Phenytoin Sodium 50 mg Film-coated Tablets

(Phenytoin sodium)

PL 16363/0253

UKPAR

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Phenytoin Sodium 50 mg Film-coated Tablets

PL 16363/0253

LAY SUMMARY

On 12th July 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Phenytoin Sodium 50 mg Film-coated Tablets (PL 16363/0253). This medicine is only available on prescription from the doctor.

Phenytoin is one of a group of medicines called anti-epileptic drugs; these medicines are used to treat epilepsy.

Phenytoin Sodium 50 mg Film-coated Tablets can be used to control a variety of epileptic conditions, to control or prevent seizures during or after brain surgery or severe head injury. Phenytoin can also be used to treat trigeminal neuralgia (facial nerve pain).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Phenytoin Sodium 50 mg Film-coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

Phenytoin Sodium 50 mg Film-coated Tablets

PL 16363/0253

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Marketing Authorisation (licence) for the medicinal product Phenytoin Sodium 50 mg Film-coated Tablets (PL 16363/0253) to Milpharm Limited on 12th July 2013. This prescription only medicine (POM) is indicated for control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. Phenytoin has also been employed in the treatment of trigeminal neuralgia but it should only be used as second line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine.

This application was originally submitted as part of a Decentralised procedure, but since there was only one member state (UK) involved for the 50 mg strength the application (PL 16363/0278) was withdrawn and re-submitted as a national application (PL 16363/0253). The 100 mg application (PL 16363/0279; UK/H/4715/002/DC) continued in the Decentralised procedure and this national 50 mg application was assessed in parallel.

This is a national abridged application for Phenytoin Sodium 50 mg film-coated tablets submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applicant cross-refers to Epanutin 50 mg Capsules (PL 00018/5079R), originally granted to Parke Davis & Company Limited on 31st October 1989. The reference product has under gone a Change of Ownership (COA) procedure and was authorised to Warner Lambert (UK) Limited on 31st October 1997 (PL 00019/0131) and then to the current Marketing Authorisation Holder, Pfizer Limited (PL 00057/0523) on 1st March 2004.

A pharmacovigilance system has been provided with this application and is satisfactory. A suitable justification for non-submission of the Risk Management Plan has been provided.

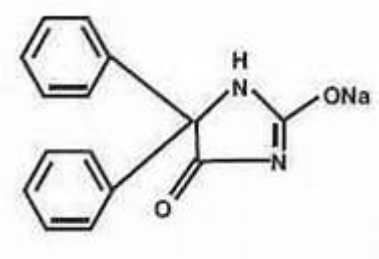
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature
rINN: Phenytoin sodium

Chemical Names: sodium 4-oxo-5,5-diphenyl-4,5-dihydro-1 *H*-imidazol-2-olate
2,4-Imidazolidinedione, 5,5-diphenyl-,monosodium salt
5,5-diphenylimidazolidine-2,4-dione, sodium salt

Structure:



Molecular Formula: $C_{15}H_{11}N_2NaO_2$

Molecular Weight: 274.3 g/mol

Appearance: White odourless powder and hygroscopic.

Solubility: Soluble in water and alcohol and practically insoluble in ether and methylene chloride.

Phenytoin sodium is the subject of an Active Substance Master File (ASMF).
.
Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof of structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

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

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the

primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients mannitol, crospovidone, magnesium stearate, croscarmellose sodium making up the tablet core, and the tablet coat consisting of hypromellose, macrogol 400, titanium dioxide and sodium lauril sulphate.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

Pharmaceutical development

The objective of the development programme was to formulate robust, stable tablets containing phenytoin sodium that could be considered a generic medicinal product of Epanutin 50 mg Hard Capsules (Pfizer Limited, UK).

Comparable dissolution and impurity profiles are provided for this product versus the originator product.

Manufacture

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Process validation data has been submitted for the minimum production batch size and the results are satisfactory. The applicant has committed to conduct the validation of any interim production batch sizes that may be manufactured until the full- scale commercial batches have been validated.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The tablets are packed in:

- Polyamide/aluminium/polyvinylchloride/aluminium blister pack containing 10, 14, 20, 28, 30, 50, 60, 84, 100, 112, 200 and 250 film-coated tablets.

- High density polyethylene (HDPE) container with a polypropylene closure and silica gel desiccant with a pack size of 30 Film-coated Tablets.

Not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with storage conditions “Store in the original package in order to protect from moisture” and “Keep the HDPE bottle tightly closed” have been set. These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically satisfactory.

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

The Marketing Authorisation Holder has committed to submit mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Form
The MAA form is pharmaceutically satisfactory.

Expert Report/Quality overall summary
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.

NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of phenytoin sodium are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of environmental risk assessment.

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

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

BIOEQUIVALENCE

In support of this application, the Marketing Authorisation holder has submitted a bioequivalence study:

A randomised, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of the test product Phenytoin Sodium 3 x 100 mg Film-coated Tablets (Aurobindo Pharma Ltd., India) and the reference product Epanutin 3 x 100 mg Hard Capsules (Pfizer Limited, UK) in healthy adult, male, human subjects under fasting conditions.

All volunteers received a single oral dose (3 x 100 mg) of either the test or the reference product with 240mL of water under fasting conditions. Serial blood samples were drawn before dosing (0.0) and at 0.33, 0.67, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.00, 18.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00 and 144.00 hours post dose. There was a washout period of 14 days between the dosings.

The pharmacokinetic results for phenytoin are presented below:

PARAMETER	**INTRA-SUBJECT C.V. (%)**	**GEOMETRIC MEANS**		**(T/R) RATIO** (%)	**90% CONFIDENCE LIMITS (%)**	
		Test	**Reference**		**Lower**	**Upper**
C_{max} (ng/ml)	11.90	1510.00	1573.44	95.97	90.82	101.41
AUC_{0-t} (hr.ng/ml)	7.79	44899.20	44458.25	100.99	97.41	104.71
AUC_{0-inf} (hr.ng/ml)	7.51	46558.16	45943.19	101.34	97.86	104.94

The results show that the 90% confidence intervals for AUC and C_{max} fell within the acceptable range (80.00-125.00%). The product also fulfills the bioequivalence criteria for Narrow Therapeutic Drugs (90.00-111.11%) as included in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) Bioequivalence has been shown for the test formulation (Phenytoin Sodium 100 mg Film-coated Tablets) and the reference formulation (Epanutin 100 mg Hard Capsules).

As the 50 mg and 100mg tablet strengths meet the biowaiver criteria as specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the results and conclusions from the bioequivalence study with the 100 mg strength can be extrapolated to the 50 mg strength.

EFFICACY

No new efficacy data have been submitted and none are required for this application.

SAFETY

No new safety data have been submitted and none are required for this application.

EXPERT REPORT

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

LABELLING
This is satisfactory

MAA FORM
This is satisfactory.

CONCLUSIONS
There are no objections to the approval of this product from a clinical point of view.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Phenytoin Sodium 50 mg Film-coated Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

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

EFFICACY

With the exception of the bioequivalence study, no new data have been submitted and none are required for applications of these type.

Bioequivalence has been demonstrated between the applicant's Phenytoin Sodium 100 mg Film-coated Tablets and the reference product, Epanutin 100 mg Hard Capsules (Pfizer Limited, UK). As the 50 mg and 100mg tablet strengths meet the biowaiver criteria as specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the results and conclusions from the bioequivalence study with the 100 mg strength can be extrapolated to the 50 mg strength.

SAFETY

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in line with current guidelines. The labelling is in line with current guidelines.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. The data provided support the claim that the applicant's product is a generic medicinal product of the reference product, Epanutin 50 mg Hard Capsules (Pfizer Limited, UK). Extensive clinical experience with phenytoin sodium is considered to have demonstrated the therapeutic value of the compound. The risk benefit assessment is, therefore, considered to be positive.

Phenytoin Sodium 50 mg Film-coated Tablets

PL 16363/0253

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the Marketing Authorisation application on 17th January 2011.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 25th January 2011.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 31st January 2011, 15th August 2011, 23rd January 2012, 27th January 2012, 2nd April 2012, 30th April 2012, 2nd May 2012 and 9th May 2012
4	The applicant responded to the MHRA's requests, providing further information to the quality section on 23rd May 2011, 18th November 2011, 26th January 2012, 27th March 2012, 19th April 2012, 2nd May 2012, 3rd May 2012 and 14th May 2012
5	The application was determined on 12th July 2013.

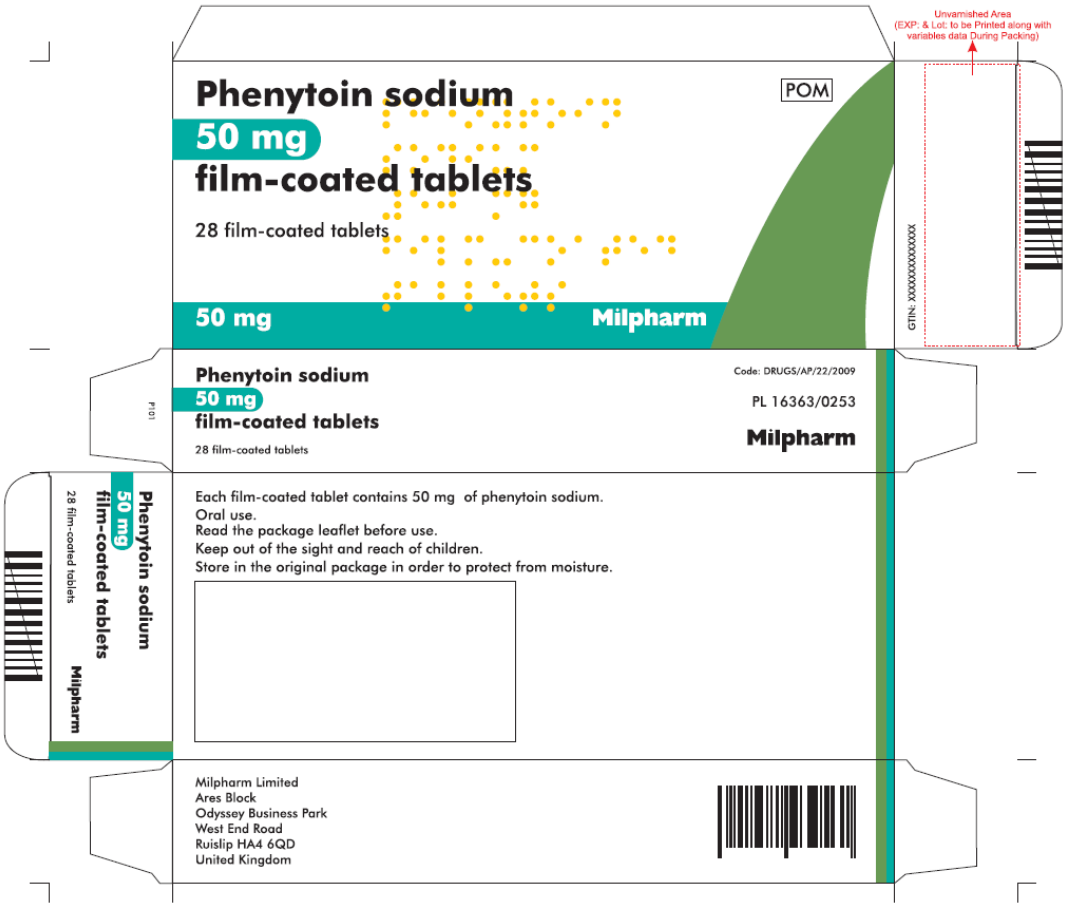
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING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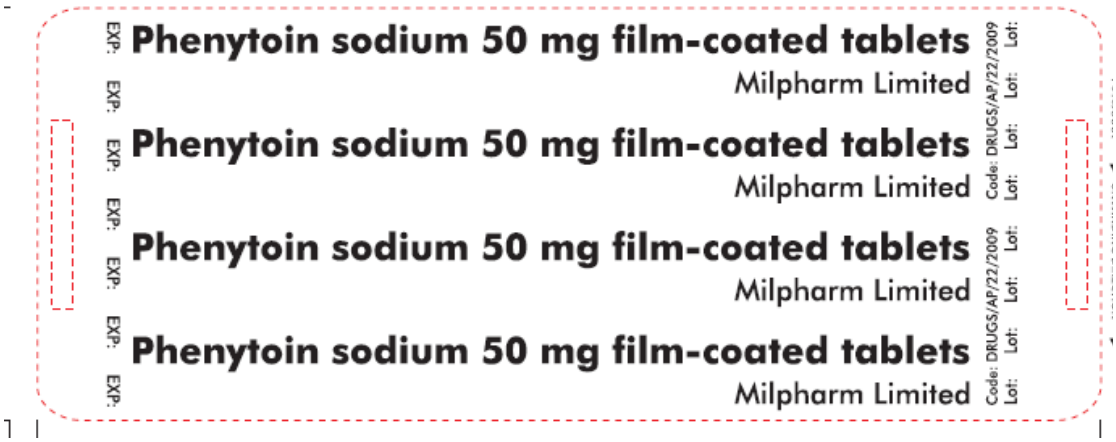
Phenytoin sodium
50 mg
film-coated tablets
28 film-coated tablets
POM
50 mg
Milpharm
GTIN: XXXXXXXXXXXXX
Phenytoin sodium
50 mg
film-coated tablets
28 film-coated tablets
Code: DRUGS/AP/22/2009
PL 16363/0253
Milpharm
Each film-coated tablet contains 50 mg of phenytoin sodium.
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store in the original package in order to protect from moisture.
Milpharm Limited
Ares Block
Odyssey Business Park
West End Road
Ruislip HA4 6QD
United Kingdom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Phenytoin sodium 50 mg film-coated tablets
Milpharm Limited
Lot:
Code: DRUGS/AP/22/2009


Phenytoin sodium
50 mg
film-coated tablets
112 film-coated tablets
POM
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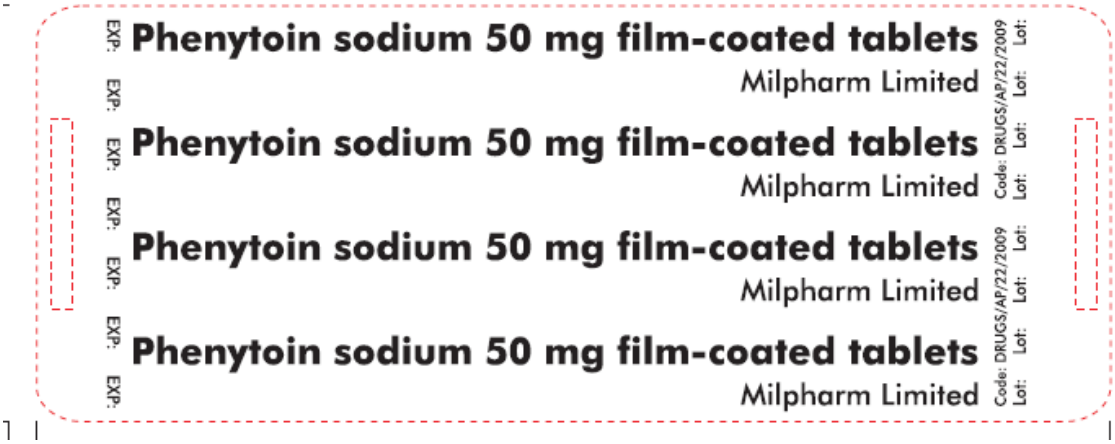
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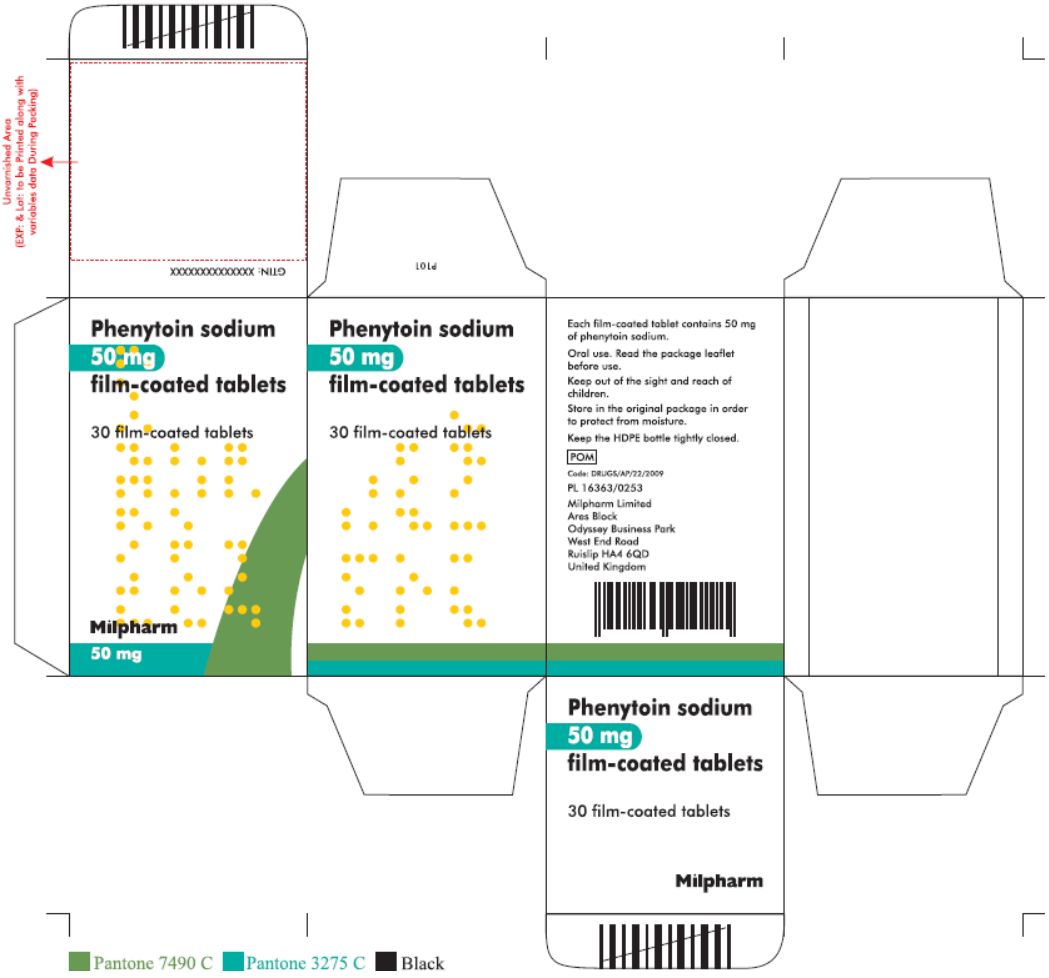
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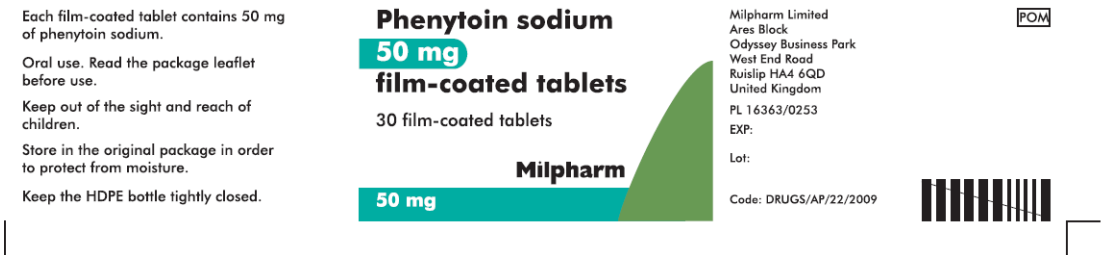
(EXP. & Lot: To Be Printed along with variables data During Packing)
GTIN: XXXXXXXXXXXXX
P101
Phenytoin sodium
50 mg
film-coated tablets
30 film-coated tablets
Milpharm
50 mg
Phenytoin sodium
50 mg
film-coated tablets
30 film-coated tablets
Each film-coated tablet contains 50 mg of phenytoin sodium.
Oral use. Read the package leaflet before use.
Keep out of the sight and reach of children.
Store in the original package in order to protect from moisture.
Keep the HDPE bottle tightly closed.
POM
Code: DRUGS/AP/22/2009
PL 16363/0253
Milpharm Limited
Ares Block
Odyssey Business Park
West End Road
Ruislip HA4 6QD
United Kingdom
Phenytoin sodium
50 mg
film-coated tablets
30 film-coated tablets
Milpharm
Pantone 7490 C
Pantone 3275 C
Black


Each film-coated tablet contains 50 mg of phenytoin sodium.
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