PHENOXYMETHYLPENICILLIN 250mg TABLETS BP

PL 17907/0033

UKPAR

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PHENOXYMETHYLPENICILLIN 250mg TABLETS BP

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LAY SUMMARY

The MHRA granted Bristol Laboratories Limited a Marketing Authorisation (licence) on the 26th January 2006, for Phenoxymethylpenicillin 250 mg Tablets BP. This Prescription Only Medicine (POM) is used to treat mild to moderately severe infections.

Phenoxymethylpenicillin 250 mg Tablets BP contain the active ingredient phenoxymethylpenicillin (as the potassium salt) which fights the bacteria that cause infections.

The applicant has supplied scientific literature to demonstrate that the active substance in Phenoxymethylpenicillin 250 mg Tablets BP has been in well-established medicinal use within the European Community, with acceptable levels of effectiveness and safety.

No new or unexpected safety concerns arose from these applications. It was therefore judged that the benefits of taking Phenoxymethylpenicillin 250 mg Tablets BP outweigh the risks. Hence a Marketing Authorisation has been granted.

PHENOXYMETHYLPENICILLIN 250mg TABLETS BP

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for Phenoxymethylpenicillin 250 mg Tablets BP to Bristol Laboratories Limited on 26th January 2006. The product is a Prescription Only Medicine (POM).

The application was submitted as a 'bibliographic application', under article 4.8 (a) (ii) of Directive 65/65/EEC [10.1 (a) (ii) of Directive 2001/83/EC]. The scientific literature demonstrated that the active substance in Phenoxymethylpenicillin 250 mg Tablets BP has been in well-established medicinal use within the European Community, with acceptable efficacy and safety.

The product contains the active ingredient phenoxymethylpenicillin (as the potassium salt) and is indicated in the treatment or prophylaxis of mild to moderately severe infections caused by penicillin-sensitive organisms.

Phenoxymethylpenicillin exerts a bactericidal action against penicillin-susceptible microorganisms. It acts through the inhibition of biosynthesis of cell wall mucopeptide rendering the cell wall osmotically unstable.

PHARMACEUTICAL ASSESSMENT

REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

The manufacturer responsible for batch release in the EEA is Bristol Laboratories Ltd. This company holds a Wholesale Dealer's (Import) Licence (WI 17907/1), a copy of which has been provided in the annexes to the MAA form.

The finished product manufacturer has been inspected for GMP compliance by the MHRA.

No further inspection action is required prior to authorisation.

INTRODUCTION

This is an abridged national application for a single strength of phenoxymethylpenicillin tablets. This has been submitted as a 'bibliographic application', under article 4.8 (a) (ii) of Directive 65/65/EEC [10.1 (a) (ii) of Directive 2001/83/EC].

Phenoxymethylpenicillin is indicated for the treatment or prophylaxis of mild to moderately severe infections caused by penicillin-sensitive organisms.

3.2.S DRUG SUBSTANCE

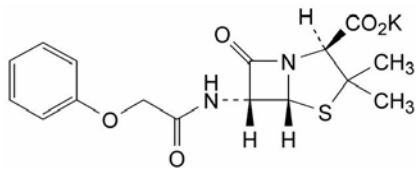
The Active Ingredient Manufacturer (AIM) has been granted a Certificate of Suitability for phenoxymethylpenicillin. A copy of this has been provided. This source of active ingredient has been seen previously by the MHRA, in relation to currently granted UK products.

3.2.S.1 General information

3.2.S.1.1 Nomenclature

INN: Phenoxymethylpenicillin potassium
Chemical name: (2*S*, 5*R*, 6*R*)-3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)-amino]4-thia-1-azobicyclo[3.2.0]heptane-2-carboxylic acid, potassium salt
Other name: Penicillin V Potassium
CAS no.: 132-98-9

3.2.S.1.2 Structure



MWt: 388.5
Molecular Formula: $C_{16}H_{17}KN_2O_5S$

3.2.S.1.3 General properties

A white, homogenous crystalline powder, odourless with a slight, characteristic odour.

3.2.S.2 Manufacture

3.2.S.2.2 Description of Manufacturing Process and Process Controls

3.2.S.2.3 Control of Materials

3.2.S.2.4 Controls of Critical Steps and Intermediates

3.2.S.2.5 Process Validation and/or Evaluation

3.2.S.2.6 Manufacturing Process Development

No information has been provided with this dossier for the above, since these have already been assessed and approved by the European Directorate for the Quality of Medicines (EDQM) prior to the grant of the Certificate of Suitability for the drug substance.

3.2.S.3 Characterisation

3.2.S.3.1 Elucidation of Structure and other Characteristics

3.2.S.3.2 Impurities

This information has not been provided, having been assessed and approved previously, in relation to the grant of the EDQM Certificate of Suitability.

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification

The specification supplied by the AIM is in line with the Ph Eur monograph for phenoxymethylpenicillin potassium, with the additional test for related substances and residual solvents as prescribed in the Certificate of Suitability. It is stated that the AIM routinely tests the drug substance to this specification.

The finished product manufacturer re-tests the drug substance prior to use, according to the Ph Eur specification. This is satisfactory.

3.2.S.4.2 Analytical Procedures

The analytical procedures used by the AIM have been assessed and approved by the EDQM in relation to the grant of the Certificate of Suitability. It is assumed that the finished product manufacturer employs the methodology prescribed by the Ph Eur monograph for phenoxymethylpenicillin potassium.

3.2.S.4.3 Validation of Analytical Procedures

Since the analytical validation performed by the AIM will have been assessed and approved by the EDQM in relation to the grant of the Certificate of Suitability, and the

finished product manufacturer presumably uses the Ph Eur methodology, no further validation is required.

3.2.S.4.4 Batch Analyses

Sample Certificates of Analysis from the AIM (5 batches) and finished product manufacturer (1 batch) have been provided. These are satisfactory.

3.2.S.4.5 Justification of Specification

The specification is considered to be justified.

3.2.S.5 Reference Standards or Materials

No details have been provided of the AIM's reference standard, since it has been granted a Ph Eur Certificate of Suitability. This can be accepted.

3.2.S.6 Container Closure System

The packaging of the drug substance by the AIM has been assessed and approved previously.

3.2.S.7 Stability

Results from stability studies have been provided and are considered supportive of the proposed retest period and storage conditions.

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The product is presented as white round biconvex film-coated tablets embossed on one side with BL/250. The qualitative composition of the tablets is given in table 1, below.

Table 1: Composition of Phenoxymethylpenicillin 250mg Tablets BP

Ingredient	***Function***	***Reference to standard***
Phenoxymethylpenicillin potassium	Active ingredient	Ph Eur
Maize starch	Diluent	Ph Eur
	Disintegrant	
Povidone	Binder	Ph Eur
Isopropyl alcohol	Solvent	Ph Eur
Magnesium stearate	Lubricant	Ph Eur
Hypromellose	Film-former	Ph Eur
Purified Talc	Glidant	Ph Eur
Titanium dioxide	Opacifier	Ph Eur
Polyethylene glycol 6000	Plasticiser	Ph.Eur.

Isopropyl alcohol	Solvent	Ph Eur
Methylene chloride	Solvent	NF

Container closure system:
The tablets are packed into PVC/PVdC/Al blister strips or into HDPE tablet containers with HDPE closures.

3.2.P.2 Pharmaceutical Development

The objective of the development programme has been stated clearly: the formulation of a robust, stable, acceptable formulation of phenoxymethylpenicillin, comparable in performance to the generic reference product, Penicillin VK Tablets (PL 04520/0005, Biochemie GmbH).

The supplier of the active ingredient holds a Certificate of Suitability for the material. Its high solubility means that particle size of the drug substance is not critical.

The role of each excipient in the formulation has been outlined, and justification provided for these and the solvents used during processing. Solvents were employed for non-aqueous granulation and film-coating due to the sensitivity of the active ingredient to hydrolysis. Compatibility studies of the active with each excipient are reported; no incompatibilities were noted.

A range of laboratory tablets with a number of formulation variables were manufactured, and analysed in terms of hardness, assay, disintegration and dissolution. The batch that gave the most satisfactory physical properties was selected for further development, with a scale-up batch prepared to investigate and optimise the critical parameters for the manufacturing process. This was carried out satisfactorily.

No discussion of the development of the dissolution method is provided, however this is acceptable since the method from the BP monograph for phenoxymethylpenicillin tablets is followed. Results from comparative dissolution studies between the development and scale-up batches of the product and that of a reference batch have been reported. In addition to testing at pH 6.8, as outlined in the monograph method, results are presented for media consisting of buffer solutions at different pH levels. Very rapid dissolution is demonstrated for all batches tested, with comparable profiles for test and reference.

The account provided in the dossier indicates that a logical and in-depth pharmaceutical development programme was carried out.

3.2.P.3 Manufacture

3.2.P.3.2 Batch Formula

The batch formula for a production scale batch has been supplied.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

A standard non-aqueous wet granulation procedure is employed, followed by compression and film-coating of tablets. An adequate description of the manufacturing process and in-process controls has been provided.

As well as monitoring of the process parameters which were optimised during process development, in-process controls are carried out on the final blend prior to compression and on the tablet cores during compression. During packaging into blister strips, leak testing is also performed. These in-process controls are satisfactory.

3.2.P.3.4 Control of Critical Steps and Intermediates

A specification has been set for the tablet cores and is satisfactory being in line with the specification of the BP monograph for Phenoxymethylpenicillin tablets as well as the Ph Eur general monograph for tablets.

3.2.P.3.5 Process Validation and/or Evaluation

Validation data have been provided for the manufacture of the scale-up batch and 2 further production scale batches. These are satisfactory, showing the process to be optimised and capable of reproducibly producing tablets of the required quality. A process validation protocol has also been provided for the first full-scale production batches. This is acceptable**.**

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

The excipients are adequately controlled according to their Ph Eur monographs, or, where relevant, to USNF specifications.

Sample certificates of analysis, documenting testing performed by the finished product manufacturer, have been provided and are satisfactory, demonstrating that the ingredients conform to their pharmacopoeial specifications.

3.2.P.4.2 Analytical Procedures

It is apparent from the certificates of analysis that pharmacopoeial analytical methodology is followed.

3.2.P.4.3 Validation of Analytical Procedures

Since pharmacopoeial methods are employed, no validation is necessary.

3.2.P.4.4 Justification of Specification

Since the specifications are pharmacopoeial, they are considered to be justified.

3.2.P.4.5 Excipients of Human or Animal Origin

It is stated that none of the excipients are of animal origin. Declarations to this effect have been included from each of the ingredient suppliers. Magnesium stearate is of vegetable origin.

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification

The finished product specification has been provided and is acceptable. The same specification is to be applied at release and over the shelf-life of the product.

This specification is largely based on that of the BP monograph for phenoxymethylpenicillin tablets and the Ph Eur general monograph for tablets. Additional tests for related substances, residual solvents and non-routine tests for identity of titanium dioxide and microbial quality are included.

3.2.P.5.2 Analytical Procedures

The analytical methods used for identification, dissolution and assay are those given in the BP monograph for phenoxymethylpenicillin tablets, and those for weight uniformity, disintegration and microbial quality are the appropriate Ph Eur standard methods for a product of this type. The determination of total viable count employs the pour plate methodology, which is acceptable. Testing for the absence of pathogens is more stringent than required by the pharmacopoeia for a category 3A product.

Related substances are determined using an HPLC method, residual solvents by GC.

3.2.P.5.3 Validation of Analytical Procedures

Validation data have been provided for the assay and dissolution method (even though these are pharmacopoeial) and for the in-house related substances, residual solvent determination and determination of microbial quality techniques. These are satisfactory.

3.2.P.5.4 Batch Analyses

Certificates of analysis have been provided for the 3 production scale batches manufactured during process development and qualification. Full details of the batch history are provided. All of the batches were manufactured using the same batch of active ingredient. The results are well within the proposed specification.

3.2.P.5.5 Characterisation of Impurities

No further characterisation of impurities has been performed or reported. This is not considered to be critical, since full assessment of the characterisation of impurities performed by the AIM will have been undertaken by the EDQM in relation to the grant of the Certificate of Suitability for the drug substance.

3.2.P.5.6 Justification of Specification

As stated above, the finished product specification is based on that of the BP monograph for phenoxymethylpenicillin tablets and can, therefore, be considered to be justified.

3.2.P.6 Reference Standards or Materials

It is stated that the Ph Eur reference standard material for phenoxymethylpenicillin potassium is used for the calibration of in-house working standards. This is satisfactory; a sample Certificate of Analysis is provided.

3.2.P.7 Container Closure System

The product is packed into either PVC (250µm)/PVdC (60µm)/Al (20µm) blisters or HDPE tablet containers with HDPE closures. Technical information and specifications for the packaging components are provided. These are satisfactory. The applicant states that the packaging complies with relevant EU legislation regarding food contact for plastic packaging materials.

It is stated that the packaging materials are routinely subject to visual checks and identification tests by the finished product manufacturer prior to use.

3.2.P.8 Stability

Stability Summary and Conclusion

The initial results of stability studies performed on production batches packaged in both of the proposed commercial package types, have been provided. Storage conditions are in accordance with ICH recommendations: 25°C/60%RH long term study, 30°C/60%RH intermediate study and 40°C/75%RH accelerated study.

Samples are tested for appearance, disintegration time, dissolution, assay and related substances, according to the proposed finished product specification. The analytical methods employed are identical to those described above, with the exception of the assay, where a stability indicating HPLC method has replaced the BP monograph assay method.

Degradation was observed under accelerated conditions, as predicted by preformulation studies on the drug substance, but the tablets have been shown to be stable for 24 months at 25°C, remaining within specification for all parameters studied. As such, a shelf life of 2 years when stored at a temperature not exceeding 25^{o}C has been proposed and is acceptable.

Post-approval Stability Protocol and Stability Commitment

Acceptable post-approval stability commitment has been given.

Stability Data

Details of the HPLC method for the stability indicating assay and its validation have been provided. This is satisfactory.

The data demonstrate that significant degradation occurs within 6 months under accelerated conditions. Under long-term and intermediate conditions, however, the product seems to be much more stable. No significant trends are noted.

APPENDICES

Facilities and Equipment

Not applicable for this application.

Adventitious Agents Safety Evaluation

Not applicable for this application.

Novel Excipients

There are none.

REGIONAL INFORMATION

Since this application has not been submitted in the CTD format, all relevant information has been included in Part II of the dossier.

SPC, LABELS AND PACKAGE LEAFLET

SPC

This is satisfactory from a pharmaceutical perspective.

Patient Information Leaflet

The PIL is acceptable.

Labelling

Colour mock-ups of the proposed labelling have been provided. These are satisfactory.

OTHER INFORMATION

Bioavailability, bioequivalence

The applicant has conducted a single dose two-way crossover bioequivalence study under fasted conditions comparing the proposed product against a marketed UK reference product. The bioanalytical method has been fully described and evidence of method validation has been provided. Results from the study demonstrate that test and reference products are bioequivalent.

Essential similarity

This is a bibliographic application and no formal claim of essential similarity is being made by the applicant. The applicant has however provided evidence of bioequivalence to a marketed UK reference product.

ADMINISTRATIVE

Comment on Expert report

The pharmaceutical expert report has been written by a chemist. The experts CV has been supplied.

The report is an adequate critical summary of the part II data.

MAA form

Satisfactory.

GMP

Satisfactory.

Guideline Compliance

The application has been put together with reference to the relevant guidelines.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

This application is of an acceptable quality. There are no objections to the granting of a Marketing Authorisation.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

1. INTRODUCTION

Phenoxymethylpenicillin is indicated for the treatment of mild or moderate infections caused by penicillin sensitive organisms. These include streptococcal, pneumococcal and staphylococcal infections. It may also be used for the prophylaxis of rheumatic fever/chorea and bacterial endocarditis as well as pneumococcal infection in post-splenectomy patients.

2. BACKGROUND

Bristol Laboratories Ltd. have applied for this licence for 250mg tablets of phenoxymethylpenicillin as a national bibliographical application.

3. INDICATIONS

These have already been mentioned in the introduction and are in line with those for other licensed tablets of phenoxymethylpenicillin.

4. DOSE AND DOSAGE SCHEDULE

The usual dose for most infections is 250mg every 6 – 8 hours for 10 days, save for pharyngitis in children which is 500mg 6 hourly. Prophylaxis usually involves just 125mg twice daily.

For prophylaxis against bacterial endocarditis prior to dental or surgical procedures, the usual adult dosage is 2g 1 hour before the procedure with a further 1g 6 hours later. (For children less than 30kg the doses are halved).

For children under 12 years of age, the dose is calculated on the basis of body weight, being 25,000- 90,000 units (15-50mg) – 250mg approximates to 400,000 units.

5. TOXICOLOGY

No formal data is presented and none is required for this application.

6. CLINICAL PHARMACOLOGY

No formal data is presented and none is required for this application.

The clinical expert provides information on pharmacodynamics and pharmacokinetics summarised adequately from the published literature following a Medline Literature search, with references ranging from 1970 to 2002.

The applicant has conducted a single dose two-way crossover bioequivalence study under fasted conditions. The test product was obtained from the proposed finished product manufacturer. The reference product was Penicillin VK tablets 250mg

which is manufactured by Sandoz GmbH and distributed by Generics UK. Test and reference products are considered appropriate.

The findings of the study a are summarised below. 90% confidence intervals reported fulfil standard acceptance criteria.

Parameter	Geometric least square mean			90% confidence limits
	Test product	Reference product	Ratio (test/reference)	
C_{max} (mcg/ml)	4.959	5.135	96.6%	87.86-106.16%
AUC_{0-t} (mch.h/ml)	5.720	6.035	94.8%	90.43-99.34%
$AUC_{0-\infty}$ (mcg.h/ml)	5.893	6.245	94.4%	90.34-98.56%

7. EFFICACY

No new data is presented and none is required for this application.

The clinical expert provides information on clinical data summarised adequately from the published literature following a Medline search. No new studies were considered as the product is so well established.

Equivalent currently licensed UK products have dates of authorisation dating back to at least 1986 with some being on the market prior to 1972.

8. SAFETY

No formal safety data is presented. The adverse effects that can be expected are listed in the Summary of Product Characteristics and are consistent with those of equivalent products. The clinical expert provides a satisfactory review of the published literature.

9. EXPERT REPORT

The clinical expert report has been written by a Consultant in Pharmaceutical Medicine. In it the author explains that a bibliographic application is necessary as there is no brand leader for which a full dossier has been submitted to allow an application under article 10.1 (a)(iii), although a number of licensed generic versions of phenoxymethylpenicillin 250mg tablets are available on the UK market**.**

The author has provided a fully adequate review of the literature on clinical pharmacology, efficacy and safety.

The author's curriculum vitae is included, as are those for the toxicological assessor and the pharmaceutical assessor.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is satisfactory.

11. PATIENT INFORMATION LEAFLET

The PIL is satisfactory.

12. LABELLING

The labelling is satisfactory.

13. MAA

The Marketing Authorisation Application is satisfactory.

14. DISCUSSION

Bristol Laboratories Ltd. have applied for a licence for 250mg tablets of phenoxymethylpenicillin, using a bibliographic application for the reasons outlined in the clinical expert report. The clinical expert has provided satisfactory bibliographic references throughout in support of the application.

15. CONCLUSION

A product licence may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Phenoxymethylpenicillin 250 mg Tablets BP 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

Phenoxymethylpenicillin is a well known drug and has been used as an antibiotic for many years. The applicant has demonstrated essential similarity to the marketed product, Penicillin VK tablets 250mg.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

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

PHENOXYMETHYLPENICILLIN 250mg TABLETS BP

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 23/12/2002.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 18/02/2003.
3	Following assessment of the application the MHRA requested further information relating to the clinical dossier on 10/04/2003.
4	The applicant responded to the MHRA's requests, providing further information relating to the clinical dossier on 06/06/2003.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 24/04/2003 and 13/09/2004.
4	The applicant responded to the MHRA's requests, providing further information on 25/02/2004, 12/03/2004 and 16/05/2005.
5	The application was determined on 26/01/2006.

PHENOXYMETHYLPENICILLIN 250mg TABLETS BP

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

PHENOXYMETHYLPENICILLIN 250mg TABLETS BP

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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Phenoxymethylpenicillin 250 mg Tablets BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Phenoxymethylpenicillin 250 mg (as Phenoxymethylpenicillin Potassium)

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

White to off white round biconvex film-coated tablets with BL/250 embossed on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Penicillin exerts high activity *in-vitro* against staphylococci (except penicillinase-producing strains), streptococci (groups A, C, G, H, L and M), pneumococci, Corynebacterium diptheriae, Bacillus anthracis, Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes, Neisseria gonorrhoeae, Treponema pallidum, Clostridium species and Leptospira.

Patients with a past history of rheumatic fever receiving continuous prophylaxis may harbour penicillin-resistant organisms. In these patients, the use of another prophylactic agent should be considered.

Phenoxymethylpenicillin is indicated in the treatment or prophylaxis of mild to moderately severe infections caused by penicillin sensitive organisms, ie.those microorganisms whose susceptibility to phenoxymethylpenicillin is within the range of serum levels attained.

NOTE: Severe pneumonia, empyema, bacteremia, pericarditis, meningitis, and arthritis should not be treated with phenoxymethylpenicillin during the acute stage. Indicated surgical procedures should be performed.

The following infections will usually respond to an adequate dosage of phenoxymethylpenicillin:

Streptococcal Infections (mild to moderately severe): Infections of the upper respiratory tract including pharyngitis, scarlet fever and mild erysipelas.

Pneumococcal Infections(mild to moderately severe): Infections of the respiratory tract, including otitis media.

Staphylococcal Infections: Mild infections of the skin and soft tissues.

Fusospirochetosis (Vincent's Gingivitis and Pharyngitis): Mild to moderately severe infections of the oropharynx.

Prophylaxis of rheumatic fever and/or chorea: Prophylaxis with oral penicillin on a continuing basis has proved effective in preventing recurrence of these conditions.

Prophylaxis against bacterial endocarditis in patients with congenital heart disease or rheumatic or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the respiratory tract.

Prophylaxis of pneumococcal infection in patients following splenectomy or patients with sickle cell disease.

4.2. Posology and method of administration

Phenoxymethylpenicillin 250 mg is approximately equivalent to 400,000 units.

The usual dosage recommendations for adults and children 12 years and over are as follows:

Streptococcal Infections:
Mild to moderately severe infections of the upper respiratory tract, including scarlet fever and mild erysipelas : 125 mg to 250 mg, every 6 to 8 hours for 10 days.

Pharyngitis in children : 500mg every 6 hours.

Pneumococcal Infections:
Mild to moderately severe infections of the respiratory tract, including otitis media : 250 mg every 6 hours until the patient has been afebrile for at least 2 days.

Staphylococcal Infections:
Mild infections of skin and soft tissue: 250 mg every 6 to 8 hours.

Fusospirochetosis (Vincent's gingivitis):
Mild to moderately severe infections of the Oropharynx : 250 mg every 6 to 8 hours.

Prophylaxis in the Following Conditions:

To prevent recurrence following rheumatic fever and/or chorea: 125 mg twice daily on a continuing basis.

For prophylaxis against bacterial endocarditis in patients with congenital heart disease or rheumatic or other acquired valvular heart disease when undergoing dental procedures or surgical procedures of the upper respiratory tract:

The usual adult dosage is 2 g (1 g for children less than 30 kg) 1 hour before the procedure and then 1 g (500 mg for children less than 30 kg) 6 hours later.

For prophylaxis of pneumococcal infection in patients following splenectomy or patients with sickle cell disease:

Adults and children over 12 years: 500mg every 12 hours.
Children 6-12 years: 250mg every 12 hours.
Children below 5 years: 125mg every 12 hours.

Children's antibiotic dosages should not exceed the maximum adult doses. Therapy for children under 12 years of age is calculated on the basis of body weight, the suggested daily dose is 25,000 to 90,000 units (15 to 50 mg)/kg in 3 to 6 divided doses.

4.3. Contraindications

A history of a previous hypersensitivity reaction to any penicillin is a contraindication.

4.4. Special warnings and precautions for use

Phenoxymethylpenicillin shares the toxic potentials of the penicillins, including the risk of hypersensitivity reactions and the usual precautions of penicillin therapy should be observed.

Prior to initiation of therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management including intubation, should also be administered as indicated.

Renal and haematologic systems should be evaluated periodically during prolonged therapy with phenoxymethylpenicillin, particularly if high dosage is used. Penicillins are excreted largely unchanged by the kidney. It should be used with caution in those with severe renal impairment, using a lower dosage or longer dosage interval.

In suspected staphylococcal infections, proper laboratory studies including susceptibility tests, should be performed. In streptococcal infections, cultures should be taken following completion of treatment to date, to determine whether streptococci have been eradicated. Therapy must be sufficient to eliminate the organism (a minimum of 10 days), otherwise the sequelae of streptococcal disease (e. g., endocarditis, rheumatic fever) may occur.

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms, including fungi. Pseudomembranous colitis has been reported with nearly all antibacterial agents including penicillins, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents. If superinfection occurs, appropriate measures should be taken.

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

Concurrent administration of bacteriostatic antibiotics (e.g., erythromycin, tetracycline, neomycin) may diminish the bactericidal effects of penicillins by slowing the rate of bacterial growth. Bactericidal agents work most effectively against the immature cell wall of rapidly proliferating microorganisms. This has been demonstrated in vitro; however, the clinical significance of this interaction is not well documented. However, in selected circumstances in which such therapy is appropriate, using adequate doses of antibacterial agents and beginning penicillin therapy first, should minimize the potential for interaction.

Penicillin blood levels may be prolonged by concurrent administration of probenecid which blocks the renal tubular secretion of penicillins.

Concurrent administration of penicillin and beta-blockers may increase the risk or severity of anaphylactic reactions.

4.6. Pregnancy and lactation

Safe use of phenoxymethylpenicillin during pregnancy has not been definitely established. There are no adequate or controlled studies using phenoxymethylpenicillin in pregnant women and the drug should be used during pregnancy only when clearly needed.

Because phenoxymethylpenicillin is distributed into milk, the drug should be used with caution in nursing women.

4.7. Effects on ability to drive and use machines

No or negligible effect

4.8. Undesirable effects

Although reactions have been reported much less frequently after oral than after parenteral penicillin therapy, it should be remembered that all degrees of hypersensitivity, including fatal anaphylaxis, have been observed with oral penicillin.

The most common reactions to oral penicillin are nausea, vomiting, epigastric distress, diarrhoea, and black, hairy tongue. The hypersensitivity reactions noted are skin eruptions (ranging from maculopapular to exfoliative dermatitis); urticaria; reactions resembling serum sickness, including chills, fever, oedema, arthralgia, and prostration; laryngeal oedema; and anaphylaxis.

Fever and eosinophilia may frequently be the only reactions observed. Haemolytic anaemia, leukopenia, thrombocytopenia, neuropathy, and nephropathy are infrequent reactions and are usually associated with high doses of parenteral penicillin.

4.9. Overdose

Symptoms of a large overdose of penicillin may cause nausea, vomiting, stomach pain, diarrhoea and in rare cases major motor seizures. If other symptoms are present, consideration must also be given to the possibility of an allergic reaction or symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: Beta lactamase sensitive penicillins ATC Code: J01C E02.

Phenoxymethylpenicillin exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide rendering the cell wall osmotically unstable. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci.

Phenoxymethylpenicillin exerts high in vitro activity against staphylococci (except penicillinase-producing strains), streptococci (groups A, C, G, H, L, and M), and pneumococci. Other organisms susceptible to Phenoxymethylpenicillin are Neisseria gonorrhoeae, Corynebacterium diphtheriae, Bacillus anthracis, Clostridia, Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes and Leptospira. Treponema pallidum is susceptible.

The *in-vitro* MIC break points are detailed below:

Organism	MIC (µg per ml)
Gram-positive bacteria	
Staph. aureus (non-penicillinase producer)	0.03
Strep. pyogenes	0.015
Strep. pneumoniae	0.03
Strep. faecalis	4.0
Bacillus anthracis	0.015
Corynebacterium diptheriae	0.03
Gram-negative bacteria	
Escherichia coli	128.0
Salmonella typhi	64.0
Neisseria gonorrhoeae	0.03
Neisseria meningitidis	0.25
Haemophilus influenzae	4.0

5.2. Pharmacokinetic properties

Phenoxymethylpenicillin (penicillin V) has the distinct advantage over benzylpenicillin (penicillin G) in being resistant to inactivation by gastric acid and is more completely absorbed from the gastrointestinal tract, following administration by the mouth. Absorption is usually rapid, although variable, with about 60% of an oral dose being absorbed. The potassium salts are better absorbed than the free acid. Peak plasma concentrations of 3 to 5 mcg per mL have been observed 30 to 60 minutes after a dose of 500 mg. It may be given with meals; the effect of food on absorption appears to be slight, blood levels are slightly higher, when the drug is given on an empty stomach.

Average blood levels are 2 to 5 times higher than those following the same dose of oral benzylpenicillin (penicillin G) and also show much less individual variation.

Once absorbed, about 80% of phenoxymethylpenicillin (penicillin V) potassium is bound to serum protein. Tissue levels are highest in the kidneys, and lesser amounts appear in the liver, skin, and intestines. Small concentrations are found in all other body tissues and the cerebrospinal fluid. The drug is excreted as rapidly as it is absorbed in individuals with normal kidney function. In individuals with impaired kidney function, excretion is considerably delayed.

5.3. Preclinical safety data

Phenoxymethylpenicillin is a drug on which extensive clinical experience has been obtained. All relevant information for the prescriber is provided in the prescribing information.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Maize Starch
Magnesium Stearate
Povidone
Hypromellose
Purified Talc
Titanium Dioxide (E171)
Macrogol 6000

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years

6.4. Special precautions for storage

Blisters: Do not store above 25ºC. Store in the original package

Containers: Do not store above 25ºC. Keep the container tightly closed

6.5. Nature and contents of container

HDPE tablet containers, pack sizes of 1000 tablets

Al /PVC/ PVdC blister, pack sizes of 28 tablets

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)

No special requirements

7. MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited,
Unit 3, Canalside,
Northbridge Road,
Berkhamsted,
Hertfordshire,
HP4 1EG

8. MARKETING AUTHORISATION NUMBER

PL 17907/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/01/2006

10 DATE OF REVISION OF THE TEXT

PHENOXYMETHYLPENICILLIN 250mg TABLETS BP

PL 17907/0033

PRODUCT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

Please read all of this leaflet carefully before you start taking this medicine. Keep the leaflet. You may need to read it again.
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 you have any further questions, please ask your doctor or pharmacist.

The name of this medicine is
PHENOXYMETHYLPENICILLIN 250 mg TABLETS BP

Each tablet contains 250mg of the active ingredient Phenoxymethylpenicillin (as Phenoxymethylpenicillin Potassium). The tablets also contain maize starch, magnesium stearate, povidone, hypromellose, purified talc, macrogol and the colouring agent titanium dioxide (E171).

The product licence holder and manufacturer is Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG.

What the tablets are and what they are used for

Phenoxymethylpenicillin belongs to a group of medicines called penicillins, which are used to fight bacteria that cause infections.

The tablets are round, white to off white film-coated tablets marked "BL/250" on one side.

The tablets are supplied to your pharmacist in packs containing 28 or 1000 tablets, who will then provide you with the required number of tablets as prescribed by your doctor (not all pack sizes may be marketed).

Phenoxymethylpenicillin tablets are used to treat a wide range of bacterial infections of the ear, throat, respiratory tract, skin and soft tissues. It may also be used to prevent infections such as rheumatic fever or chorea recurring, for the prevention of bacterial endocarditis in susceptible patients before surgery and prevention of infection in patients without a spleen or patients with sickle cell disease.

Before you take the tablets

Please read the following questions. If the answer is YES to any of these questions, you MUST speak to your doctor before taking this medicine.

- Are you pregnant, or trying to become pregnant or are you breast feeding?
- Have you ever had a bad reaction or are you allergic to phenoxymethylpenicillin, any other penicillin or cephalosporin drug, or to any other drug?
- Are you allergic to any of the other ingredients in the tablets which are listed above?
- Do you suffer from kidney problems?
- Are you suffering from any stomach or intestinal problems?
- Are you taking any other medicines, including those you may have bought over the counter? Particularly any of the following:

- Any other antibiotics (such as erythromycin, neomycin or tetracycline)
- Probenecid (used to treat gout)
- Beta blockers (used to lower blood pressure)

Taking your Medicine

Take the tablets exactly as directed by your doctor. If you do not understand the directions, ask your pharmacist, nurse or doctor to explain them to you. The dosage and duration of treatment will depend on the type and severity of the infection.

The usual doses are detailed overleaf. Doctors sometimes prescribe different doses to these and if this applies to you, discuss it with your doctor if you have not already done so. You should always follow your doctor's instructions as to how and when to take your medicine.

Swallow the tablets whole with a full glass of water. The tablets preferably should be taken on an empty stomach but they may also be taken with or after food.

For the treatment of bacterial infections:
For adults and children over 12 years the usual dose ranges from 125mg (half a tablet) to 500mg (2 tablets) every 6-8 hours, depending on the condition being treated. In poor kidney function the dose may be lowered.

For preventing the recurrence of rheumatic fever or chorea: 125mg (half a tablet) twice daily.

For the prevention of bacterial endocarditis in susceptible patients before surgery:
For adults and children over 12 years the usual dose is 2g (8 tablets) one hour before the procedure and a further 1g (4 tablets) six hours later.
For children weighing less than 30 kg the usual dose is 1g (4 tablets) one hour before the procedure and a further 500mg (2 tablets) six hours later.

For the prevention of infection in patients without a spleen or patients with sickle cell disease:
Adults and children over 12 years: 500mg (2 tablets) every 12 hours.
Children 6-12 years: 250mg (1 tablet) every 12 hours.
Children below 5 years: 125mg (half a tablet) every 12 hours.

For children over 12 years the dose should not exceed the maximum adult doses. For children under 12 years of age the usual daily dose is 15-50mg per kg body weight to be taken in 3 to 6 divided doses.

Take all of the tablets that have been prescribed for you, even if you begin to feel better. Your symptoms may start to improve before the condition is completely treated. If you stop taking the tablets too soon, your symptoms may return.

If you take too much:
If you, a child or someone else has taken too many tablets, contact your doctor or hospital casualty department immediately.

If you miss a dose:
Take the missed dose as soon as you remember, however, if it is almost time for your next dose, skip the missed dose and then take your next dose when it is due. Do not take a double dose to make up for the missed dose. You can then take the rest of your doses for the day at evenly spaced intervals.

Possible Side Effects

As with all medicines there is a possibility of unwanted effects whilst taking this medicine, if you experience any of the following, stop taking the tablets and tell your doctor IMMEDIATELY:

- An allergic reaction - symptoms such as shortness of breath, skin rash or itching, hives, swelling of your lips, face or tongue, chills or fever or painful joints.
- Unusual bleeding or bruising.
- Seizures.

Other unwanted effects which are more likely to occur are:

- Nausea, vomiting or stomach upset.
- Diarrhoea.
- Black hairy tongue.

If you notice any of the above side effects, or you notice any other unusual or unexpected effects and think your tablets may be causing them, please inform your doctor or pharmacist.

Storing the tablets

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Blisters: Do not store above 25°C. Store in the original package (blister carton) to protect the tablets from moisture.
Tablet Containers: Do not store above 25°C. Keep the container tightly closed to protect the tablets from moisture.

Do not use the tablets after the expiry date shown on the carton and label.

Unless your doctor tells you to, do not keep any tablets that you no longer need.
Give them back to your pharmacist.

This leaflet was prepared in April 2005.

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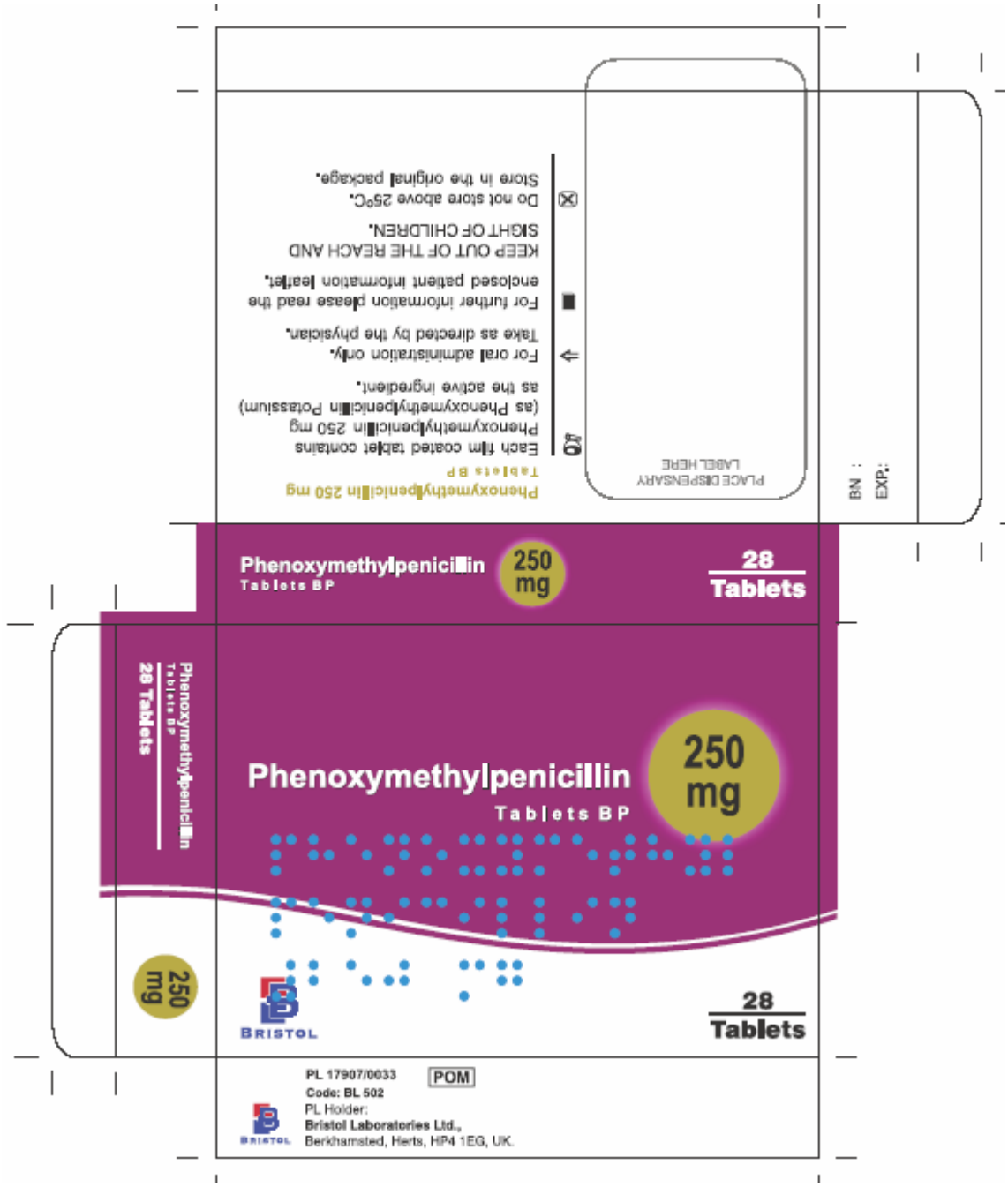
PHENOXYMETHYLPENICILLIN 250mg TABLETS BP

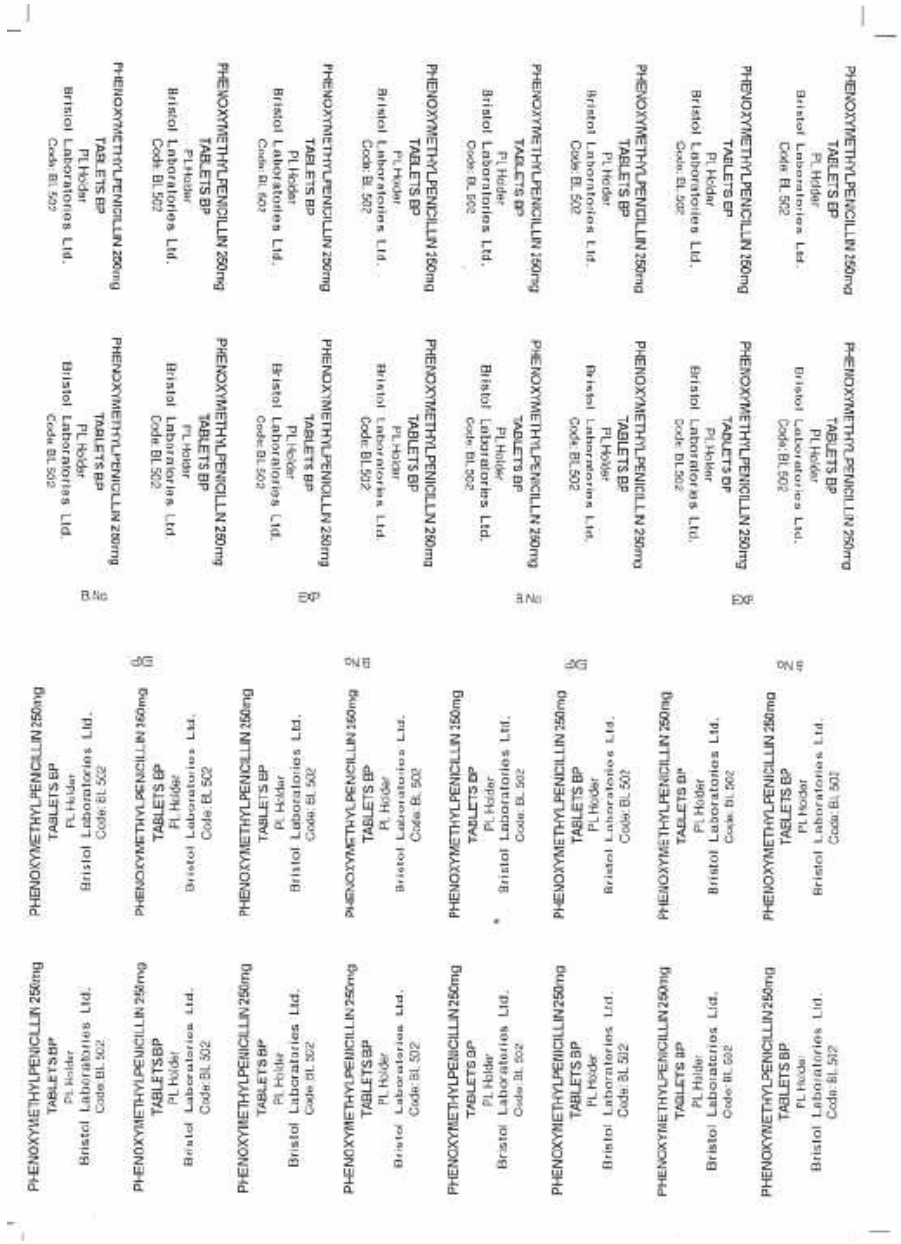
PL 17907/0033

LABELLING

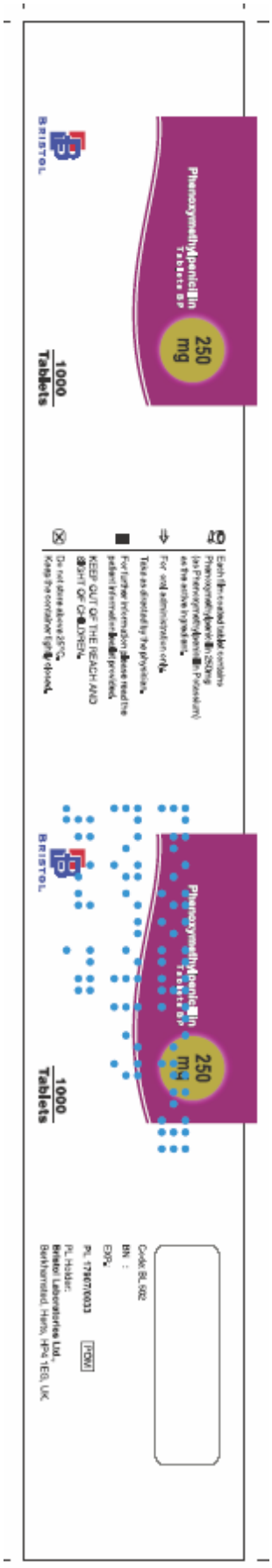
Carton



Blister


PHENOXYMETHYLPENICILLIN 250mg
TABLETS BP
PL Holder
Bristol Laboratories Ltd.
Code BL 502
B.No
Exp

Container


Phenoxymethylpenicillin
Tablets BP
250
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BRISTOL
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