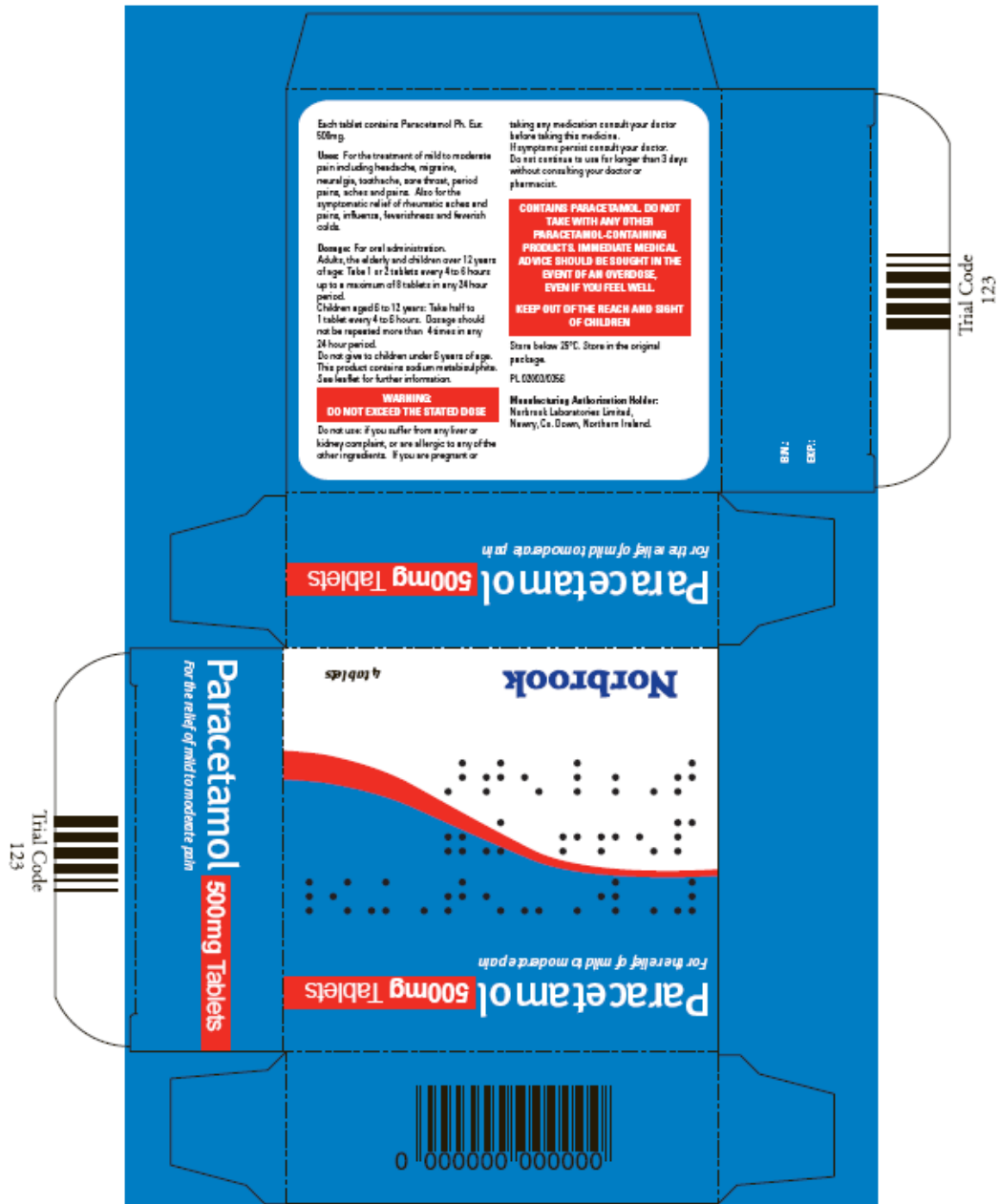
PARACETAMOL TABLETS 500MG PL 02000/0056

LABELLING

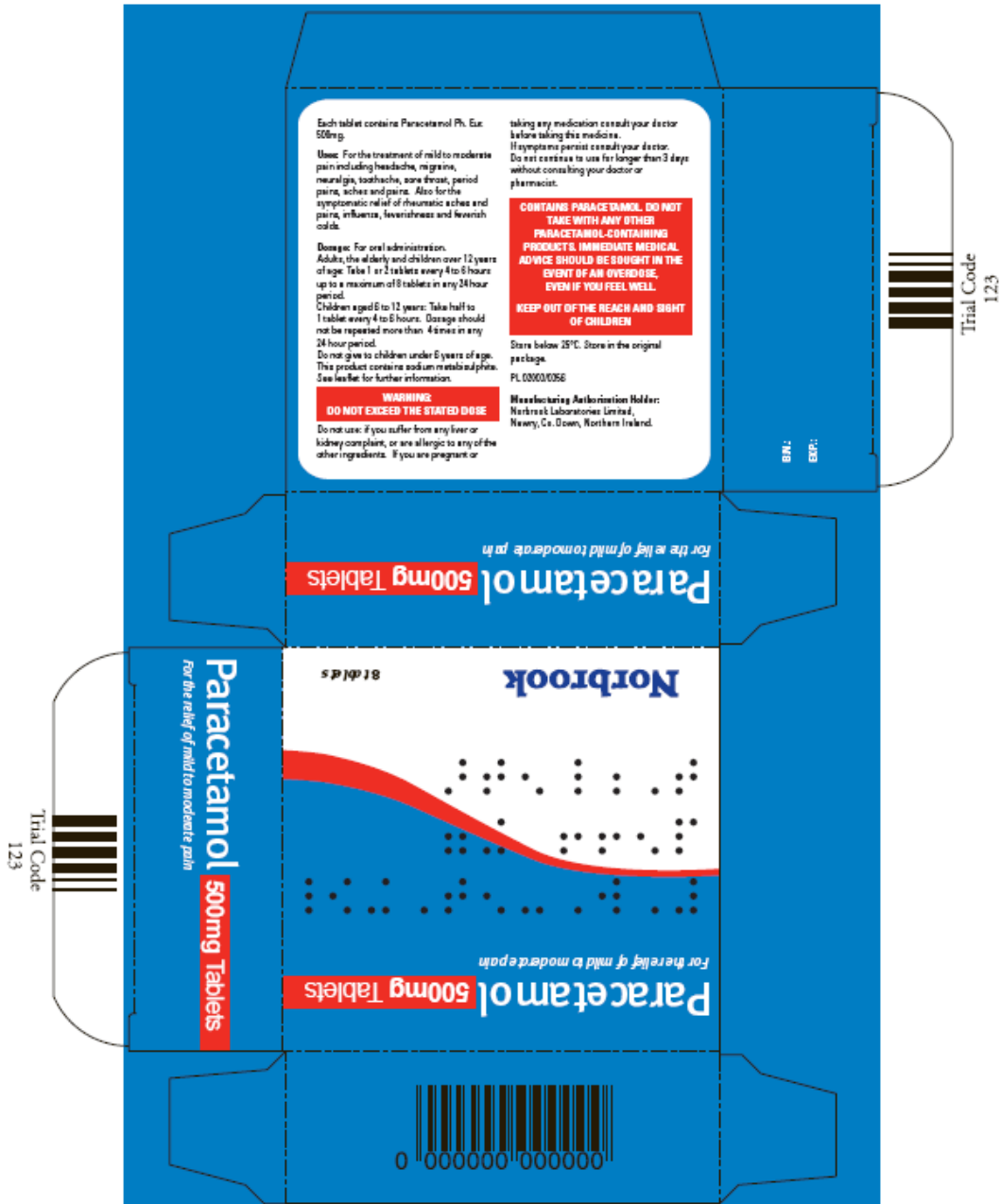
CARTON
PACK SIZE- 2 CAPSULES



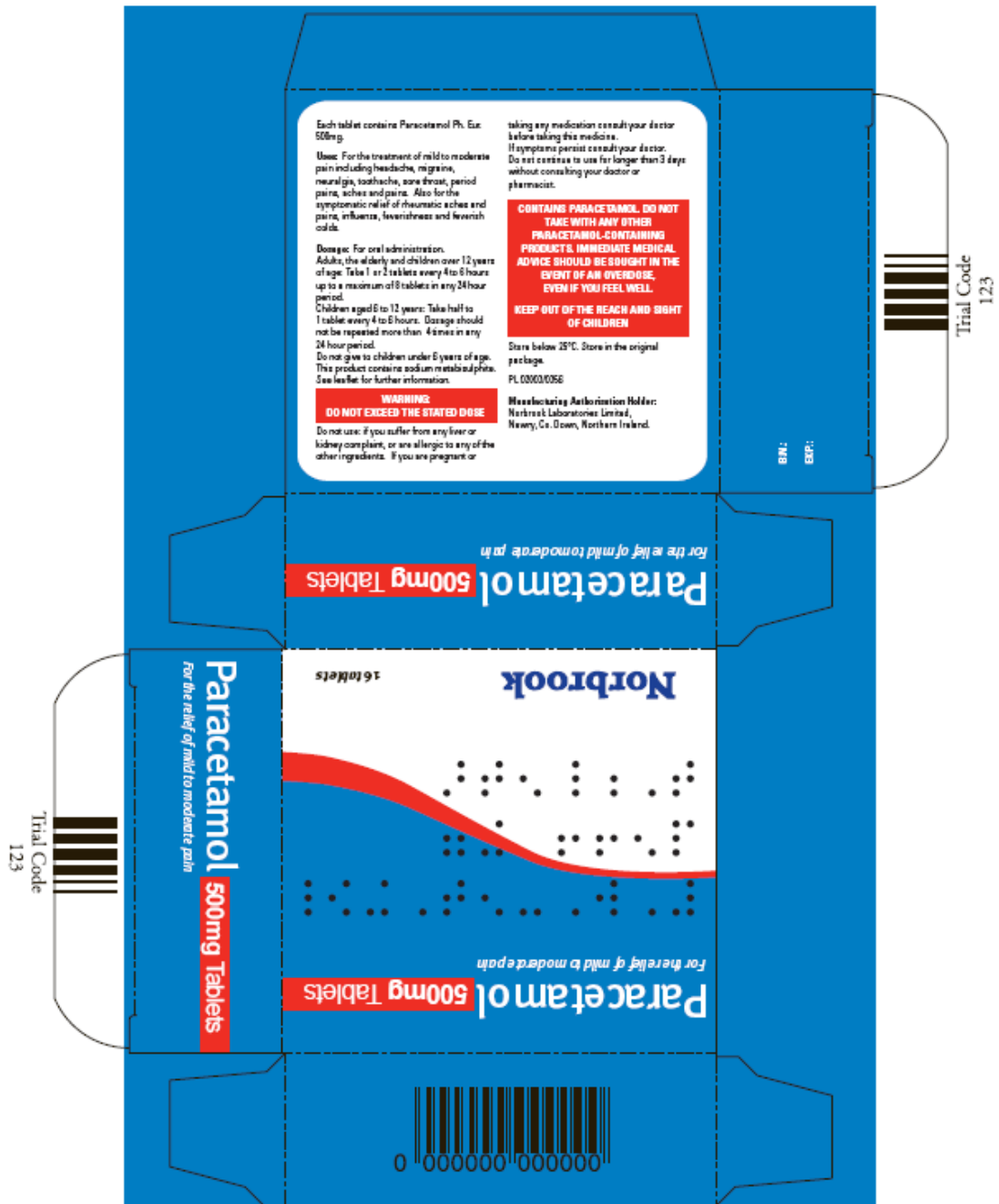
CARTON
PACK SIZE- 4 CAPSULES



**CARTON
PACK SIZE- 8 CAPSULES**



**CARTON
PACK SIZE- 16 CAPSULES**



**CONTAINER
BLISTER FOIL**

