Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

LEVETIRACETAM 250MG FILM-COATED TABLETS
LEVETIRACETAM 500MG FILM-COATED TABLETS
LEVETIRACETAM 750MG FILM-COATED TABLETS
LEVETIRACETAM 1000 MG FILM-COATED TABLETS

(Levetiracetam)

Procedure No: UK/H/4062/001-4/DC

UK Licence No: PL 29831/0360-3

WOCKHARDT UK LTD

LAY SUMMARY

On 03 May 2012, Germany, Malta, Netherlands, and the UK agreed to grant Marketing Authorisations to Wockhardt UK Ltd for the medicinal products Levetiracetam 250mg, 500mg, 750mg and 1000mg Film-Coated Tablets (PL 29831/0360-3; UK/H/4062/001-4/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 28 June 2012. These are Prescription-Only Medicines (POM).

Levetiracetam 250mg, 500mg, 750mg and 1000mg Film- Coated Tablets are an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

Levetiracetam is used:

- on its own in adults and adolescents from 16 years of age with newly diagnosed epilepsy, to treat partial onset seizures with or without secondary generalisation.
- as an add-on to other antiepileptic medicines to treat:
  i) partial onset seizures with or without generalisation in adults, adolescents, children and infants from one month of age.
  ii) myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy
  iii) primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Levetiracetam 250mg, 500mg, 750mg and 1000mg Film-Coated Tablets outweigh the risks and Marketing Authorisations were granted.

TABLE OF CONTENTS

Module 1

Product Name	Levetiracetam 250mg Film-Coated Tablets Levetiracetam 500mg Film-Coated Tablets Levetiracetam 750mg Film-Coated Tablets Levetiracetam 1000mg Film-Coated Tablets
Type of Application	Generic, Article 10 (1)
Active Substances	Levetiracetam
Form	Film-coated tablets
Strength	250 mg, 500 mg, 750 mg and 1000 mg.
MA Holder	Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK
Reference Member State (RMS)	UK
Concerned Member State (CMS)	Germany, Malta and the Netherlands.
Procedure Number	UK/H/4062/001-4/DC
Timetable	Day 210– 03 May 2012

Module 2
Summary of Product Characteristics

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

Module 3

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

Module 4
Labelling

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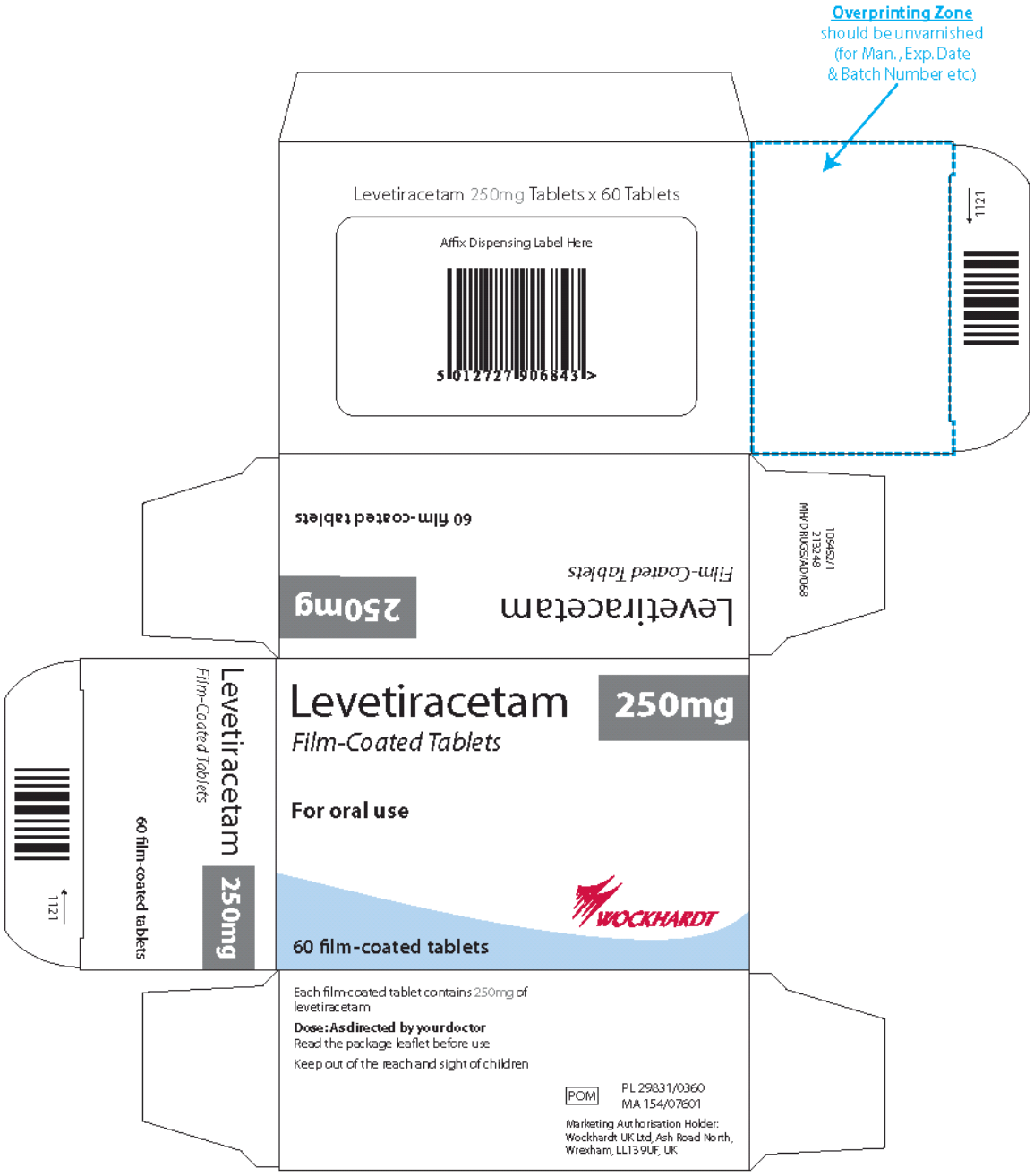

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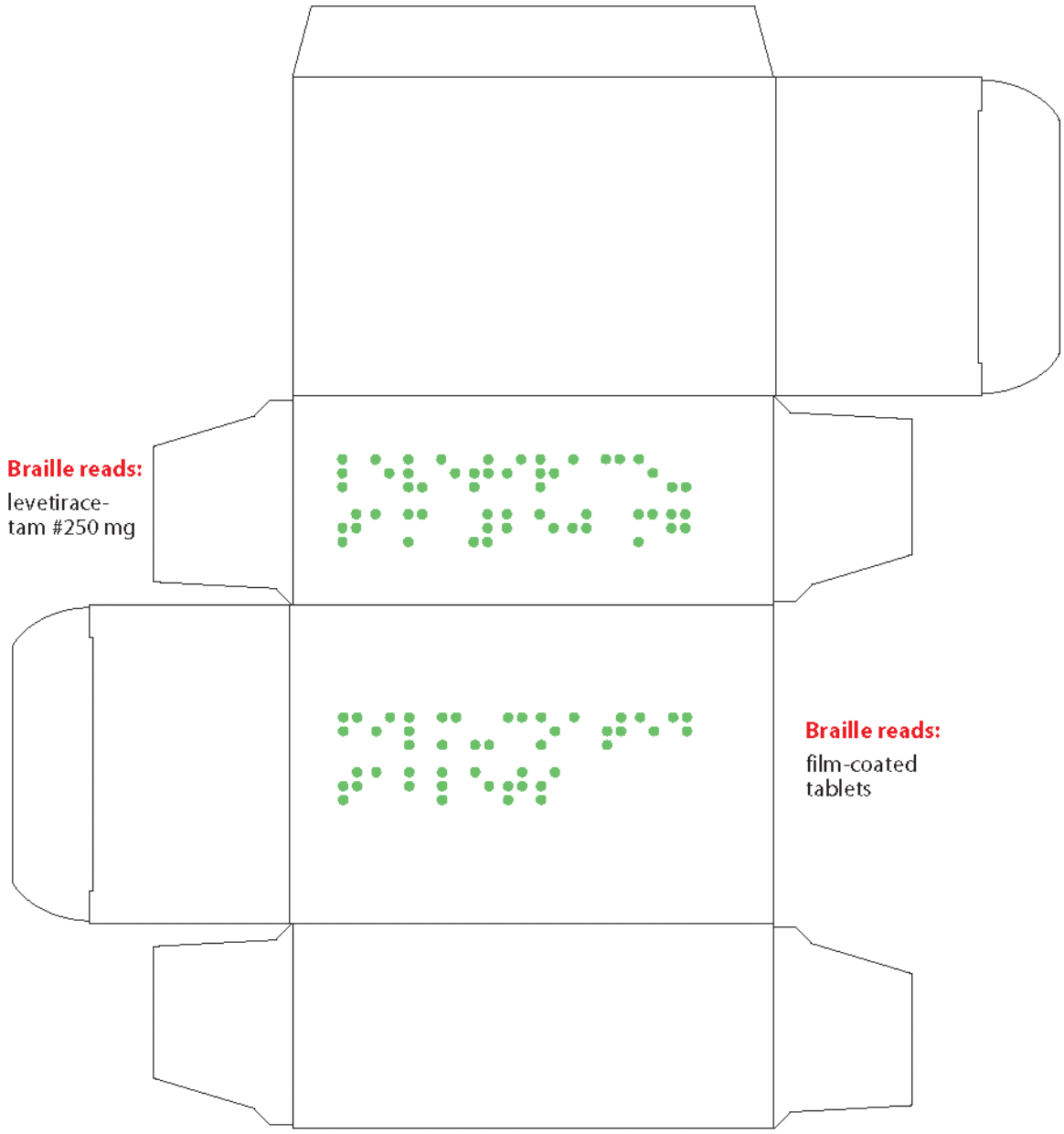

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tam #250 mg

Braille reads:
film-coated
tablets

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film-coated
tablets

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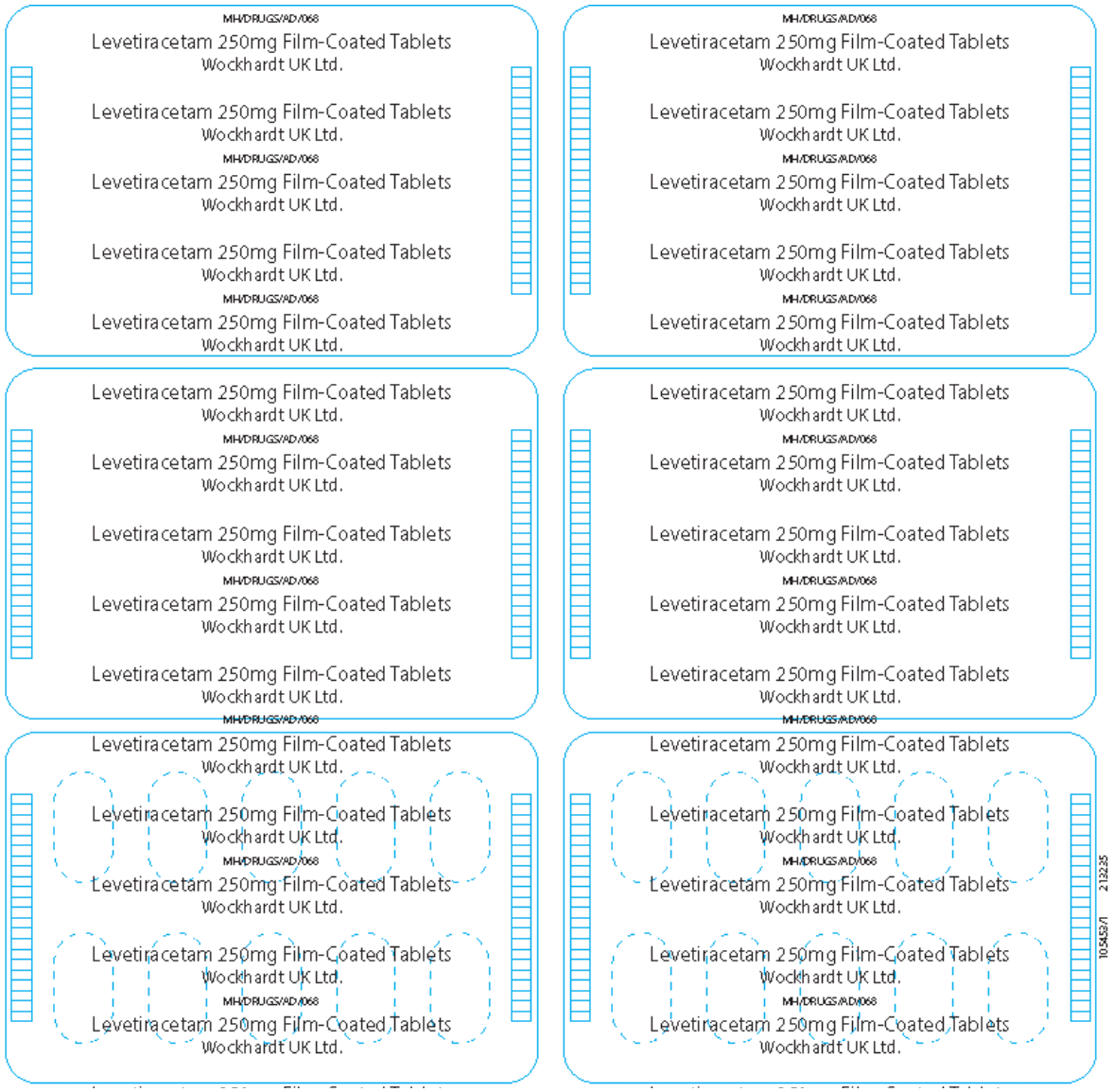
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Levetiracetam 250mg Film-Coated Tablets
Wockhardt UK Ltd.
105453/1 212235

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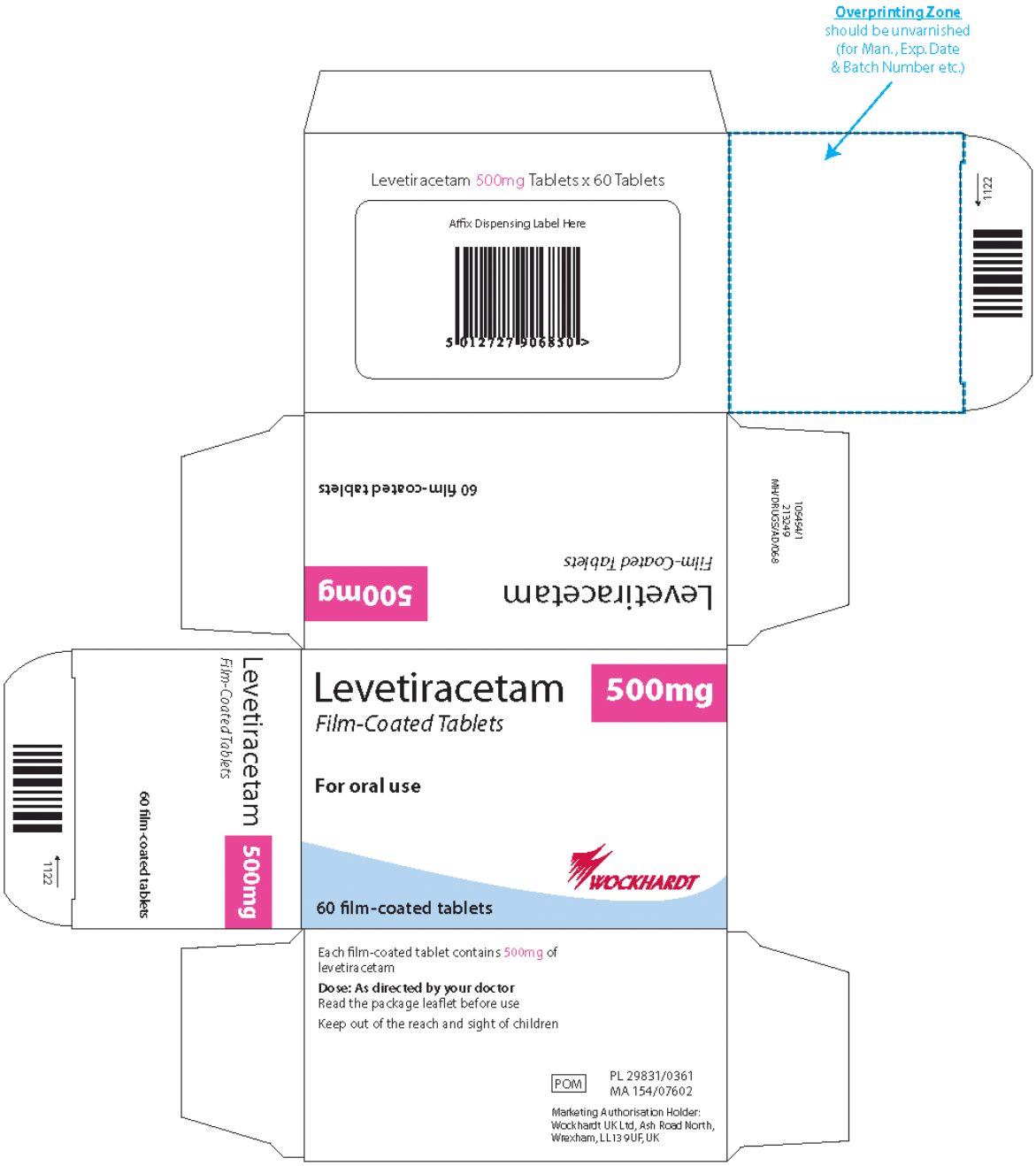
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& Batch Number etc.)
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1122
60 film-coated tablets
500mg
Levetiracetam
Film-Coated Tablets
Levetiracetam
Film-Coated Tablets
500mg
60 film-coated tablets
1122
Levetiracetam 500mg
Film-Coated Tablets
For oral use
WOCKHARDT
60 film-coated tablets
Each film-coated tablet contains 500mg of levetiracetam
Dose: As directed by your doctor
Read the package leaflet before use
Keep out of the reach and sight of children
POM
PL 29831/0361
MA 154/07602
Marketing Authorisation Holder:
Wockhardt UK Ltd, Ash Road North,
Wrexham, LL13 9UF, UK

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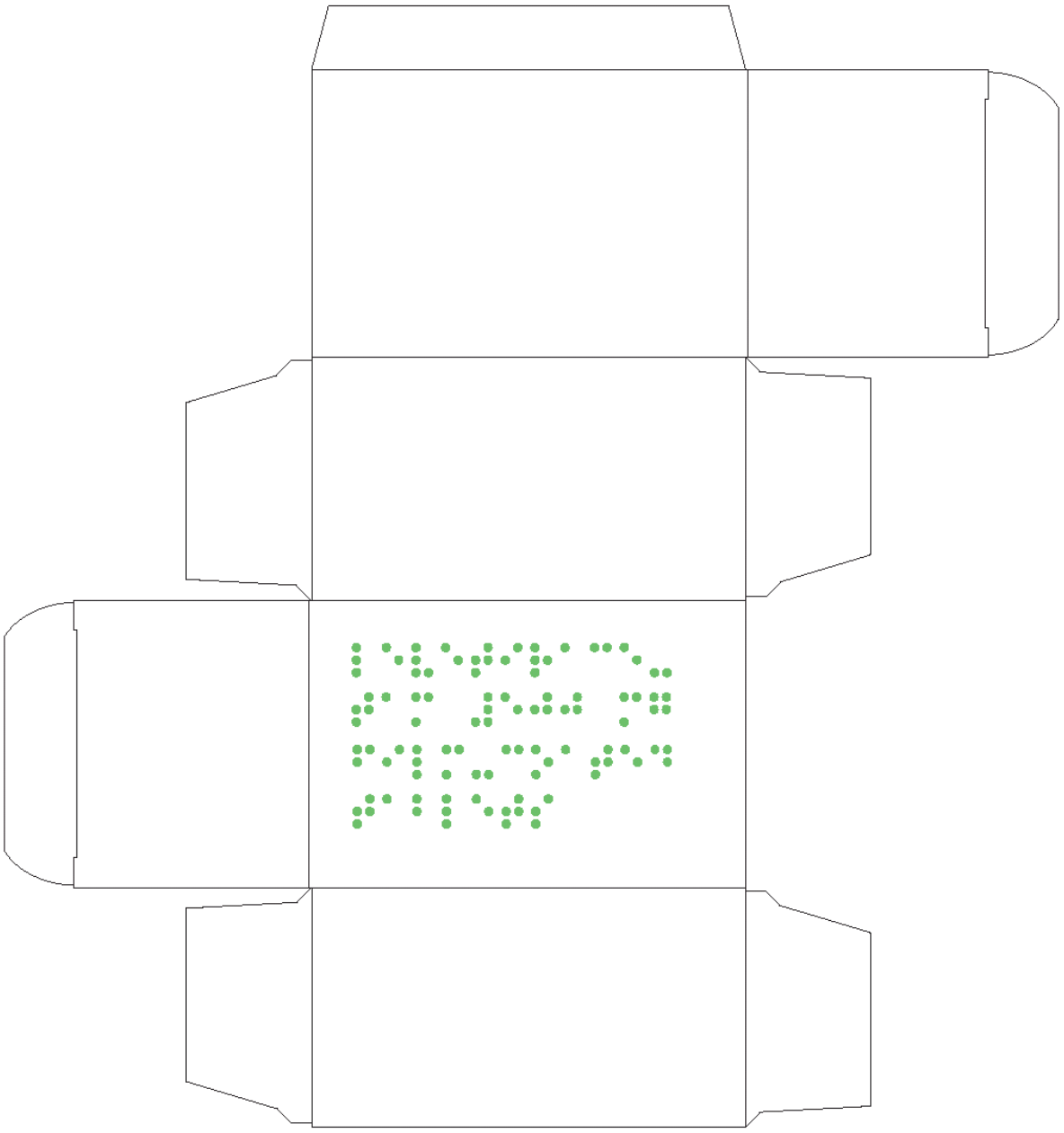

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tam #500 mg
film-coated
tablets

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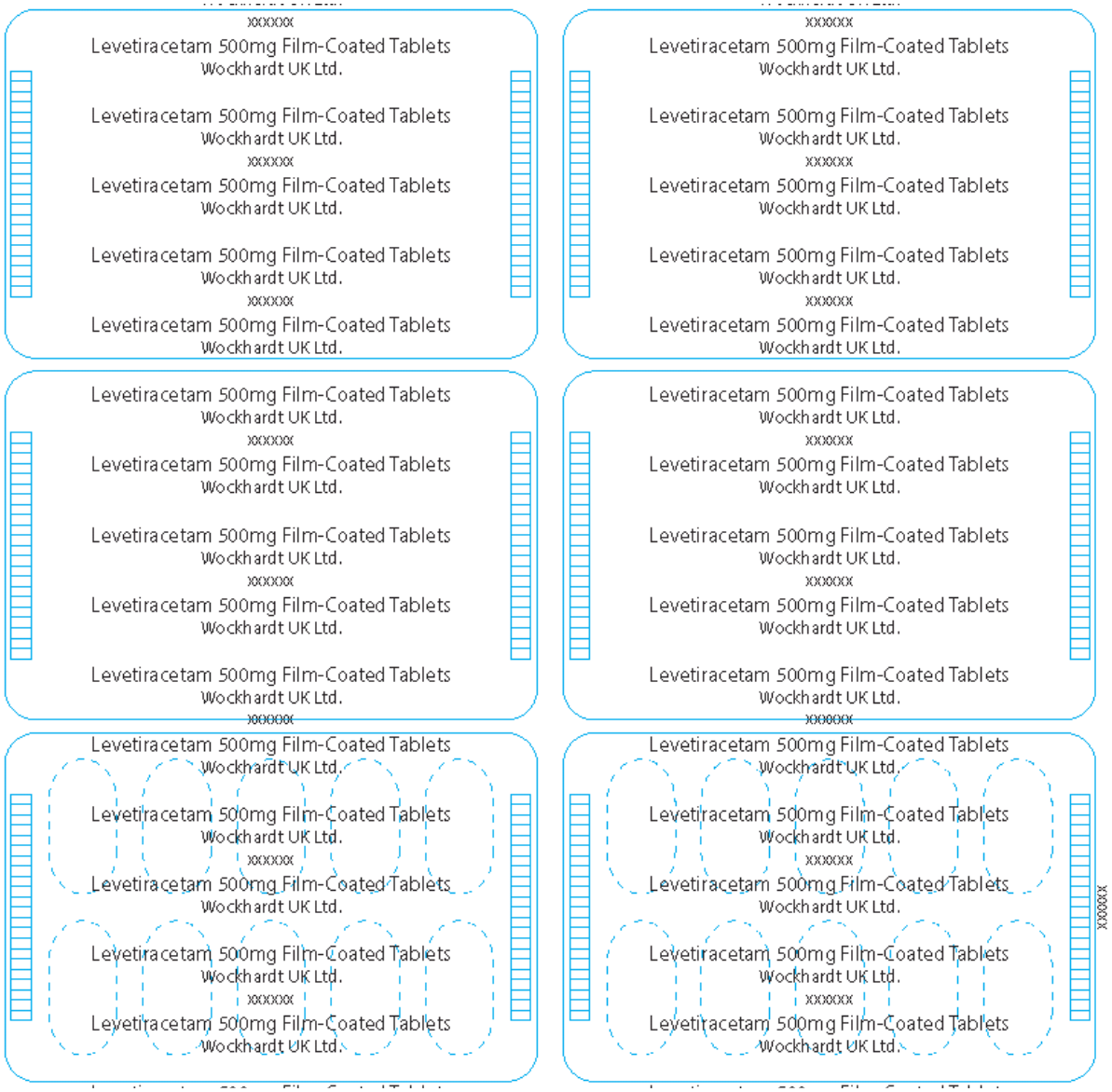
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Levetiracetam 500mg Film-Coated Tablets
Wockhardt UK Ltd.
xxxxxx

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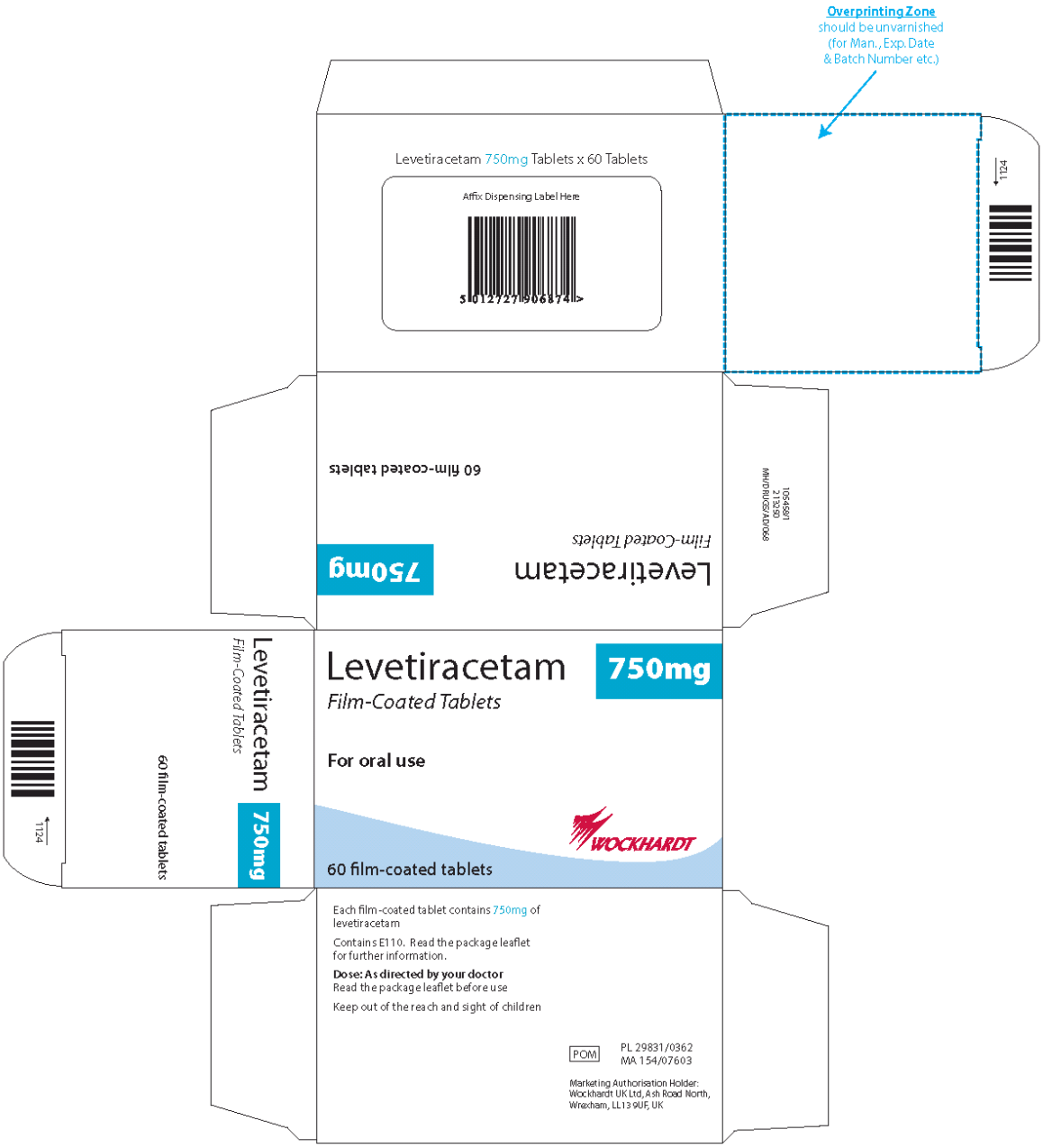
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(for Man., Exp. Date
& Batch Number etc.)
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1124
60 film-coated tablets
750mg
Levetiracetam
Film-Coated Tablets
Levetiracetam
Film-Coated Tablets
750mg
For oral use
WOCKHARDT
60 film-coated tablets
Each film-coated tablet contains 750mg of levetiracetam
Contains E110. Read the package leaflet for further information.
Dose: As directed by your doctor
Read the package leaflet before use
Keep out of the reach and sight of children
POM
PL 29831/0362
MA 154/07603
Marketing Authorisation Holder:
Wockhardt UK Ltd, Ash Road North,
Wrexham, LL13 9UF, UK

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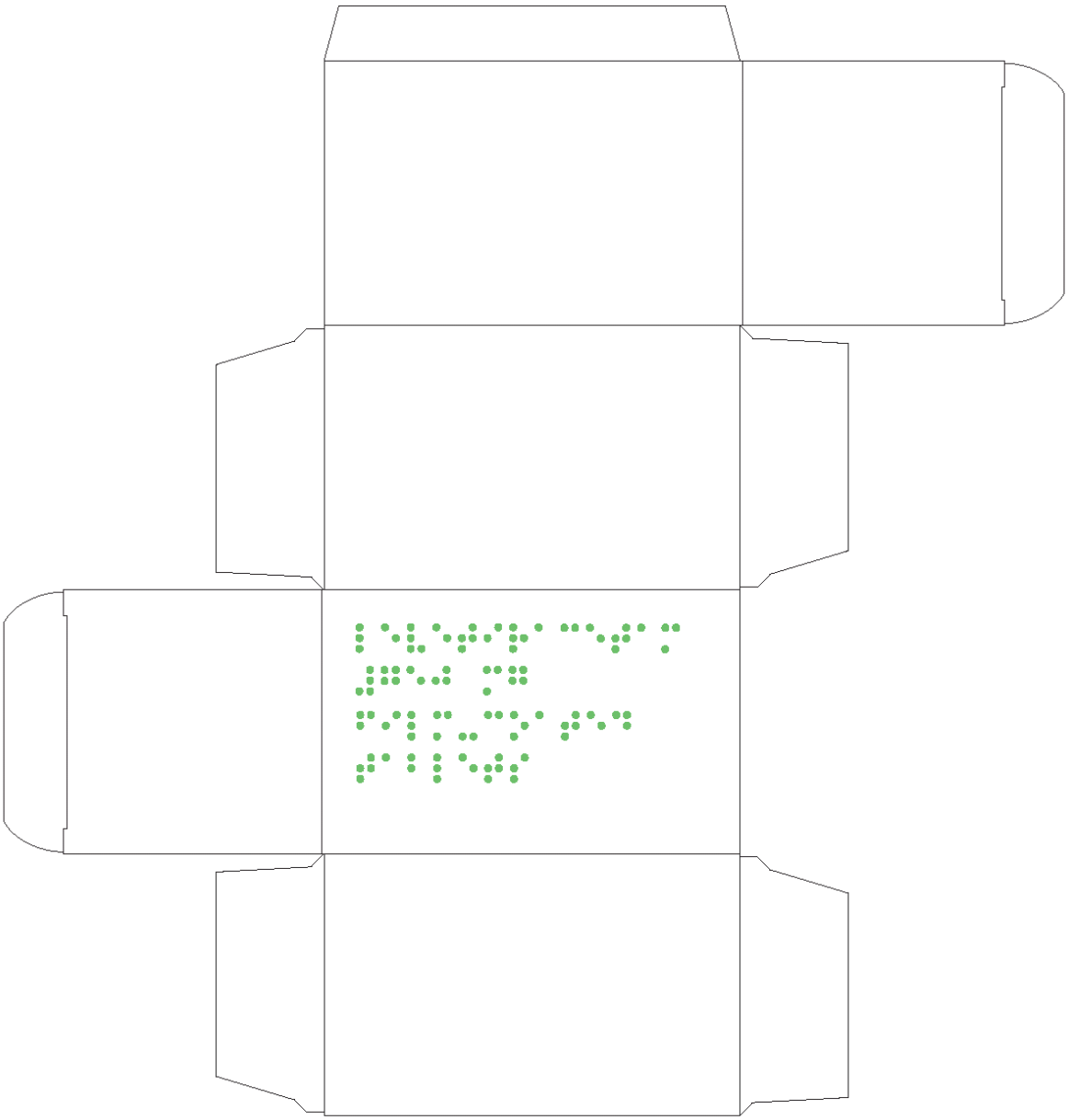

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film-coated
tablets

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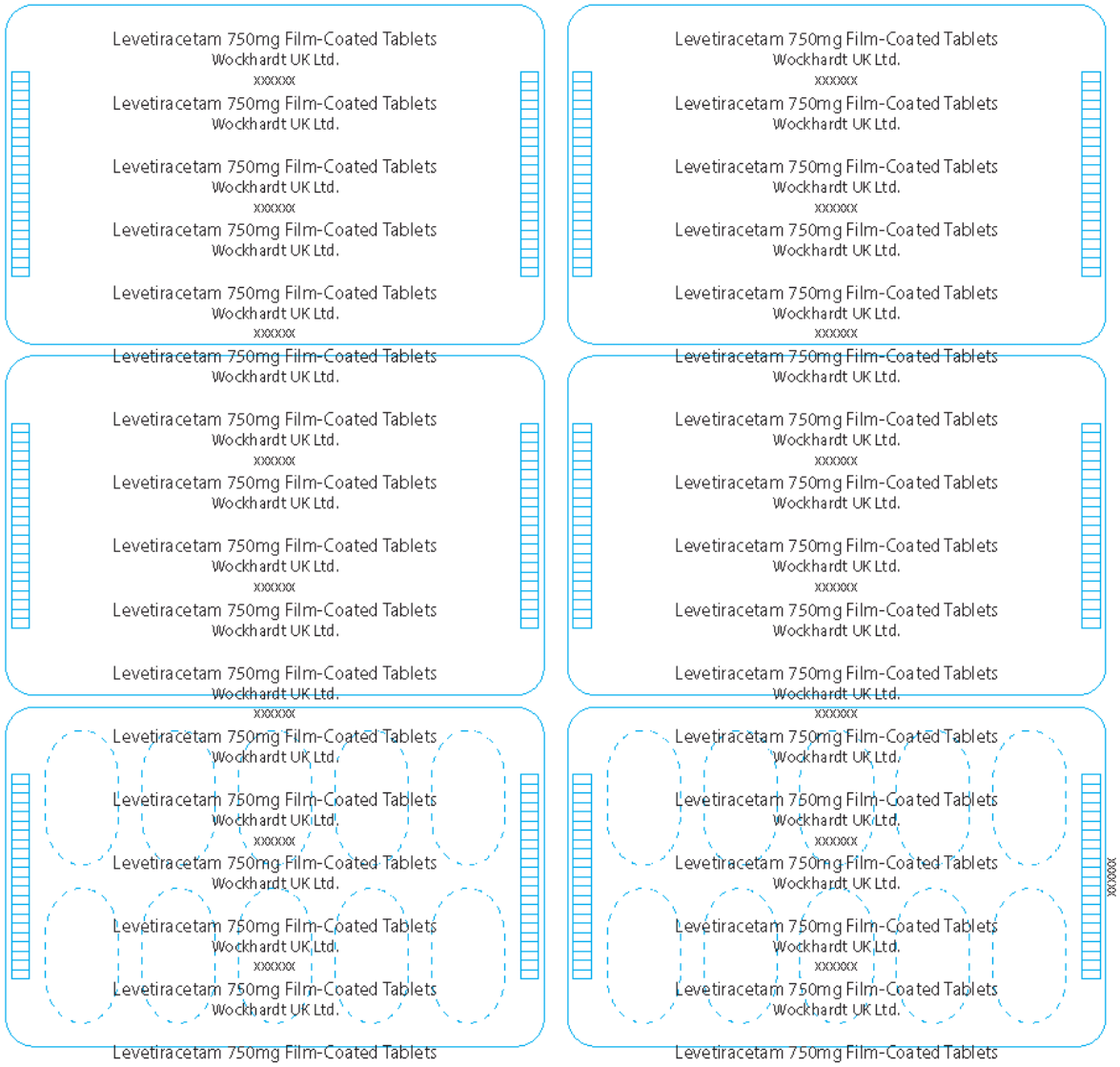
Levetiracetam 750mg Film-Coated Tablets
Wockhardt UK Ltd.
xxxxxx

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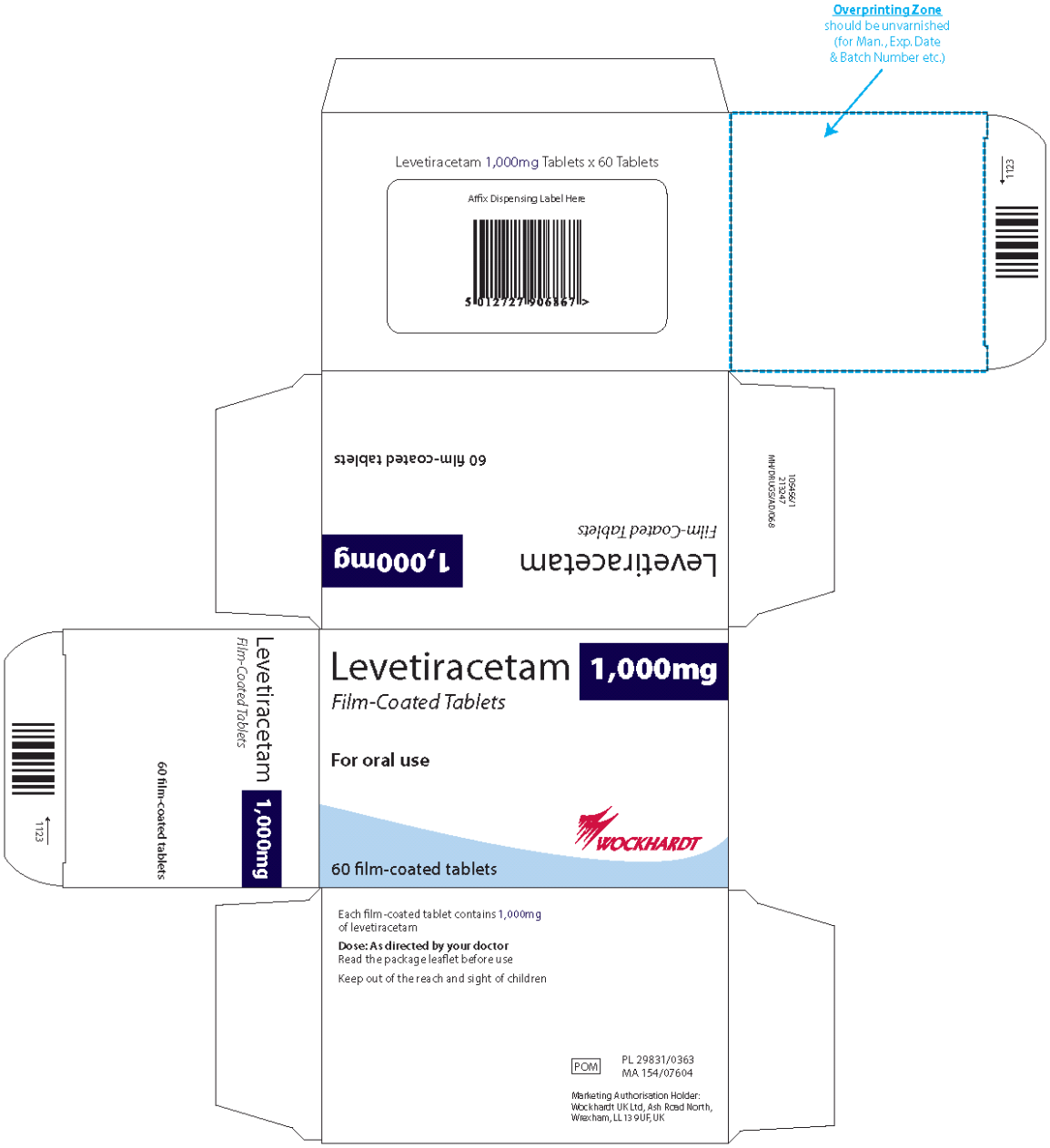
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(for Man., Exp. Date
& Batch Number etc.)
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1123
60 film-coated tablets
1,000mg
Levetiracetam
Film-Coated Tablets
Levetiracetam
Film-Coated Tablets
1,000mg
60 film-coated tablets
1123
Levetiracetam 1,000mg
Film-Coated Tablets
For oral use
WOCKHARDT
60 film-coated tablets
Each film-coated tablet contains 1,000mg
of levetiracetam
Dose: As directed by your doctor
Read the package leaflet before use
Keep out of the reach and sight of children
POM
PL 29831/0363
MA 154/07604
Marketing Authorisation Holder:
Wockhardt UK Ltd, Ash Road North,
Wrexham, LL13 9UF, UK

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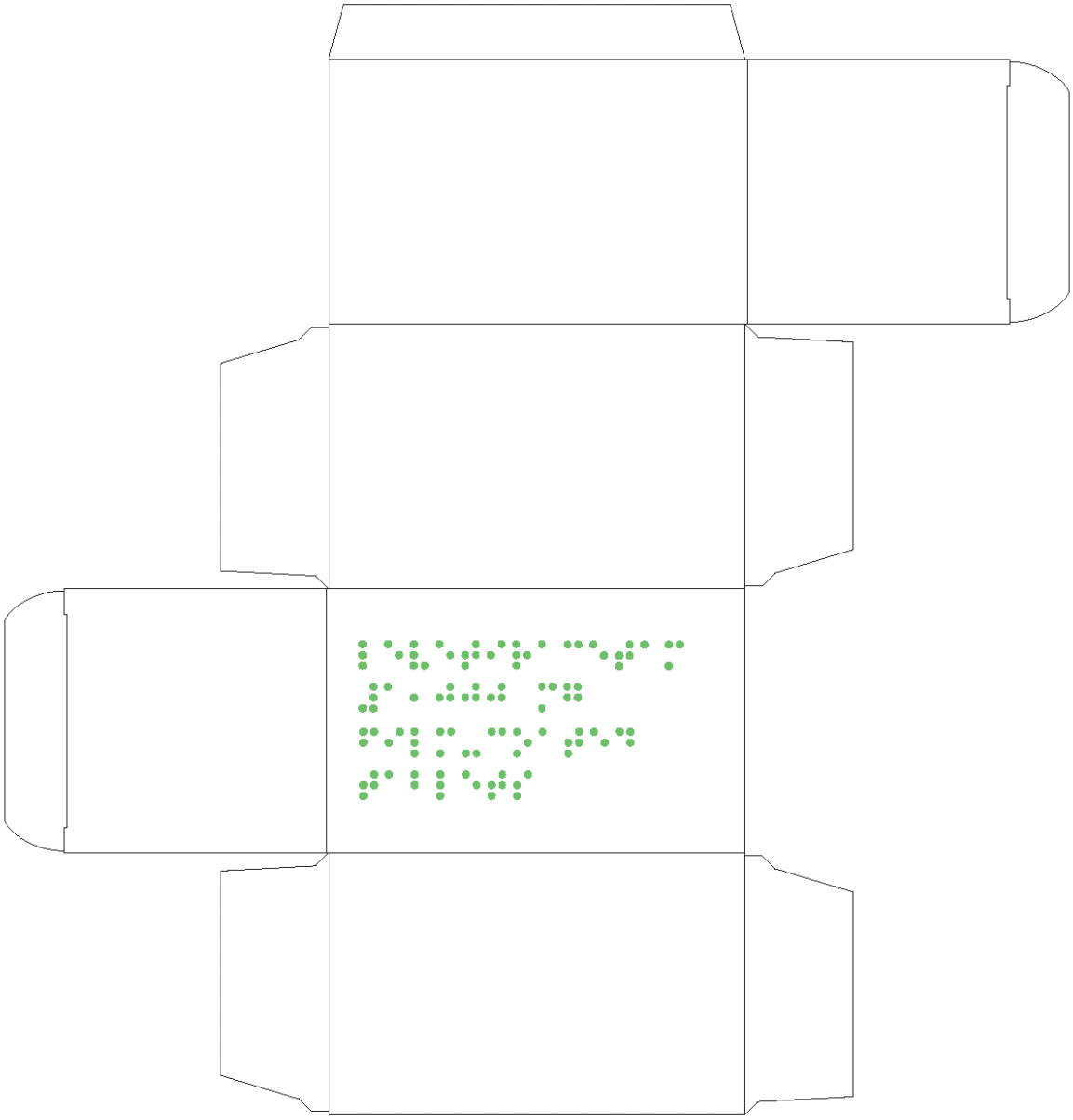

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film-coated
tablets

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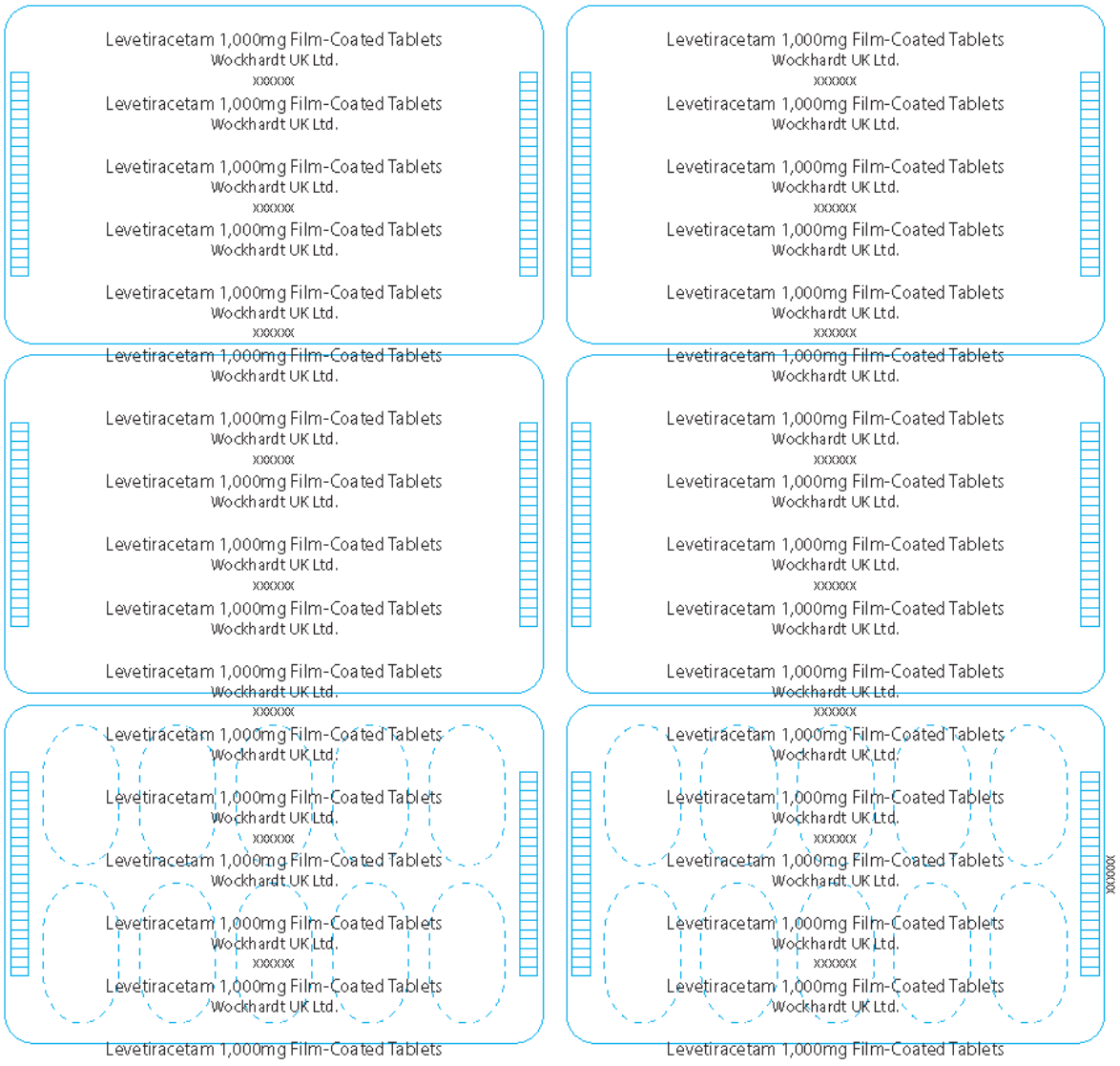

Levetiracetam 1,000mg Film-Coated Tablets
Wockhardt UK Ltd.
xxxxxx

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Levetiracetam 250mg, 500mg, 750mg and 1000mg Film-Coated Tablets (PL 29831/0360-3; UK/H/4062/001-4/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Germany, Malta and the Netherlands as Concerned Member State (CMS). These products are prescription-only medicines (POM).

Levetiracetam is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Levetiracetam is indicated as adjunctive therapy:

- in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Keppra 250mg, 500mg, 750mg and 1000mg film-coated tablets (UCB Pharma SA, Belgium), which have been authorised in the EEA since September 2000.

Levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances. The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

In vitro studies show that levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic versions of the originator products that have been licensed for over 10 years.

Two bioequivalence studies (single dose) were submitted to support these applications comparing the test product Levetiracetam 1000 mg Film-Coated Tablets (Wockhardt UK Ltd) with the reference product Keppra 1000mg film-coated tablets (UCB Pharma SA).

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic versions of the originator products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 03 May 2012. After a subsequent national phase, the licences were granted in the UK on 28 June 2012.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Levetiracetam 250mg Film-Coated Tablets Levetiracetam 500mg Film-Coated Tablets Levetiracetam 750mg Film-Coated Tablets Levetiracetam 1000mg Film-Coated Tablets
Name(s) of the active substance(s) (INN)	Levetiracetam
Pharmacotherapeutic classification (ATC code)	Antiepileptics, other antiepileptics (N03AX14)
Pharmaceutical form and strength(s)	250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/4062/001-4/DC
Reference Member State	United Kingdom
Concerned Member State	Germany, Malta and the Netherlands..
Marketing Authorisation Number(s)	PL 29831/0360-3
Name and address of the authorisation holder	Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

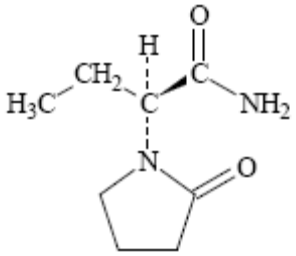
III.1 QUALITY ASPECTS

S. Active substance

INN: Levetiracetam

Chemical name: 2(S)-2-(2-Oxopyrrolidin-I-yl)butanamide

Structure:



Molecular formula: $C_8H_{14}N_2O_2$
Molecular mass: 170.2
Appearance: Levetiracetam is a white or almost white powder.
Solubility: Levetiracetam is very soluble in water, soluble in acetonitrile, practically insoluble in hexane..

Levetiracetam is the subject of a European Pharmacopoeia 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 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 active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients maize starch, croscarmellose sodium, povidone (K-30), purified talc, colloidal anhydrous silica and magnesium stearate. In addition:

- the 250 mg strength also contains Opadry II Blue 85F90694 [consisting of poly (vinyl alcohol)- part hydrolysed, talc (E553b), titanium dioxide (E 171), macrogol 4000, talc (E553b) and indigo carmine aluminium lake (E 132)]
- The 500 mg strength contains Opadry II Yellow 85F32004 [consisting of poly (vinyl alcohol)- part hydrolysed, titanium dioxide (E 171), macrogol 4000, talc (E553b) and iron oxide yellow (E 172)]
- The 750 mg strength contains Opadry II Orange 85F23452 [consisting of poly (vinyl alcohol)-part hydrolysed, titanium dioxide (E171), macrogol 4000, talc (E553b) and sunset yellow FCF aluminium lake (E110)].
- The 1000 mg strength also contains Opadry II White 85F18422 [consisting of poly (vinyl alcohol)-part hydrolysed, titanium dioxide (E171), macrogol 4000 and talc (E553b)].

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry II Blue 85F90694, Opadry II Yellow 85F32004, Opadry II Orange 85F23452 and Opadry II White 85F18422 which are compliant with suitable in-house specifications. The ingredients in the film coating comply with pharmacopoeial requirements and colouring agents with current EU directives concerning the use of colouring agents. Satisfactory Certificates of Analysis and batch analysis results have been provided for all excipients.

With the exception of magnesium stearate, none of the excipients contain materials of animal or human origin. The supplier of magnesium stearate has provided a Certificate of Suitability from the European Directorate for the Quality of medicines (EDQM) to show that this excipient has been manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Transmissible Spongiform Encephalopathies (TSE).

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate stable, robust, tablets containing 250 mg, 500 mg and 750 mg and 1000 mg levetiracetam which could be considered generic medicinal products of Keppra 250mg, 500mg, 750mg and 1000mg film-coated tablets (UCB Pharma SA).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results. In addition the marketing authorisation holder has provided confirmation that process validation studies will be performed on future additional consecutive full scale production batches prior to marketing the product.

Finished Product Specification
The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
All strengths of the finished product are packaged in aluminium/clear polyvinylchloride (PVC)-polyvinylidene chloride (PVDC) blister strips in pack sizes of 60 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with no special storage conditions.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable.

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

Marketing Authorisation Application (MAA) form
The MAA forms are satisfactory.

Expert report
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of levetiracetam are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

Since Levetiracetam 250mg, 500mg, 750mg and 1000mg Film-Coated Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following two bioequivalence studies:

STUDY 1

A randomised, single dose, open-label, two-period, two-treatment, two sequence, crossover study to compare the pharmacokinetics of the test product Levetiracetam 1000mg Film-Coated Tablets (Wockhardt UK Ltd) versus the reference product Keppra 1000 mg film-coated tablets (UCB Pharma SA) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 1000 mg tablet administered under fasting conditions. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for levetiracetam are presented below (log-transformed values; geometric least squares mean, ratios and 90% confidence intervals):

Parameter	Geometrical Least square			90 % Confidence Interval	Intra subject variability (CV %)	Power %
	Test	Reference	% Ratio			
C_{max} (µg/mL)	27.14	27.37	99.17	94.18-104.43 %	11.58	100.00
AUC_{0-t} (µg.hr/mL)	276.87	276.15	100.26	98.39-102.16 %	4.20	100.00
$AUC_{0-\infty}$ (µg.hr/mL)	286.33	284.87	100.51	98.66-102.41 %	4.17	100.00

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

STUDY 2

A randomised, single dose, open-label, two-period, two-treatment, two sequence, crossover study to compare the pharmacokinetics of the test product Levetiracetam 1000mg Film-Coated Tablets (Wockhardt UK Ltd) versus the reference product Keppra 1000 mg film-coated tablets (UCB Pharma SA) in healthy adult volunteers under fed conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 1000 mg tablet administered in the fed state. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for levetiracetam are presented below (log-transformed values; geometric least squares mean, ratios and 90% confidence intervals):

Parameter	Geometrical Least square			90 % Confidence Interval	Intra subject variability (CV %)	Power (%)
	Test	Reference	% Ratio			
C_{max} (µg/mL)	25.07	24.54	102.19	97.35-107.26 %	10.80	100.00
AUC_{0-t} (µg.hr/mL)	252.16	250.21	100.78	98.17-103.45 %	5.83	100.00
$AUC_{0-\infty}$ (µg.hr/mL)	263.56	260.16	101.31	98.27-104.44 %	6.78	100.00

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

The 90% confidence intervals for AUC and C_{max} for test versus reference product for levetiracetam for both studies (under fasting conditions and in the fed state) are within predefined acceptance criteria specified in the ”Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev 1/, Corr**). Thus, the data support the claim that the 1000 mg test product is bioequivalent to the 1000 mg reference product.

As the 250 mg, 500 mg, 750 mg and 1000 mg strengths of the product meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev 1/, Corr**), the results and conclusions of the bioequivalence studies on the 1000 mg strength can be extrapolated to the other strengths.

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. Suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The quality characteristics of Levetiracetam 250mg, 500mg, 750mg and 1000mg 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 this type. The pharmacodynamic, pharmacokinetic and toxicological properties of levetiracetam are well-known.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant's Levetiracetam 1000mg Film-Coated Tablets and its respective reference product (Keppra 1000mg film-coated tablets, UCB Pharma SA). As the 250 mg, 500 mg, 750 mg and 1000 mg strengths of the product meet the biowaiver criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev 1/, Corr**), the results and conclusions of the bioequivalence studies on the 1000 mg strength can be extrapolated to the 250 mg, 500 mg and 750 mg strengths.

SAFETY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of levetiracetam is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence studies.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products, where appropriate, and in line with current guidelines.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant's products and the originator products are interchangeable. Extensive clinical experience with

levetiracetam is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome