Ampicillin 500 mg Powder for Solution for Injection

PL 02000/0001

UKPAR

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Ampicillin 500 mg Powder for Solution for Injection

PL 02000/0001

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Norbrook Laboratories Limited a Marketing Authorisation (licence) for the medicinal product Ampicillin 500 mg Powder for Solution for Injection (PL 02000/0001) on 24th October 2011. This is a prescription-only medicine (POM).

Ampicillin 500 mg Powder for Solution for Injection contains the active ingredient ampicillin. Each vial contains 500 mg of ampicillin (as ampicillin sodium). Ampicillin is an antibiotic medicine. It belongs to a group of antibiotics called penicillins and it works by killing bacteria that cause infections. Ampicillin can be used for the treatment of a wide range of bacterial infections which result in conditions not amenable to oral therapy such as:

- Ear, nose and throat infections
- Respiratory tract infections such as bronchitis and pneumonia
- Urinary tract infections
- Gonorrhoea (a sexually transmitted infection)
- Female reproductive system infections
- Stomach or intestinal infections such as enteric fever or peritonitis
- Heart infections such as endocarditis
- Infections of the membranes of the brain such as meningitis

Based on the data submitted by Norbrook Laboratories Limited, Ampicillin 500 mg Powder for Solution for Injection was considered to be a generic version of the reference product, Penbritin® Vials for Injection 500mg (PL 00038/5061R, GlaxoSmithKline UK).

No new or unexpected safety concerns arose from this application. It was judged that the benefits of Ampicillin 500 mg Powder for Solution for Injection outweigh the risks; hence a Marketing Authorisation has been granted.
Ampicillin 500 mg Powder for Solution for Injection

PL 02000/0001

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Norbrook Laboratories Limited a Marketing Authorisation for the medicinal product Ampicillin 500 mg Powder for Solution for Injection (PL 02000/0001) on 24th October 2011. The product is a prescription-only medicine (POM).

This is a generic application for Ampicillin 500 mg Powder for Solution for Injection, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The application refers to the UK reference product, Penbritin® Vials for Injection 500mg (PL 00038/5061R), authorised to Beecham Group plc (trading as GlaxoSmithKline UK) on 4th November 1987. The reference product has been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

Ampicillin 500 mg Powder for Solution for Injection is indicated for the treatment of a wide range of bacterial infections caused by ampicillin-sensitive organisms which result in conditions not amenable to oral therapy (see section 5.1 of the SmPC):

- Ear, nose and throat infections
- Respiratory tract infections such as bronchitis and pneumonia
- Urinary tract infections
- Gonorrhoea
- Gynaecological infections
- Enteric fever
- Peritonitis
- Endocarditis
- Meningitis.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available. Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

Ampicillin is an aminopenicillin (ATC classification – J01CA01) that has a bactericidal action due to its inhibition of the synthesis of the bacterial cell wall.

Bacteria may be resistant to ampicillin due to either production of beta-lactamases which hydrolyse aminopenicillins, or to alteration in penicillin-binding proteins, or to impermeability to the drug, or to drug efflux pumps. One or more of these mechanisms may co-exist in the same organism, leading to variable and unpredictable cross-resistance to other beta-lactams and to antibacterial drugs of other classes.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that this is a generic application cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Ampicillin sodium

Nomenclature:

INN: Ampicillin sodium

Chemical names:

i) Sodium 7-(2-amino-2-phenyl-acetyl)amino-3,3-dimethyl-6-oxo-2-thia-5-azabicyclo[3.2.0]heptane-4-carboxylic acid

ii) Sodium (2S,5R,6R)-6-[(2R)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate

iii) Sodium (6R, 7R)-3-[(acetyloxy)methyl]-8-oxo-7-[[2-(thiophen-2-yl)acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

iv) 4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, [2S [2α, 5α, 6β (S*)]]

Structure:

\[
\begin{align*}
\text{N} & \quad \text{H} \\
\text{NH} & \quad \text{COONa} \\
\text{H} & \quad \text{CH}_3 \\
\text{NH}_2 & \quad \text{CH}_3 \\
\text{O} & \\
\text{S} &
\end{align*}
\]

Molecular formula: \( C_{16}H_{18}N_3NaO_4S \)

Molecular weight: 371.4 g/mol

CAS No: 69-52-3

Physical form: A white or almost white hygroscopic crystalline powder

Solubility: Freely soluble in water, sparingly soluble in acetone, practically insoluble in fatty oils and in liquid paraffin

The active substance, ampicillin sodium, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active substance are not of animal, biological or genetically modified origin.
Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been applied.

MEDICINAL PRODUCT

Description & Composition
Ampicillin 500 mg Powder for Solution for Injection is presented as a white to almost white powder for solution for injection. The medicinal product is supplied in a glass vial containing 500 mg ampicillin, as ampicillin sodium. The powder should be reconstituted with one of the intravenous fluids listed in section 6.6 of the Summary of Product Characteristics (SmPC). The medicinal product contains no excipients.

Pharmaceutical development
Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The aim was to develop a stable, generic medicinal product, pharmaceutically equivalent to the reference product, Penbritin® Vials for Injection 500mg (Beecham Group plc).

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrate consistency of the manufacturing process.

Finished product specification
The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.
Container Closure System

Ampicillin 500 mg Powder for Solution for Injection is supplied in packs of 10 x 10 ml, clear, type III glass vials complete with bromobutyl stoppers and aluminium seals. The vials are packaged, with the product information leaflet, into a cardboard outer carton.

Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. The vials satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support a shelf-life of 3 years for the unopened vial, with storage instructions ‘Do not store above 25°C’.

From a microbiological point of view, the reconstituted product should be used immediately after reconstitution, unless reconstitution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8 °C.

Chemical and physical compatibility of Ampicillin powder for solution for injection have been demonstrated with the intravenous fluids and the periods and temperatures stated in section 6.6 of the SmPC, which also provides information regarding disposal of the product.

Quality Overall Summary

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

PRODUCT INFORMATION:

The approved Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The PIL user-testing report has been evaluated and is accepted. It supports the readability of the package leaflet.

Conclusion

The proposed product has been shown to be a generic version of the reference product, Penbritin® Vials for Injection 500mg (Beecham Group plc), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the EU for over 10 years.

The quality grounds for this application are considered adequate. There are no objections to approval of Ampicillin 500 mg Powder for Solution for Injection from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

This generic application, submitted under Article 10(1) of Directive 2001/83/EC, as amended, is for Ampicillin 500 mg Powder for Solution for Injection, claiming to be a generic medicinal version of the UK reference product, Penbritin® Vials for Injection 500mg (PL 00038/5061R, Beecham Group plc).

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

A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

There are no objections to approval of this product from a non-clinical point of view.
CLINICAL ASSESSMENT

INDICATIONS

Ampicillin 500 mg Powder for Solution for Injection is indicated for the treatment of a wide range of bacterial infections caused by ampicillin-sensitive organisms which result in conditions not amenable to oral therapy (see section 5.1 of the SmPC):

- Ear, nose and throat infections
- Respiratory tract infections such as bronchitis and pneumonia
- Urinary tract infections
- Gonorrhoea
- Gynaecological infections
- Enteric fever
- Peritonitis
- Endocarditis
- Meningitis.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available. Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

The indications are consistent with those of the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY

The toxicology of ampicillin is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of ampicillin is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

CLINICAL EFFICACY

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of ampicillin is well-established from its extensive use in clinical practice.

Ampicillin 500 mg Powder for Solution for Injection is to be administered as an intravenous solution and contains the same active substance, in the same concentration, as the UK reference product, Penbritin® Vials for Injection 500mg (Beecham Group plc). Thus, in accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), Section 5.1.6 Parenteral solutions, the applicant is not required to submit a bioequivalence study.
CLINICAL SAFETY

No new data have been submitted and none are required for this type of application. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of ampicillin is well-known.

Clinical overview

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product and is acceptable.

Patient Information Leaflet (PIL)

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

The labelling is satisfactory.

CONCLUSION

Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Ampicillin 500 mg Powder for Solution for Injection 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview.

The applicant’s Ampicillin 500 mg Powder for Solution for Injection has been demonstrated to be a generic version of the UK reference product, Penbritin® Vials for Injection 500mg (Beecham Group plc).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is consistent with that for the UK reference product and is satisfactory.

The final PIL is in line with the SmPC and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Ampicillin 500 mg Powder for Solution for Injection and the reference product, Penbritin® Vials for Injection 500mg (Beecham Group plc), are interchangeable. Extensive clinical experience with ampicillin is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Amoxicillin 500 mg Powder for Solution for Injection

PL 02000/0001

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application on 9th February 1999.

2. Following standard checks and communication with the applicant the MHRA considered the application valid on 15th February 1999.


5. The application was determined on 24th October 2011.
Ampicillin 500 mg Powder for Solution for Injection

PL 02000/0001

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ampicillin 500 mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Ampicillin 500 mg Powder for Solution for Injection contains ampicillin 500 mg, equivalent to 531.3 mg of ampicillin sodium.

For excipients see section 6.1.

3 PHARMACEUTICAL FORM
Powder for Solution for Injection.
White or almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ampicillin 500 mg Powder for Solution for Injection is indicated for the treatment of a wide range of bacterial infections caused by ampicillin-sensitive organisms which result in conditions not amenable to oral therapy (see section 5.1):

- Ear, nose and throat infections
- Respiratory tract infections such as bronchitis and pneumonia
- Urinary tract infections
- Gonorrhoea
- Gynaecological infections
- Enteric fever
- Peritonitis
- Endocarditis
- Meningitis.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Ampicillin 500 mg Powder for Solution for Injection is indicated for intramuscular or intravenous administration at the following dosages:

Usual dosage for Adults, the elderly and children over 10 years:
500 mg four to six times a day
The intravenous dose is given by slow injection (3-4 minutes) but may also be added to infusion fluids or be injected, suitably diluted, into the drip tube over 3-4 minutes.

Endocarditis: 500 mg four to six times a day IM or IV for one to six weeks
Peritonitis: 500 mg four times a day IM or IV
Meningitis: Adult dosage: 2 g six-hourly IV
                Children’s dosage: 150 mg/kg daily IV in divided doses

Usual children’s dosage (under 10 years):
Half the adult routine dosage.
All recommended dosages are a guide only. In severe infections the above dosages may be increased.
Renal Impairment
In the presence of severe renal impairment (creatinine clearance < 10 ml/min) a reduction in dose or extension of dose interval should be considered. In cases of dialysis, an additional dose should be administered after the procedure.

Reconstitution instructions: See Section 6.6 for Instructions for use/handling.

Preparation of injections:
Intramuscular: Dissolve 500 mg in 1.5 ml Water for Injections.
Intravenous: Dissolve 500 mg in 10 ml Water for Injections.
Shake to dissolve.

4.3 Contraindications
Ampicillin is a penicillin and should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (e.g. ampicillin, penicillins, cephalosporins). It should not be given to patients with glandular fever or acute lymphatic leukaemia.

4.4 Special warnings and precautions for use
Before initiating therapy with ampicillin, careful enquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving beta-lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity.

Ampicillin should be avoided if infectious mononucleosis and/or acute or chronic leukaemia of lymphoid origin are suspected. The occurrence of a skin rash has been associated with these conditions following the administration of ampicillin.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Dosage should be adjusted in patients with renal impairment (see Section 4.2).

This medicinal product contains 31.3mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
If ampicillin is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

Bacteriostatic drugs may interfere with the bactericidal action of ampicillin.

In common with other oral broad-spectrum antibiotics, ampicillin may reduce the efficacy of oral contraceptives.

Probenecid decreases the renal tubular secretion of ampicillin. Concurrent use with ampicillin may result in increased and prolonged blood levels of ampicillin.

Concurrent administration of allopurinol during treatment with ampicillin can increase the likelihood of allergic skin reactions.

It is recommended that when testing for the presence of glucose in urine during ampicillin treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of ampicillin, false positive readings are common with chemical methods.

Methotrexate excretion is reduced by penicillins.
4.6 Fertility, Pregnancy and lactation

Pregnancy:
Animal studies with ampicillin have shown no teratogenic effects. The product has been in extensive clinical use since 1961 and its use in human pregnancy has been well documented in clinical studies. When antibiotic therapy is required during pregnancy Ampicillin for Injection may be considered appropriate.

Lactation:
During lactation, trace quantities of penicillins can be detected in breast milk. Adequate human and animal data on use of Ampicillin during lactation are not available. While adverse effects are apparently rare, three potential problems exist for the nursing infant:
- modification of bowel flora.
- direct effects on the infant such as allergy/sensitisation.
- interference with interpretation of culture results when a pyrexia of unknown origin occurs.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

The following convention has been used for the classification of undesirable effects in terms of frequency:

<table>
<thead>
<tr>
<th>Classification</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common:</td>
<td>$\geq 1/10$</td>
</tr>
<tr>
<td>Common:</td>
<td>$\geq 1/100$ and $&lt; 1/10$</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>$\geq 1/1000$ and $&lt; 1/100$</td>
</tr>
<tr>
<td>Rare:</td>
<td>$\geq 1/10,000$ and $&lt; 1/1000$</td>
</tr>
<tr>
<td>Very Rare:</td>
<td>$&lt; 1/10,000$</td>
</tr>
</tbody>
</table>

Skin and subcutaneous tissue disorders
- Common: skin rash, pruritus and urticaria. The incidence is higher in patients suffering from infectious mononucleosis and acute or chronic leukaemia of lymphoid origin. Purpura has also been reported.
- Uncommon: skin reactions such as erythema multiforme (Stevens-Johnson syndrome), and toxic epidermal necrolysis have been reported.
- Rare: anaphylaxis

Renal and urinary disorders
- Uncommon: Interstitial nephritis

Gastrointestinal disorders:
- Common: nausea, vomiting and diarrhoea.
- Uncommon: Pseudomembranous colitis and haemorrhagic colitis.

Hepatobiliary disorders
- Common: a moderate and transient increase in transaminases
- Uncommon: hepatitis and cholestatic jaundice

Blood and lymphatic system disorders:
- Uncommon: haematological effects including transient leucopenia, transient thrombocytopenia and haemolytic anaemia. Prolongation of bleeding time and prothrombin.

4.9 Overdose

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically.

Ampicillin may be removed from the circulation by haemodialysis.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactam antibacterials, penicillins
ATC-Code: J01CA01

Mode of action
Ampicillin is an aminopenicillin that has a bactericidal action due to its inhibition of the synthesis of the bacterial cell wall.

Mechanism of resistance
Bacteria may be resistant to ampicillin due to production of beta-lactamases which hydrolyse aminopenicillins, due to alteration in penicillin-binding proteins, due to impermeability to the drug, or due to drug efflux pumps. One or more of these mechanisms may co-exist in the same organism, leading to variable and unpredictable cross-resistance to other beta-lactams and to antibacterial drugs of other classes.

Breakpoints
The MIC breakpoints for susceptible organisms vary according to species.

Susceptibility:
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Gram positive aerobes
Listeria monocytogenes
Streptococcus agalactiae
Streptococcus pyogenes
Gram negative aerobes
Neisseria meningitidis
Anaerobes
Bacteroides spp.
Clostridium spp
Fusobacterium spp
Peptostreptococci

Species for which acquired resistance may be a problem
Gram positive aerobes
Enterococcus faecalis
Staphylococcus aureus
Streptococcus pneumoniae
Gram negative aerobes
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus spp.
Salmonella spp
Shigella spp

Inherently resistant organisms
Gram negative aerobes
Acinetobacter spp
Citrobacter spp
Enterobacter spp
**5.2 Pharmacokinetic properties**
Following the intramuscular administration of 500 mg, ampicillin reaches peak plasma concentrations within about 1 hour which are reported to range from 7 to 14 µg/ml.

Ampicillin is widely distributed and therapeutic concentrations can be achieved in ascitic, pleural and joint fluids.

Ampicillin is around 20% bound to plasma proteins and the plasma half-life is about 1 to 1½ hours.

Ampicillin is metabolised to some extent to penicilloic acid which is excreted in the urine.

Renal clearance of ampicillin occurs partly by glomerular filtration and partly by tubular secretion; it is retarded by the concomitant administration of probenecid. Following parenteral administration, about 60 to 80% is excreted in the urine within 6 hours. Ampicillin is removed by haemodialysis. High concentrations are reached in bile, it undergoes enterohepatic recycling and some is excreted in the faeces.

**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**
None

**6.2 Incompatibilities**
If Ampicillin is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set; because loss of activity of the aminoglycoside can occur under these conditions.

Ampicillin should not be mixed with blood products or other proteinaceous fluids (e.g. protein hydrolysates) or with intravenous lipid emulsions.

**6.3 Shelf life**
Unopened vial: 3 years.

After reconstitution: From a microbiological point of view, the reconstituted product should be used immediately, unless reconstitution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8 °C.

**6.4 Special precautions for storage**
Unopened: Do not store above 25°C.
For storage conditions of the reconstituted/diluted medicinal product, see section 6.3
6.5 Nature and contents of container

Ampicillin 500 mg Powder for Solution for Injection is supplied in packs of 10 x 10 ml, clear, type III glass vials complete with bromobutyl stoppers and aluminium seals.

6.6 Special precautions for disposal

Ampicillin vials are not suitable for multidose use.

Chemical and physical compatibility of Ampicillin powder for solution for injection have been demonstrated with the following intravenous fluids for the periods and temperatures stated:

<table>
<thead>
<tr>
<th>Intravenous fluids</th>
<th>Stability time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 % Procaine Hydrochloride at ambient temperature</td>
<td>Use Immediately</td>
</tr>
<tr>
<td>Water for Injection at ambient temperature</td>
<td>Use Immediately</td>
</tr>
<tr>
<td>Sodium Chloride 0.9 % Solution at 25 °C</td>
<td>4 hours</td>
</tr>
<tr>
<td>Ringers Solution at 25 °C</td>
<td>3 hours</td>
</tr>
<tr>
<td>Compound Sodium Lactate Solution at 25 °C</td>
<td>3 hours</td>
</tr>
<tr>
<td>5 % Glucose Solution at 2-8°C</td>
<td>Use Immediately</td>
</tr>
<tr>
<td>Sodium Chloride 0.9 % Solution at 2-8°C</td>
<td>10 hours</td>
</tr>
<tr>
<td>Ringers Solution at 2-8°C</td>
<td>10 hours</td>
</tr>
<tr>
<td>Compound Sodium Lactate Solution at 2-8°C</td>
<td>9 hours</td>
</tr>
<tr>
<td>1.4 % Sodium Bicarbonate at 2-8°C</td>
<td>3 hours</td>
</tr>
</tbody>
</table>

Any remaining solution should be discarded. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Norbrook Laboratories Ltd.,
Newry,
Co. Down,
Northern Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 02000/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/10/2011

10 DATE OF REVISION OF THE TEXT

24/10/2011
UKPAR Ampicillin 500 mg Powder for Solution for Injection
PL 02000/0001

PRODUCT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

Ampicillin 500 mg Powder for Solution for Injection

Please read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ampicillin 500 mg Powder for Solution for Injection is and what it is used for
2. Before you take Ampicillin 500 mg Powder for Solution for Injection
3. How to take Ampicillin 500 mg Powder for Solution for Injection
4. Possible side effects
5. How to store Ampicillin 500 mg Powder for Solution for Injection
6. Further Information

1. What Ampicillin 500 mg Powder for Solution for Injection is and what it is used for

Ampicillin 500 mg Powder for Solution for Injection contains one active ingredient called ampicillin. Each vial contains 500 mg of ampicillin (as ampicillin sodium). Ampicillin is an antibiotic medicine. It belongs to a group of antibiotics called penicillins and it works by killing bacteria that cause infections. Ampicillin can be used for the treatment of a wide range of bacterial infections which result in conditions not amenable to oral therapy such as:

- Ear, nose and throat infections
- Respiratory tract infections such as bronchitis and pneumonia
- Urinary tract infections
- Gonorrhoea (sexually transmitted infection)
- Female reproductive system infections
- Stomach or intestinal infections such as enteric fever or parotitis
- Heart infections such as endocarditis
- Infections of the membranes of the brain such as meningitis.

2. Before you take Ampicillin 500 mg Powder for Solution for Injection

Do not take Ampicillin:
- If you know you are allergic to ampicillin, penicillin, coxoharlespin (or any other antibiotic).
- If you have glandular fever.
- If you have a blood disease called acute lymphatic leukaemia.

Take special care with Ampicillin:
- If you have ever had a skin rash or swelling of the face or neck when taking any antibiotic. You should let your doctor or nurse know before you receive ampicillin.
- If you are being treated for kidney problems. The doctor may need to adjust the dose depending on how your kidneys work.
- If you need a urine test for glucose. Ampicillin may give falsely high results unless the correct method is used.
- This medicinal product contains 31 mg of sodium per dose which needs to be taken into consideration by patients on a controlled sodium diet.

Taking Ampicillin with other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Make sure to tell your doctor or pharmacist if you are taking any of these medicines before taking ampicillin:

- Allopurinol (for gout): When taken with ampicillin, the risk of allergic skin reactions is increased.
- Probenecid (for gout): This medicine can increase the amount of ampicillin in your blood
- Other antibiotics can interfere with the effect of ampicillin making it ineffective.
- Methotrexate (for cancer or arthritis): this medicine can reduce the amount of ampicillin that is excreted.
- Oral contraceptives: If you are taking birth control pills, ampicillin may reduce its efficacy. Please let your doctor or pharmacist know as you may need to use alternative contraceptive methods.

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy and breastfeeding:
There is no evidence that ampicillin will harm your baby if you are pregnant. However, if you are pregnant, think you may be pregnant or are trying for a baby you should let your doctor know. Very small quantities of ampicillin can be detected in breast milk but adverse effects on the nursing baby appear to be rare. It is possible that these small quantities may affect the baby's normal bowel flora (the normal bacteria in the gut), may provoke allergy or sensitisation, or may interfere with the results of blood cultures should your baby require them if she/he becomes sick. If you are breast feeding you should tell your doctor or nurse before you receive this medication.

Driving and using machines:
Ampicillin is not expected to impair your ability to drive or to operate machinery.

3. How to take Ampicillin 500 mg Powder for Solution for Injection

You will never give yourself this medicine. The medicine will be given to you by a qualified person such as a doctor, pharmacist or nurse via injection or infusion into a vein (intravenous) or a muscle (intramuscular).

Your doctor will decide how much you need each day and how often the injections should be given. The doctor, nurse or pharmacist will make up the injection before using an appropriate fluid (such as Water for Injections or an Injection Infusion Fluid).

The usual dose for treating infections are:
- Adults, the elderly and children over 10 years: 500 mg four to six times a day.
- Children under 10 years usually receive half the above adult dose.
- Infections of the heart (endocarditis): 500 mg four to six times a day by intramuscular or intravenous injection for one to six weeks.
- Infections of the stomach and/or gut (parotitis): 500 mg four times a day by intramuscular or intravenous injection.
UKPAR Ampicillin 500 mg Powder for Solution for Injection

- Infections of the membranes of the brain (meningitis):
  - Adult dosage: 2 g every six hours by intravenous injection. Children's dosage: 150 mg/kg daily in divided doses by intravenous injection.
  - All of these doses can be increased in serious infections.
  - If your kidneys are not working very well, your doctor may reduce the dose you take, if appropriate. Your doctor will give you special instructions if you are on kidney dialysis.
  - If you take more Ampicillin than you should
    - Since Ampicillin will be administered to you it is unlikely that you will take more than you should. However, if you think that you have, you should tell your doctor or pharmacist.
  - If you forget to take Ampicillin
    - If you think you have missed an injection, speak to your doctor or nurse.
  - If you stop taking Ampicillin
    - It is important that you complete your treatment with ampicillin as recommended by your doctor. If the treatment is stopped too early the infection may not be resolved and your symptoms will come back.
  - If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like many medicines, Ampicillin for injection may occasionally cause side effects in some patients.

The side effects listed below have been experienced by people taking this medicine and they are listed according to frequency.

Common (effects less than 1 in 10 but more than 1 in 100 patients):
- Skin rash
- Itching (pruritus)
- Raised itchy bumps/hives (urticaria)
- Red/purple discoloration of the skin (purpura)
- Feeling sick (nausea)
- Vomiting
- Diarrhoea

The above effects are often mild and may disappear during treatment. If they are severe or last for more than a few days, tell your doctor.

You are unlikely to experience any of the following side effects but if you do - see your doctor as soon as possible:

Uncommon (effects less than 1 in 100 patients but more than 1 in 1000 patients):
- Fever
- General ill feeling
- Joint ache
- Skin lesions
- Skin peeling
- An increase or decrease in urine output
- Blood in the urine or stools
- Weight gain from fluid retention
- Abdominal cramps or urges to have bowel movement
- Loss of appetite
- Yellowing of the skin or whites of eyes (jaundice)
- Darkening of the urine
- Facies becoming paler
- Increased feeling of tiredness
- Shortness of breath
- Abnormally heavy and prolonged menstrual periods

Rare (effects less than 1 in 1000 patients but more than 1 in 10,000 patients):
- Allergic reactions (hypersensitivity) - signs include
  - Runny nose, sneezing, swelling of the face, neck, lips, tongue or throat, difficulty in breathing, blistering or peeling of the skin, with or without ulceration in the mouth, sore eyes or sore genitals, joint pain, fever; rapid heart beat or loss of consciousness may be signs of an allergic reaction. If any of these symptoms occur, STOP taking Ampicillin for Injection and seek immediate medical attention as you may require hospitalisation.

5. How to store Ampicillin 500 mg Powder for Solution for Injection

- Ampicillin for Injection should not be stored above 25°C prior to use.
- After reconstitution, Ampicillin solutions for injection can be stored at 2-8°C in a refrigerator.
- Chemical and physical compatibility of Ampicillin powder for solution for injection have been demonstrated with the following intravenous fluids for the periods and temperatures stated:

<table>
<thead>
<tr>
<th>Intravenous fluid</th>
<th>Stability time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 % Proline Hydrochloride</td>
<td>Use immediately</td>
</tr>
<tr>
<td>at ambient temperature</td>
<td>Use immediately</td>
</tr>
<tr>
<td>Water for injection at ambient temperature</td>
<td>Use immediately</td>
</tr>
<tr>
<td>Sodium Chloride 0.9 % Solution at 25°C</td>
<td>4 hours</td>
</tr>
<tr>
<td>Ringsers Solution at 25°C</td>
<td>3 hours</td>
</tr>
<tr>
<td>5 % Glucose Solution at 2-8°C</td>
<td>Use immediately</td>
</tr>
<tr>
<td>Sodium Chloride 0.9 % Solution at 2-8°C</td>
<td>10 hours</td>
</tr>
<tr>
<td>Ringsers Solution at 2-8°C</td>
<td>10 hours</td>
</tr>
<tr>
<td>Compound Sodium Lactate Solution at 2-8°C</td>
<td>9 hours</td>
</tr>
<tr>
<td>1.4 % Sodium Bicarbonate at 2-8°C</td>
<td>3 hours</td>
</tr>
</tbody>
</table>

- There is an expiry date on the label, the doctor or nurse will check that this date has not passed before giving you the medicine.
- Keep out of the reach and sight of children.
- Ampicillin vials are not suitable for multidose use.
- Any unused product or waste material should be disposed of in accordance with local requirements.

6. Further information

What Ampicillin 500 mg Powder for Solution for Injection contains

Ampicillin for Injection contains one active ingredient called Ampicillin. Ampicillin for Injection contains no other ingredients.

What Ampicillin 500 mg Powder for Solution for Injection looks like and contents of the pack

Ampicillin for Injection is a white powder that is made up into a solution for Injection. Each vial contains 500 mg of ampicillin as Ampicillin Sodium. The vials are supplied to doctors in packs of 10.

Marketing Authorisation Holder and Manufacturer
Norbrook Laboratories Limited.
Newry, Co. Down, Northern Ireland

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

Leaflet prepared:
10/2011
UKPAR Ampicillin 500 mg Powder for Solution for Injection
PL 02000/0001

TECHNICAL INFORMATION LEAFLET

Ampicillin 500 mg Powder for Solution for Injection

The following information is intended for medical or healthcare professional only

CONTENT
Ampicillin 500 mg Powder for Solution for Injection is available in vials containing the equivalent of 500 mg ampicillin (presented as Ampicillin Sodium) as a powder for reconstitution for injection.

THERAPEUTIC INDICATIONS
Ampicillin 500 mg Powder for Solution for Injection is indicated for the treatment of a wide range of bacterial infections caused by ampicillin-sensitive organisms which result in conditions not amenable to oral therapy such as:

- Ear, nose and throat infections
- Respiratory tract infections such as bronchitis and pneumonia
- Urinary tract infections
- Gastroenteritis
- Osteoarticular infections
- Enteric fever
- Peritonitis
- Septicaemia
- Puerperal fever
- Meningitis.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

Consideration should be given to official local guidelines on the appropriate use of antibacterial agents.

POSSIBILITY AND METHOD OF ADMINISTRATION
Ampicillin 500 mg Powder for Solution for Injection is indicated for intramuscular or intravenous administration at the following dosage:

Usual dosage for Adults, the elderly and children over 10 years:

600 mg to be given six times a day

The infusional dose is given over one injection (3-4 minutes) but may also be given by intravenous infusion, usually diluted, into the drip tube over 3-4 minutes.

Endocarditis:

500 mg to be given six times a day for 5 to 7 days

Rectal:

500 mg to be given two times a day

Children's dosage:

Usual intravenous dosage (adults and children 10 years):

Half the adult intravenous dosage.

All recommended dosages are a guide only. In severe infections the above dosages may be increased.

Renal impairment:

In the presence of severe renal impairment (creatinine clearance < 10 ml/min), production in dose or duration of dose interval should be considered. In cases of dialysis, an additional dose should be administered after the procedure.

Administration:

Parenteral:

Dose: 500 mg in 2.5 ml Sodium Chloride for injection in a single dose. Reconstitute as directed. Add the contents of the vial to 2.5 ml of Sodium Chloride for injection and inject over a period of three to four minutes.

CONTRA-INDICATIONS:

Ampicillin is a penicillin and should not be given to patients with a allergy to penicillin or to related antibiotics (e.g. cephalosporins, monobactams, carbapenems).

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Ampicillin should not be given to patients receiving beta-lactam antibiotics. Although ampicillin is more frequently following parenteral therapy, it has caused in some patients an unusual type reaction consisting of a severe rash and has been associated with the administration of ampicillin. Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Doseage should be adjusted in patients with renal impairment (see dosage section).

This medicinal product contains 31.5 mg of sodium per 500 mg which needs to be taken into consideration by patients on a controlled sodium diet.

INTERACTION WITH OTHER MEDICATIONS AND OTHER FORMS OF INTERACTION

If ampicillin is prescribed concurrently with an anticoagulant, the anticoagulant should not be given in the evening, intravenous injection or intravenous infusion should not be given because of the potential for interference of the anticoagulant with the anticoagulant's effect. As omeprazole, ampicillin may interfere with the bactericidal action of ampicillin. In common with other broad-spectrum antibiotics, ampicillin may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Ampicillin decreases the renal clearance of ampicillin. Concurrent use will therefore result in increased and prolonged blood levels of ampicillin.

Concurrent administration of ampicillin during treatment with ampicillin can increase the likelihood of allergic skin reactions. It is recommended that when testing for the presence of a rash in children, during ampicillin treatment, any other skin rash should be avoided for as long as possible. The possibility of an allergic reaction should be considered.

Methotrexate excretion is reduced by penicillins.

PREGNANCY AND LACTATION

Pregnancy:

Animal studies with ampicillin have shown no teratogenic effects. However, potential effects have been observed in humans. The product has been used in pregnancy and its use in human pregnancy has been documented in clinical studies. When antibiotic therapy is required during pregnancy, Ampicillin for Injection may be considered appropriate.

Lactation:

During lactation, trace quantities of penicillin can be detected in breast milk. Adequate human and animal data on use of Ampicillin during lactation are not available. The possibility of fetal or neonatal toxicity should be considered.

Potential problems arise for the nursing infant:

- increased risk of infection
- potential for transmission of drug-resistant organisms
- allergic reactions
- intolerance of drugs
- relationship of clinical symptoms to the presence of clinical symptoms

EFFECTS ON ABILITY TO DRIVE AND USE MACHINERY

Ampicillin may affect the ability to drive or operate machinery.

UNDISCOVERED EFFECTS

The following reaction has been used for the classification of undiscovered effects in terms of frequency:

Very Common: > 1/10

Common: 1/100 to < 1/10

Uncommon: 1/10 000 to < 1/100

Rare: < 1/10 000

Skin and subcutaneous tissue disorders

Common: rash, pruritus and urticaria.

Uncommon: fixed drug eruption, urticaria, angioedema, thrombocytopenic purpura.

Uncommon: severe cutaneous reactions such as toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, erythema multiforme, systemic lupus erythematosus, and severe adverse reactions have been reported.

Rare: angioedema

Rash and urticaria

Rash and urticaria

Uncommon: urticarial pruritus.

Gastrointestinal disorders

Common: nausea, vomiting and diarrhea.

Uncommon: pseudomembranous colitis and other gastrointestinal effects.

Hepatobiliary disorders


Blood and lymphatic system disorders

Uncommon: as with other beta-lactams, haematological effects including transient leucopenia, increased thrombocyte and monoocyte counts. Prolongation of bleeding time and prothrombin time.

OVERDOSE

In common with other beta-lactams, haematological effects including transient leucopenia, increased thrombocyte and monoocyte counts. Prolongation of bleeding time and prothrombin time.
UKPAR Ampicillin 500 mg Powder for Solution for Injection

PL 02000/0001

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Beta lactam antibiotics, pencillins
ATC-Code: J01C00

Mode of action

Ampicillin is an amoxicillin-like that has a bactericidal action due to its inhibition of the synthesis of the bacterial cell wall.

Mechanism of resistance

Bacteria may be resistant to ampicillin due to production of beta-lactamases which hydrolyze amoxicillin, due to inactivation of ampicillin-clinching proteins, due to impermissibility to the drug, or due to drug efflux pumps. One or more of these mechanisms may co-exist in the same organism, leading to variable and unpredictable rates of resistance to other beta-lactam antibiotics and to antibacterial drugs of other classes.

Breakpoints

The NCCLS breakpoints for susceptible organisms vary according to species.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable. As necessary, expert advice should be sought when the local prevalence of resistance is such that the ability of the agent is at least some types of infections is questionable.

Commonly susceptible species

Gram positive aerobes

Enterococcus species

Streptococcus pneumoniae

Streptococcus pyogenes

Gram negative aerobes

Enterobacteriaceae

Escherichia coli

Klebsiella pneumoniae

Proteus spp.

Salmonella spp.

Shigella spp.

Intrinsically resistant species

Gram negative aerobes

Acinetobacter spp.

Citrobacter spp.

Enterobacter spp.

Klebsiella spp.

Pseudomonas spp.

Serratia spp.

Other

Chryseae

Mycoplasma

Legionella

Pharmacokinetic properties

Following the intramuscular administration of 500 mg, ampicillin reaches peak plasma concentrations within about 1 hour which are expected to range from 7 to 14 μg/ml.

Ampicillin is widely distributed and therapeutic concentrations can be achieved in serum, pleural and joint fluids.

Ampicillin is bound to plasma proteins and the plasma half-life is about 1 to 1.5 hours.

Ampicillin is metabolized to some extent to penicillin and which is excreted in the urine.

Renal clearance of ampicillin occurs partly by glomerular filtration and partly by tubular secretion; it is inhibited by the concomitant administration of probenecid. Following, intravenous administration, about 10 to 20% is excreted in the urine within 5 hours. Ampicillin is removed by haemodialysis. High concentrations are reached in bile, it undergoes enterohepatic recirculation and some is excreted in the faeces.

Preclinical safety data

No further information of relevance.

DIRECTIONS FOR USE

Preparation of injections:

Intramuscular: Dissolve 500 mg in 1.5 ml Water for Injections.

Intravenous: Dissolve 500 mg in 10 ml Water for Injections.

Shake to dissolve.

Ampicillin solutions for injection should be used immediately.

Chemical and physical compatibility of Ampicillin powder for solution for injection have been demonstrated with the following intravenous fluids for the periods and temperatures stated (when constituted at 5 % w/w):

- Intravenous fluids
  - 0.9 % Sodium Chloride at ambient temperature: Use immediately
  - 0.9 % Sodium Chloride at 25 °C: Use immediately
  - Propylene Solution at 25 °C: Use immediately

Stability time

No change is noticeable for 4 hours.

DOSAGE

Ampicillin solutions are not suitable for multidosing.

Any unused solution should be discarded. Any unused product or waste material should be disposed of in accordance with local requirements.

INCOMPATIBILITIES

If Ampicillin is prescribed concurrently with an aminoglycoside, the antibiotic should not be mixed in the syringe, intravenous fluid container or given concomitantly because loss of activity of the aminoglycoside can occur under these conditions.

Ampicillin should not be mixed with iv compatable fluids or other parenteral fluids (e.g. protein hydrates) or with intravenous lipid emulsions.

SHELF-LIFE AND STORAGE

UNOPENED VIALS

Do not store above 25°C.

Do not use this product after the expiry date printed on the vial. If the expiry date refers to this last day of that month.

AFTER RECONSTITUTION

From a microbiological point of view, the reconstituted product should be used immediately, unless aseptic conditions are maintained. If not used immediately, storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

AVAILABILITY

Strength

500 mg

Pack

10

Product licence

PL 02000/0001

LEGAL CATEGORY

POU

MANUFACTURER AND PRODUCT LICENSE HOLDER

Norbrook Laboratories Limited,

Navy, Co. Down, Northern Ireland.

Leaflet prepared: 10/2011

Norbrook
UKPAR Ampicillin 500 mg Powder for Solution for Injection

PL 02000/0001

LABELLING

Each vial contains 500 mg of Ampicillin equivalent to 531.3 mg of Ampicillin Sodium.
Contains: Pencillin PL 02000/0001
Norbrook Laboratories Limited, Newry, Co. Down, Northern Ireland.