LEVETIRACETAM 250 MG, 500 MG, 750 MG AND 1000 MG FILM COATED TABLETS

PL 14017/0228-0231

UKPAR

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LEVETIRACETAM 250 MG, 500 MG, 750 MG AND 1000 MG FILM COATED TABLETS

PL 14017/0228-0231

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Dexcel Pharma Ltd Marketing Authorisations (licences) for the medicinal products Levetiracetam 250 mg, 500 mg, 750 mg and 1000 mg Film-Coated Tablets (PL 14017/0228-0231) on 15th May 2012. These prescription-only medicines (POM) belong to a group of medicines called “antiepileptic medicines”. They are used:

- On their own in patients 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:
  - partial onset seizures with or without generalisation in patients from one month of age,
  - myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy,
  - primary generalised tonic-clonic seizures in patients 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 250 mg, 500 mg, 750 mg and 1000 mg Film Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Marketing Authorisations for the medicinal products Levetiracetam 250 mg, 500 mg, 750 mg and 1000 mg Film-Coated Tablets (PL 14017/0228-0231) to Dexcel Pharma Ltd on 15th May 2012. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC as amended. The products are claimed to be generic medicinal products of the innovator products, Keppra® 250 mg, 500 mg, 750 mg and 1000 mg Film Coated Tablets (EU/1/00/146/004; EU/1/00/146/010; EU/1/00/146/017 and EU/1/00/146/024), licensed to UCB Pharma SA via the Centralised Procedure since September 2000. The innovator products have been authorised in the EEA for over 10 years.

The active ingredient, 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 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. Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect.

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of the innovator products that have been in clinical use for over 10 years.

A single-dose, bioequivalence study was submitted to support these applications, comparing the test product Levetiracetam 1000 mg Film Coated Tablets (Dexcel Ltd) versus the reference product Keppra® 1000 mg Film Coated Tablets (UCB Pharma SA) under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Levetiracetam 250 mg, 500 mg, 750 mg 1000 mg Film-Coated Tablets outweigh the risks; hence Marketing Authorisations were granted.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Levetiracetam
INN/ BAN: Levetiracetam

Chemical name: (S)-ethyl-2-oxo-1-pyrrolidineacetamide
(2S)-2-oxopyrrolidin-1-yl) butanamide

Structure

Molecular formula: C₈H₁₄N₂O₂
Molecular weight: 170.21

General Properties

Description: White or almost white powder

Solubility: Very soluble in water, soluble in acetonitrile, practically insoluble in hexane.

The active substance, levetiracetam, is the subject of a European Pharmacopoeia (Ph. Eur) monograph.

Manufacture

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 specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate data have been supplied to characterise 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 foodstuffs.

Appropriate stability data have been generated to support a suitable re-test period when stored in the proposed packaging.
DRUG PRODUCT
Description and Composition
The drug products are presented as oblong, biconvex film-coated tablets with different sizes and colours (see SmPCs/patient information leaflet for full descriptions of tablets). Each tablet contains 250 mg, 500 mg, 750 mg and 1000 mg of levetiracetam respectively. The tablets all have score-lines to enable the tablets to be divided into equal halves.

Other ingredients consist of pharmaceutical excipients, microcrystalline cellulose, povidone, silica colloidal anhydrous, croscarmellose sodium, glyceryl behenate making up the tablet core; polyvinyl alcohol partially hydrolyzed, marcrogol 3350, talc, titanium dioxide (E171), indigo carmine lake (E132) (250 mg strength only), yellow iron oxide (E172) (500mg strength only), sunset yellow (E110) and iron oxide red (E172) (750 mg strength only) making up the film coating for the tablets and carnauba wax making up the tablet polish. All ingredients within the tablet core comply with relevant Ph. Eur monographs with the exception of glyceryl behenate which complies with USP monograph; the ingredients within the film-coating and the polishing agent comply with their relevant Ph.Eur monographs.

Appropriate justification for the inclusion of each excipient has been provided. Satisfactory Certificates of Analysis have been provided for all the excipients.

None of the excipients used contain material derived from animal or human origin. Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.

Pharmaceutical Development
The objective of the pharmaceutical development of these products was to develop bioequivalent and pharmaceutically equivalent to the innovator’s products Keppra® 250 mg, 500 mg, 750 mg and 1000 mg Film Coated Tablets (UCB Pharma SA).

Comparative dissolution and impurity profiles of the drug products were found to be similar to those of the reference products.

The applicant has provided suitable product development sections.

Manufacture
A description and flow-chart of the manufacturing method has been provided. In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted on pilot scale batches and results were acceptable. The Marketing Authorisation Holder has committed to performing process validation studies on the first 3 full-scale production batches for each product strength.

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

**Container Closure System**
The finished products are licensed for marketing in polyvinylidene chloride (PVdC) coated polyvinylchloride (PVC) blister strips sealed with aluminium foil. The blister strips are packed with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 60 tablets.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been approved, with the following storage instructions, “Do not store above 25°C”.

**Bioequivalence Study**
A bioequivalence study was presented comparing the test product, Levetiracetam 1000 mg Film Coated Tablets, to the innovator’s product; Keppra® 1000 mg Film Coated Tablets (UCB Pharma SA) marketed and sourced in the UK.

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

**Expert Report**
A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the innovator product Keppra® 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets (EU/1/00/146/004; EU/1/00/146/010; EU/1/00/146/017 and EU/1/00/146/024). The bridging report submitted by the applicant has been found acceptable.

**Marketing Authorisation Application (MAA) Forms**
The MAA forms are satisfactory.

**Conclusion**
There are no objections to approval of Levetiracetam 250 mg, 500 mg, 750 mg and 1000 mg Film-Coated Tablets from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC, as amended, for Levetiracetam 250 mg, 500 mg, 750 mg and 1000 mg Film Coated Tablets.

The pharmacodynamic, pharmacokinetic and toxicological properties of levetiracetam are well-known. Therefore, no further studies are required and the applicant has provided none. The non-clinical overview was written by a suitably qualified person and is satisfactory. The curriculum vitae of the expert has been provided.

No formal Environmental Risk Assessment has been provided. The applicant has justified the absence adequately. As the products have been used for over 10 years, the use of these products are not expected to increase the overall use of levetiracetam and so no additional increase in environmental risk has been identified.

The SmPCs are satisfactory from a non-clinical viewpoint.

There are no objections to the approval of Levetiracetam 250 mg, 500 mg, 750 mg and 1000 mg Film Coated Tablets from a non-clinical point of view.
CLINICAL ASSESSMENT

BACKGROUND
Epilepsy is a common neurological condition characterised by recurrent seizures which can be generalised, partial or partial with secondary generalisation. It is caused by unprovoked or provoked uncontrolled electrical discharge of cortical neurones. Epilepsy can start at any age.

THERAPEUTIC INDICATIONS
Levetiracetam is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients 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, 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.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPCs. The posology is identical to that for the reference products Keppra® 250 mg, 500 mg, 750 mg and 1000 mg Film Coated Tablets SmPCs and is satisfactory.

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

CLINICAL PHARMACOLOGY

Pharmacokinetics
The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product Levetiracetam 1000 mg Film Coated Tablets, to that of the reference product Keppra® 1000 mg Film Coated Tablets (UCB Pharma SA). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference products.

This was an open label, balanced, randomised, two-treatment, two-period, two-sequence single dose, crossover oral bioavailability study of conventional design in 28 healthy adult male volunteers under fasting conditions. Following an overnight fast of at least 10 hours, a single dose of the investigational products was administered orally to each subject in each period. A washout period of at least 7 days was maintained between the two dosing days in each group.
Blood samples were taken pre-dose and at specified time points up to 36 hours after administration of test or reference products. Plasma levels of levetiracetam were detected by a validated LC MS/MS analytical method.

The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference products was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00-125.00%), for log-transformed $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$.

A summary of the results of the bioequivalence study is tabulated below:

Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) of levetiracetam

<table>
<thead>
<tr>
<th>Parameters</th>
<th>*Geometric mean</th>
<th>% Ratio</th>
<th>90 % Confidence Interval for Log-transformed data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (A)</td>
<td>Reference (B)</td>
<td>A/B</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$</td>
<td>317015.50</td>
<td>314758.80</td>
<td>100.7169</td>
</tr>
<tr>
<td>$AUC_{0-t}$</td>
<td>298053.60</td>
<td>295873.70</td>
<td>100.7368</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>31625.60</td>
<td>32953.38</td>
<td>95.9709</td>
</tr>
</tbody>
</table>

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.

C\text{max} maximum plasma concentration

AUC\text{0-t} area under the plasma concentration-time curve from time zero to t hours

AUC\text{0-}\infty area under the plasma concentration-time curve from time zero to infinity

**Conclusion on Bioequivalence**

The results of the bioequivalence study show that the test and the reference products are bioequivalent, under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ for levetiracetam, fall within the acceptance criteria ranges of 80.00-125.00% in line with current guidelines.

Satisfactory justification is provided for a bio-waiver for Levetiracetam 250 mg, 500 mg and 750 mg Film-Coated Tablets. The absorption of Levetiracetam is fully linear across the therapeutic range. There is no evidence for any relevant gender, race or circadian variability. As Levetiracetam 250 mg, 500 mg and 750 mg Film-Coated Tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev.1/Curr**), the results and conclusions of the bioequivalence study on the 1000 mg strength can be extrapolated to the 250 mg, 500 mg and 750 mg strength tablets.

**Efficacy**

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of levetiracetam is well-established from its extensive used in clinical practice.

**Safety**

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of levetiracetam is well-known.
The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected occurring either in the Community or in a third country.

The applicant did not submit a Risk Management Plan. They justified this approach by similarity of the risks and benefits of their product to those of the reference product, which at the time of the application did not have a Risk Management Plan in place. This justification has been accepted. If in future risk minimisation measures are adopted for the reference product, the applicant will be obliged to implement similar measures for their product.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)
The approved SmPCs are fully harmonised with those for the reference products and are acceptable.

Patient Information Leaflet (PIL)
The PIL is in line with the approved SmPCs and is satisfactory.

Labelling
The labelling is satisfactory.

Clinical Overview
A satisfactory clinical overview was provided and prepared by an appropriately qualified expert. The CV of the clinical expert was supplied.

CONCLUSIONS
Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Levetiracetam 250 mg, 500 mg 750 mg and 1000 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 this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Levetiracetam 1000 mg Film Coated Tablets and Keppra® 1000 mg Tablets (UCB Pharma SA) marketed and sourced in the UK. Given that linear kinetics apply to the 250 mg, 500 mg, 750 mg and 1000 mg tablets, that proportional formulae for the tablets have been used and that similar dissolution results have been shown for the all strengths, separate bioequivalence studies using the 250 mg, 500 mg and 750 mg tablets are not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the innovator products.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with levetiracetam is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 25 March 2011.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 7 April 2011.</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 11 July 2011 and 6 January 2012 and the clinical dossiers on 15 November 2011 and 16 March 2012</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 11 December 2011 and 7 March 2012 and the clinical dossier on 7 March 2012 and 22 March 2012.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 5 May 2012.</td>
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# LEVETIRACETAM 250 MG, 500 MG, 750 MG AND 1000 MG FILM COATED TABLETS

PL 14017/0228-0231

## STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<th>Scope</th>
<th>Outcome</th>
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</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPCs) for Levetiracetam 250 mg, 500 mg, 750 mg and 1000 mg Film-Coated Tablets (PL 14017/0228-0231) is as follows. Differences between the SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT
Levetiracetam 250 mg film-coated tablets.
Levetiracetam 500 mg film-coated tablets.
Levetiracetam 750 mg film-coated tablets.
Levetiracetam 1000 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 250 mg, 500 mg, 750 mg and 1000 mg levetiracetam respectively.

Levetiracetam 750 mg film-coated tablets only
Excipient with known effect:
Each film-coated tablet contains 0.24 mg of sunset yellow (E110).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Levetiracetam 250 mg film-coated tablets.
Levetiracetam 250 mg film-coated tablets are blue, oblong, biconvex tablets, scored on one side.
The tablet can be divided into equal halves.
The dimensions are approximately 12.1×6.1 mm

Levetiracetam 500 mg film-coated tablets.
Levetiracetam 500 mg film-coated tablets are yellow, oblong, biconvex tablets, scored on one side.
The tablet can be divided into equal halves.
The dimensions are approximately 16.4×7.7

Levetiracetam 750 mg film-coated tablets.
Levetiracetam 750 mg film-coated tablets are orange, oblong, biconvex tablets, scored on one side.
The tablet can be divided into equal halves.
The dimensions are approximately 18.6×8.8 mm

Levetiracetam 1000 mg film-coated tablets.
Levetiracetam 1000 mg film-coated tablets are white, oblong, biconvex tablets, scored on one side.
The tablet can be divided into equal halves.
The dimensions are approximately 19.1×10.3 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Levetiracetam is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients 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, 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.

4.2 Posology and method of administration
Posology

Monotherapy for adults and adolescents from 16 years of age

The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily.

Add-on therapy for adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more

The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment. Depending upon the clinical response and tolerability, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Special populations

Elderly (65 years and older)

Adjustment of the dose is recommended in elderly patients with compromised renal function (see “Renal impairment” below).

Renal impairment

The daily dose must be individualised according to renal function.

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination, for adults and adolescents weighing 50 kg or more, the following formula:

\[
\text{CLcr} (\text{ml/min}) = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times 0.85 \text{ for women}
\]

Then CLcr is adjusted for body surface area (BSA) as follows:

\[
\text{CLcr} (\text{ml/min}) = \frac{\text{CLcr (ml/min/1.73 m}^2\text{)}}{\text{BSA subject (m}^2\text{)}} \times 1.73
\]

Dosing adjustment for adult and adolescents patients weighing more than 50 kg with impaired renal function

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min/1.73 m²)</th>
<th>Dose and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 80</td>
<td>500 to 1,500 mg twice daily</td>
</tr>
<tr>
<td>Mild</td>
<td>50-79</td>
<td>500 to 1,000 mg twice daily</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-49</td>
<td>250 to 750 mg twice daily</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 30</td>
<td>250 to 500 mg twice daily</td>
</tr>
<tr>
<td>End-stage renal disease patients</td>
<td>-</td>
<td>500 to 1,000 mg once daily (2)</td>
</tr>
</tbody>
</table>
A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.

Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73 m² may be estimated from serum creatinine (mg/dl) determination, for young adolescents, children and infants, using the following formula (Schwartz formula):

\[
\text{CLcr (ml/min/1.73 m²)} = \frac{\text{Height (cm)} \times \text{ks}}{\text{Serum Creatinine (mg/dl)}}
\]

ks = 0.45 in Term infants to 1 year old; ks = 0.55 in Children to less than 13 years and in adolescent female; ks = 0.7 in adolescent male

(*) Dosing adjustment for infants, children and adolescents patients weighing less than 50 kg with impaired renal function:

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min/1.73 m²)</th>
<th>Dose and frequency(1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Infants 1 to less than 6 months</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Infants 6 to 23 months, children and adolescents weighing less than 50 kg</strong></td>
</tr>
<tr>
<td>Normal</td>
<td>&gt; 80</td>
<td>7 to 21 mg/kg (0.07 to 0.21 ml/kg) twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily</td>
</tr>
<tr>
<td>Mild</td>
<td>50-79</td>
<td>7 to 14 mg/kg (0.07 to 0.14 ml/kg) twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-49</td>
<td>3.5 to 10.5 mg/kg (0.035 to 0.105 ml/kg) twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 30</td>
<td>3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily</td>
</tr>
<tr>
<td>End-stage renal disease patients undergoing dialysis</td>
<td>--</td>
<td>7 to 14 mg/kg (0.07 to 0.14 ml/kg) once daily (2) (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily (3) (5)</td>
</tr>
</tbody>
</table>

(*) Certain formulations are not available in Dexcel Pharma Ltd. Product line but are available on the market from other manufacturers.

Levetiracetam Tablets are supplied as divisible coated tablets with smallest strength of 125 mg, which may limit the ability of prescribers to adjust dosages for some paediatric patients.

(1) Levetiracetam oral solution should be used for doses under 250 mg and for patients unable to swallow tablets.

(2) A 10.5 mg/kg (0.105 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

(3) A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.

(4) Following dialysis, a 3.5 to 7 mg/kg (0.035 to 0.07 ml/kg) supplemental dose is recommended.
(5) Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

Hepatic impairment
No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m².

Pediatric population
The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose.

Levetiracetam tablets are not adapted for use in infants and children under the age of 6 years. Levetiracetam oral solution is the preferred formulation for use in this population. Levetiracetam oral solution is not available in Dexcel Pharma Ltd. product line but is available on the market from other manufacturers.

In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases oral solution should be used.

Monotherapy
The safety and efficacy of Levetiracetam in children and adolescents below 16 years as monotherapy treatment have not been established. There are no data available.

Add-on therapy for infants aged from 6 to 23 months, children (2 to 11 years) and adolescents (12 to 17 years) weighing less than 50 kg
Levetiracetam oral solution is the preferred formulation for use in infants and children under the age of 6 years.

The initial therapeutic dose is 10 mg/kg twice daily.
Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used.

Dose in children 50 kg or greater is the same as in adults.

Dose recommendations for infants from 6 months of age, children and adolescents (Levetiracetam 250 mg, 750 mg and 1000 mg film coated tablets):

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Starting dose: 10 mg/kg twice daily</th>
<th>Maximum dose: 30 mg/kg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (1)</td>
<td>60 mg (0.6 ml) twice daily</td>
<td>180 mg (1.8 ml) twice daily</td>
</tr>
<tr>
<td>10 (1)</td>
<td>100 mg (1 ml) twice daily</td>
<td>300 mg (3 ml) twice daily</td>
</tr>
<tr>
<td>15 (1)</td>
<td>150 mg (1.5 ml) twice daily</td>
<td>450 mg (4.5 ml) twice daily</td>
</tr>
<tr>
<td>20 (1)</td>
<td>200 mg (2 ml) twice daily</td>
<td>600 mg (6 ml) twice daily</td>
</tr>
<tr>
<td>25</td>
<td>250 mg twice daily</td>
<td>750 mg twice daily</td>
</tr>
<tr>
<td>From 50 (2)</td>
<td>500 mg twice daily</td>
<td>1,500 mg twice daily</td>
</tr>
</tbody>
</table>

Dose recommendations for children from 6 years of age and adolescents (Levetiracetam 500 mg film coated tablets):

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Starting dose: 10 mg/kg twice daily</th>
<th>Maximum dose: 30 mg/kg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (1)</td>
<td>60 mg (0.6 ml) twice daily</td>
<td>180 mg (1.8 ml) twice daily</td>
</tr>
</tbody>
</table>
10 kg (1) 100 mg (1 ml) twice daily 300 mg (3 ml) twice daily
15 kg (1) 150 mg (1.5 ml) twice daily 450 mg (4.5 ml) twice daily
20 kg (1) 200 mg (2 ml) twice daily 600 mg (6 ml) twice daily
25 kg  250 mg twice daily 750 mg twice daily
From 50 kg (2) 500 mg twice daily 1,500 mg twice daily

(1) Children 25 kg or less should preferably start the treatment with levetiracetam 100 mg/ml oral solution.
(2) Dose in children and adolescents 50 kg or more is the same as in adults.

Add-on therapy for infants from 1 month to less than 6 months

The tablet formulation is not adapted for use in children under the age of 6 years.
The oral solution is the formulation to use in infants.

Method of administration
The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid
and may be taken with or without food. The daily dose is administered in two equally
divided doses.

4.3 Contraindications
Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the
excipients.

4.4 Special warnings and precautions for use
Discontinuation
In accordance with current clinical practice, if Levetiracetam have to be discontinued it is
recommended to withdraw the medication gradually (e.g. in adults and adolescents
weighing more than 50 kg: 500 mg decreases twice daily every two to four weeks; in
infants older than 6 months, children and adolescents weighing less than 50 kg: dose
decrease should not exceed 10 mg/kg twice daily every two weeks; in infants (less than 6
months): dose decrease should not exceed 7 mg/kg twice daily every two weeks).

Renal insufficiency
The administration of Levetiracetam to patients with renal impairment may require dose
adjustment. In patients with severely impaired hepatic function, assessment of renal
function is recommended before dose selection (see section 4.2).

Suicide
Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients
treated with anti-epileptic agents (including levetiracetam). A meta-analysis of
randomized placebo-controlled trials of anti-epileptic medicinal products has shown a small
increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known.

Therefore, patients should be monitored for signs of depression and/or suicidal ideation and
behaviours and appropriate treatment should be considered. Patients (and caregivers of
patients) should be advised to seek medical advice should signs of depression and/or
suicidal ideation or behaviour emerge.

Paediatric population
The tablet formulation is not adapted for use in infants and children under the age of 6 years
(Levetiracetam 250 mg, 500 mg & 750 mg tablets only). The tablet formulation is not
adapted for use in children under the age of 6 years (Levetiracetam 1000 mg tablets).
Available data in children did not suggest impact on growth and puberty. However, long
term effects on learning, intelligence, growth, endocrine function, puberty and childbearing
potential in children remain unknown.

The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with
epilepsy aged less than 1 year. Only 35 infants aged less than 1 year with partial onset
seizures have been exposed in clinical studies of which only 13 were aged < 6 months.
Levetiracetam 750 mg film-coated tablets only

Excipients
Levetiracetam 750 film-coated tablets contain E110 colouring agent which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Antiepileptic medicinal products
Pre-marketing data from clinical studies conducted in adults indicate that Levetiracetam Tablets did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Levetiracetam Tablets.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam. A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 20% higher levetiracetam clearance in children taking enzymeinducing antiepileptic medicinal products. Dose adjustment is not required.

Probenecid
Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite, but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low. It is expected that other medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicinal products, e.g. NSAIDs, sulfonamides and methotrexate, is unknown.

Oral contraceptives and other pharmacokinetics interactions
Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinylestradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. -Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

Antacids
No data on the influence of antacids on the absorption of levetiracetam are available.

Food and alcohol
The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was slightly reduced.

No data on the interaction of levetiracetam with alcohol are available.

4.6 Fertility, Pregnancy and lactation

Pregnancy
There are no adequate data available from the use of levetiracetam in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for human is unknown. Levetiracetam Tablets are not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary. As with other antiepileptic medicinal products, physiological changes during pregnancy may affect levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with levetiracetam should be ensured. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.
Breastfeeding
Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. However, if levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding.

Fertility
No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

4.8 Undesirable effects
Summary of the safety profile
The adverse event profile presented below is based on the analysis of pooled placebo-controlled clinical trials with all indications studied, with a total of 3,416 patients treated with levetiracetam.
These data are supplemented with the use of levetiracetam in corresponding open-label extension studies, as well as post-marketing experience. The most frequently reported adverse reactions were nasopharyngitis, somnolence, headache, fatigue and dizziness. The safety profile of levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications.

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies (adults, adolescents, children and infants > 1 month) and from post-marketing experience are listed in the following table per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000)

<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>Frequency category</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Nasopharyngitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytopenia, leukopenia&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Pancytopenia&lt;sup&gt;(1,2)&lt;/sup&gt;, neutropenia&lt;sup&gt;(1)&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td>Weight decreased&lt;sup&gt;1”, weight increase&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depression, hostility/aggression, anxiety(^1), insomnia, nervousness/irritability</td>
<td>Suicide attempt(^1), suicidal ideation(^1), psychotic disorder(^1), abnormal behaviour(^1), hallucination(^1), anger(^1), confusional state(^1), affect lability/mood swings, agitation</td>
<td>Completed suicide(^1), personality disorder, thinking abnormal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Somnolence, headache</td>
<td>Convulsion, balance disorder, dizziness, lethargy, tremor</td>
<td>Amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia(^1), disturbance in attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>Choreoathetosis(^1), dyskinesia(^1), hyperkinesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>Cough</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea</td>
<td></td>
<td>Pancreatitis(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Liver function test abnormal(^1)</td>
<td>Hepatic failure(^1), hepatitis(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Alopecia(^1), eczema, pruitus,</td>
<td>Toxic epidermal necrolysis(^1), Stevens-Johnson syndrome(^1), erythema multiforme(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>Muscular weakness, myalgia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia/fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Description of selected adverse reactions
The risk of anorexia is higher when topiramate is coadministered with levetiracetam. In several cases of alopecia, recovery was observed when levetiracetam was discontinued.

Paediatric population
In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. Sixty (60) of these patients were treated with levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of levetiracetam.

The adverse event profile of levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse reactions which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2%), agitation (common, 3.4%), mood swings (common, 2.1%), affect lability (common, 1.7%), aggression (common, 8.2%), abnormal behaviour (common, 5.6%), and lethargy (common, 3.9%) were reported more frequently than in other age ranges or in the overall safety profile. In infants and children aged 1 month to less than 4 years, irritability (very common, 11.7%) and coordination abnormal (common, 3.3%) were reported more frequently than in other age groups or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that levetiracetam was not different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Results related to behavioral and emotional functioning indicated a worsening in levetiracetam treated patients on aggressive behavior as measured in a standardised and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took levetiracetam in the long-term open label follow-up study, did not experience a worsening, on average, in their behavioural and emotional functioning; in particular measures of aggressive behavior were not worse than baseline.

4.9 Overdose
Symptoms
Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with levetiracetam overdoses.

Management of overdose
After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60 % for levetiracetam and 74 % for the primary metabolite.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX14.
The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

**Mechanism of action**

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 Ca2+ levels by partial inhibition of N-type Ca2+ currents and by reducing the release of Ca2+ 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.

**Pharmacodynamic effects**

Levetiracetam induces seizure protection in a broad range of animal models of partial and primary generalised seizures without having a pro-convulsant effect. The primary metabolite is inactive. In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has confirmed the broad spectrum pharmacological profile of levetiracetam.

**Clinical efficacy and safety**

Note that reports of pharmacodynamic studies include information about some paediatric patients treated with a liquid formulation. Levetiracetam tablets should be used only in adults and children for whom the dosage form and strengths are appropriate.

**Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in adults, adolescents, children and infants from 1 month of age with epilepsy:**

In adults, levetiracetam efficacy has been demonstrated in 3 double-blind, placebo-controlled studies at 1000 mg, 2000 mg, or 3000 mg/day, given in 2 divided doses, with a treatment duration of up to 18 weeks. In a pooled analysis, the percentage of patients who achieved 50 % or greater reduction from baseline in the partial onset seizure frequency per week at stable dose (12/14 weeks) was of 27.7 %, 31.6 % and 41.3 % for patients on 1000, 2000 or 3000 mg levetiracetam respectively and of 12.6 % for patients on placebo.

**Paediatric population**

In paediatric patients (4 to 16 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 198 patients and had a treatment duration of 14 weeks. In this study, the patients received levetiracetam as a fixed dose of 60 mg/kg/day (with twice a day dosing). 44.6 % of the levetiracetam treated patients and 19.6 % of the patients on placebo had a 50 % or greater reduction from baseline in the partial onset seizure frequency per week. With continued long-term treatment, 11.4 % of the patients were seizure-free for at least 6 months and 7.2 % were seizure free for at least 1 year.

In paediatric patients (1 month to less than 4 years of age), levetiracetam efficacy was established in a double-blind, placebo-controlled study, which included 116 patients and had a treatment duration of 5 days. In this study, patients were prescribed 20 mg/kg, 25 mg/kg, 40 mg/kg or 50 mg/kg daily dose of oral solution based on their age titration schedule. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for infants one month to less than six month and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for infants and children 6 month to less than 4 years old, was used in this study. The total daily dose was administered b.i.d.
The primary measure of effectiveness was the responder rate (percent of patients with ≥ 50% reduction from baseline in average daily partial onset seizure frequency) assessed by a blinded central reader using a 48-hour video EEG. The efficacy analysis consisted of 109 patients who had at least 24 hours of video EEG in both baseline and evaluation periods. 43.6% of the levetiracetam treated patients and 19.6% of the patients on placebo were considered as responders. The results are consistent across age group. With continued long-term treatment, 8.6% of the patients were seizure-free for at least 6 months and 7.8% were seizure-free for at least 1 year.

**Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.**

Efficacy of levetiracetam as monotherapy was established in a double-blind, parallel group, noninferiority comparison to carbamazepine controlled release (CR) in 576 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial seizures or with generalized tonic-clonic seizures only. The patients were randomized to carbamazepine CR 400 – 1200 mg/day or levetiracetam 1000 - 3000 mg/day, the duration of the treatment was up to 121 weeks depending on the response. Six-month seizure freedom was achieved in 73.0% of levetiracetam-treated patients and 72.8% of carbamazepine-CR treated patients; the adjusted absolute difference between treatments was 0.2% (95% CI: -7.8 8.2). More than half of the subjects remained seizure free for 12 months (56.6% and 58.5% of subjects on levetiracetam and on carbamazepine CR respectively).

In a study reflecting clinical practice, the concomitant antiepileptic medication could be withdrawn in a limited number of patients who responded to levetiracetam adjunctive therapy (36 adult patients out of 69).

**Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.**

Levetiracetam efficacy was established in a double-blind, placebo-controlled study of 16 weeks duration, in patients 12 years of age and older suffering from idiopathic generalized epilepsy with myoclonic seizures in different syndromes. The majority of patients presented with juvenile myoclonic epilepsy.

In this study, levetiracetam, dose was 3000 mg/day given in 2 divided doses. 58.3% of the levetiracetam treated patients and 23.3% of the patients on placebo had at least a 50% reduction in myoclonic seizure days per week. With continued long-term treatment, 28.6% of the patients were free of myoclonic seizures for at least 6 months and 21.0% were free of myoclonic seizures for at least 1 year.

**Adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.**

Levetiracetam efficacy was established in a 24-week double-blind, placebo-controlled study which included adults, adolescents and a limited number of children suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures in different syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, or epilepsy with Grand Mal seizures on awakening). In this study, levetiracetam dose was 3000 mg/day for adults and adolescents or 60 mg/kg/day for children, given in 2 divided doses. 72.2% of the levetiracetam treated patients and 45.2% of the patients on placebo had a 50% or greater decrease in the frequency of PGTC seizures per week. With continued long-term treatment, 47.4% of the patients were free of tonic-clonic seizures for at least 6 months and 31.5% were free of tonic-clonic seizures for at least 1 year.

**5.2 Pharmacokinetic properties**

Levetiracetam is a highly soluble and permeable compound. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. There is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.
Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg bodyweight. Therefore there is no need for plasma level monitoring of levetiracetam.

A significant correlation between saliva and plasma concentrations has been shown in adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1.7 for oral tablet formulation and after 4 hours post-dose for oral solution formulation).

**Adults and adolescents**

**Absorption**
Levetiracetam is rapidly absorbed after oral administration. Oral absolute bioavailability is close to 100%.
Peak plasma concentrations (Cmax) are achieved at about 1 hour after dosing.
Steady-state is achieved after two days of a twice daily administration schedule.
Peak concentrations (Cmax) are typically about 31 and 43 μg/ml following a single 1,000 mg dose and repeated 1,000 mg twice daily dose, respectively.
The extent of absorption is dose-independent and is not altered by food.

**Distribution**
No tissue distribution data are available in humans.
Neither levetiracetam nor its primary metabolite are significantly bound to plasma proteins (< 10 %). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 l/kg, a value close to the total body water volume.

**Biotransformation**
Levetiracetam is not extensively metabolised in humans. The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of the acetamide group. Production of the primary metabolite, ucb L057, is not supported by liver cytochrome P450 isoforms.
Hydrolysis of the acetamide group was measurable in a large number of tissues including blood cells. The metabolite ucb L057 is pharmacologically inactive.
Two minor metabolites were also identified. One was obtained by hydroxylation of the pyrrolidone ring (1.6 % of the dose) and the other one by opening of the pyrrolidone ring (0.9 % of the dose). Other unidentified components accounted only for 0.6 % of the dose.
No enantiomeric interconversion was evidenced in vivo for either levetiracetam or its primary metabolite.

*In vitro*, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 AND UGT1A6)) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.
In human hepatocytes in culture, levetiracetam had little or no effect on CYP1A2, SULT1E1 or UGT1A1. Levetiracetam caused mild induction of CYP2B6 and CYP3A4.
The *in vitro* data and *in vivo* interaction data on oral contraceptives, digoxin and warfarin indicate that no significant enzyme induction is expected in vivo. Therefore, the interaction of levetiracetam with other substances, or vice versa, is unlikely.

**Elimination**
The plasma half-life in adults was about 7±1 hours and did not vary either with dose, route of administration or repeated administration. The mean total body clearance was 0.96 ml/min/kg. The major route of excretion was via urine, accounting for a mean 95 % of the dose (approximately 93 % of the dose was excreted within 48 hours). Excretion via faeces accounted for only 0.3 % of the dose. The cumulative urinary excretion of levetiracetam and its primary metabolite accounted for 66 % and 24 % of the dose, respectively during the first 48 hours. The renal clearance of levetiracetam and ucb L057 is 0.6 and 4.2 ml/min/kg respectively indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular reabsorption and that the primary metabolite is also excreted by active tubular secretion in addition to glomerular filtration. Leviteracetam elimination is correlated to creatinine clearance.

**Elderly**
In the elderly, the half-life is increased by about 40 % (10 to 11 hours). This is related to the decrease in renal function in this population (see section 4.2).
Renal impairment
The apparent body clearance of both levetiracetam and of its primary metabolite is correlated to the creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of Levetiracetam Tablets, based on creatinine clearance in patients with moderate and severe renal impairment (see section 4.2).

In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively. The fractional removal of levetiracetam was 51 % during a typical 4-hour dialysis session.

Hepatic impairment
In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of levetiracetam. In most subjects with severe hepatic impairment, the clearance of levetiracetam was reduced by more than 50 % due to a concomitant renal impairment (see section 4.2).

Pediatric population
Note that reports of pharmacokinetic studies include information about some paediatric patients treated with a liquid formulation. Levetiracetam tablets should be used only in adults and children for whom the dosage form and strengths are appropriate.

Children (4 to 12 years)
Following single oral dose administration (20 mg/kg) to epileptic children (6 to 12 years), the half-life of levetiracetam was 6.0 hours. The apparent body weight adjusted clearance was approximately 30 % higher than in epileptic adults.

Following repeated oral dose administration (20 to 60 mg/kg/day) to epileptic children (4 to 12 years), levetiracetam was rapidly absorbed. Peak plasma concentration was observed 0.5 to 1.0 hour after dosing. Linear and dose proportional increases were observed for peak plasma concentrations and area under the curve. The elimination half-life was approximately 5 hours. The apparent body clearance was 1.1 ml/min/kg.

Infants and children (1 month to 4 years)
Following single dose administration (20 mg/kg) of a 100 mg/ml oral solution to epileptic children (1 month to 4 years), levetiracetam was rapidly absorbed and peak plasma concentrations were observed approximately 1 hour after dosing. The pharmacokinetic results indicated that half-life was shorter (5.3 h) than for adults (7.2 h) and apparent clearance was faster (1.5 ml/min/kg) than for adults (0.96 ml/min/kg).

In the population pharmacokinetic analysis conducted in patients from 1 month to 16 years of age, body weight was significantly correlated to apparent clearance (clearance increased with an increase in body weight) and apparent volume of distribution. Age also had an influence on both parameters. This effect was pronounced for the younger infants, and subsided as age increased, to become negligible around 4 years of age.

In both population pharmacokinetic analyses, there was about a 20 % increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing AED.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity. Adverse effects not observed in clinical studies but seen in the rat and to a lesser extent in the mouse at exposure levels similar to human exposure levels and with possible relevance for clinical use were liver changes, indicating an adaptive response such as increased weight and centrilobular hypertrophy, fatty infiltration and increased liver enzymes in plasma.
No adverse effects on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m² or exposure basis) in parents and F1 generation.

Two embryo-fetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in fetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m² basis) and 1200 mg/kg/day for fetuses.

Four embryo-fetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in fetal weight associated with increased incidence of fetuses with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m² basis).

A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was ≥ 1800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning (x 6 the MRHD on a mg/m² basis).

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6 – 17 the MRHD on a mg/m² basis).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Core:**
- Mycrocystalline cellulose
- Povidone
- Silica, colloidal anhydrous
- Croscarmellose sodium
- Glyceryl behenate

**Coating:**
- Polyvinyl alcohol partially hydrolyzed
- Macrogol 3350
- Talc
- Titanium dioxide (E171)
  - indigo caramine lake (E132) (Levetiracetam 250 mg only)
  - yellow iron oxide (E172) (Levetiracetam 500 mg only)
- Sunset yellow (E110) (Levetiracetam 750 mg only)
- Iron oxide red (E172) (Levetiracetam 750 mg only)

**Polishing:**
- Carnauba wax

6.2 Incompatibilities
- Not applicable

6.3 Shelf life
- 2 years.

6.4 Special precautions for storage
- Do not store above 25°C.

6.5 Nature and contents of container
- The tablets are packed in PVDC-coated PVC blister strips, sealed with aluminium foil, in packs of 60 tablets.

6.6 Special precautions for disposal
- No special requirements
MARKETING AUTHORISATION HOLDER
Dexcel Pharma Ltd.
7 Sopwith Way, Drayton Fields, Daventry, Northamptonshire, NN11 8PB, UK.

MARKETING AUTHORISATION NUMBER(S)
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LEVETIRACETAM 250 mg, 500 mg, 750 mg AND 1000 mg FILM COATED TABLETS
PL 14017/0228-0231
PATIENT INFORMATION LEAFLET

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

Levetiracetam

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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

Levetiracetam is an antiepileptic medicine (a medicine used to treat seizures in epilepsy).

Levetiracetam is used:
- On its own in patients 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:
  - partial onset seizures with or without generalisation in patients from one month of age
  - myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy
  - primary generalised tonic-clonic seizures in patients from 12 years of age with idiopathic generalised epilepsy

2. BEFORE YOU TAKE LEVETIRACETAM TABLETS

Levetiracetam Tablets are used in adults and in children over 6 years of age.
Do not take Levetiracetam Tablets:
- If you are allergic (hypersensitive) to levetiracetam or any of the other ingredients of Levetiracetam Tablets.

Take special care with Levetiracetam Tablets:
- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- If you notice any slow down in the growth or unexpected puberty development of your child, please contact your doctor.
- If you notice an increase in seizure severity (e.g. increased number), please contact your doctor.

A small number of people being treated with antiepileptics such as Levetiracetam have had thoughts of harming or killing themselves. If you have any symptoms of depression and/or suicidal ideation, please contact your doctor.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Levetiracetam Tablets with food and drink

You may take Levetiracetam Tablets with or without food. As a safety precaution, do not take Levetiracetam Tablets with alcohol.

Pregnancy and Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or if you think you may be pregnant, please inform your doctor.

Levetiracetam Tablets should not be used during pregnancy unless clearly necessary.
This potential risk to your unborn child is unknown.
Levetiracetam Tablets may affect the reproductive effects in animal studies at dose levels higher than what you would need to control your seizures.
Breast-feeding is not recommended during treatment.

Driving and using machines
Levetiracetam Tablets may impair your ability to drive or operate any tools or machinery, as Levetiracetam Tablets may make you feel sleepy.
This is more likely at the beginning of treatment or after an increase in the dose. You should not drive or use machines until it is established that your ability to perform such activities is not affected.

Important information about some of the ingredients of Levetiracetam Tablets
Levetiracetam 750 mg Tablets contain Sunset Yellow (E110), Sudan Yellow (E110) colouring agent may cause allergic reactions.

3. HOW TO TAKE LEVETIRACETAM TABLETS

Always take Levetiracetam Tablets exactly as your doctor has told you. You should check with your doctor if you are not sure.
Levetiracetam Tablets must be taken twice daily, once in the morning and once in the evening, at about the same time each day.
Take the number of tablets following your doctor's instructions.

Monotherapy

Dose in adults and adolescents (from 16 years of age):
General dose: between 1000 mg and 3000 mg each day.

When you will start taking Levetiracetam Tablets, your doctor will prescribe you a lower dose during 2 weeks before giving you the lowest general dose.

Add-on therapy

Dose in adults and adolescents (12 to 17 years):
General dose: between 1000 mg and 3000 mg each day.

Dose in infants (6 to 23 months), children (2 to 11 years) and adolescents (12 to 17 years)

- For children weighing less than 50 kg:
  - Your doctor will prescribe the most appropriate pharmacological form of Levetiracetam Tablets according to the age, weight and dose
- For children weighing less than 50 kg:
  - Your doctor will prescribe the most appropriate pharmacological form of Levetiracetam Tablets according to the age, weight and dose

Levetiracetam oral solution is a presentation more appropriate to infants and children under the age of 6 years.

General dose: between 20 mg per kg bodyweight and 60 mg per kg bodyweight each day.

Example: a general dose of 20 mg per kg bodyweight each day, you must give your 25 kg child 1 tablet of 250 mg in the morning and 1 tablet of 250 mg in the evening.
Dose in infants (1 month to less than 6 months):
(7) Levetiracetam oral solution is a presentation more appropriate to infants.
(7) Levetiracetam oral solution is not available in Dexcel Pharma Ltd. product line but is available on the market from other manufacturers.

Method of administration:
Swallow Levetiracetam Tablets with a sufficient quantity of liquid (e.g. a glass of water).

Duration of treatment:
Levetiracetam Tablets are used as a chronic treatment. You should continue Levetiracetam Tablets treatment for as long as your doctor has told you.

Do not stop your treatment without your doctor’s advice as this could increase your seizures.

Should your doctor decide to stop your Levetiracetam Tablets treatment, they will instruct you about the gradual withdrawal of Levetiracetam Tablets.

If you take more Levetiracetam Tablets than you should:
The possible side effects of an overdose of Levetiracetam Tablets are sleepiness, agitation, aggression, decrease of alertness, inhibition of breathing and coma.

Contact your doctor if you feel more tablets than you should. Your doctor will establish the best possible treatment of overdose.

If you forget to take Levetiracetam Tablets:
Contact your doctor if you have missed one or more doses.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking Levetiracetam Tablets:
If stopping treatment, as with other anti-epileptic medicines, Levetiracetam Tablets should be discontinued gradually to avoid an increase of seizures.

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

4. POSSIBLE SIDE EFFECTS
Like all medicines, Levetiracetam Tablets can cause side effects, although not everybody gets them. Tell your doctor if you have any of the following and they worry you.

Some of the side effects like sleepiness, tiredness and dizziness may be more common at the beginning of the treatment or at dose increase. These effects should however decrease over time.

The frequency of possible side effects listed below is defined using the following convention:
Very common (affects more than 1 user in 10)
Common (affects 1 to 10 users in 100)
Uncommon (affects 1 to 10 users in 1,000)
Rare (affects 1 to 10 users in 10,000)
Very rare (affects less than 1 user in 10,000)
Not known (frequency cannot be estimated from the available data)

Very common:
- dizziness;
- somnolence (sleepiness), headache.

Common:
- anorexia (loss of appetite);
- depression, hostility or aggression, anxiety;
- insomnia, nervousness or irritability;
- confusion, balance disorder (equilibrium disorder), dizziness (perception of unsteadiness), lethargy, tremor (voluntary trembling);
- vertigo (sensation of rotation);
- cough;
- abdominal pain, diarrhoea, dyspepsia (indigestion), vomiting, nausea;
- rash;
- asthenia (fatigue, tiredness).

Uncommon:
- decreased number of blood platelets, decreased number of white blood cells;
- weight decrease, weight increase;
- suicide attempt and suicidal ideation, mental disorder, abnormal behaviour, hallucination, anger, confusion, emotional instability, mood swings, agitation;
- amnesia (loss of memory), memory impairment (forgetfulness), abnormal coordination, asthenia (impairments in coordinated movements), paraesthesia (tingling), disturbance in attention (loss of concentration);
- diplopia (double vision), vision blurred;
- liver function test abnormal;
- haemorrhage, purpura;
- muscle weakness, myalgia (muscle pain);
- injury.

Rare:
- infections;
- decreased number of red blood cells and/or white blood cells;
- disease, personality disorders (behavioural problems), thinking abnormal (slow thinking, unable to concentrate);
- uncontrolled muscle spasms affecting the head, torso and limbs, difficulty in controlling movements, hyperreflexia (hyperactivity);
- pancreatitis;
- hepatic failure, hepatitis;
- blistering of the skin, mouth, eyes and genital area, skin erosion.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE LEVETIRACETAM TABLETS
Keep out of the reach and sight of children.
Do not use after the expiry date which is stated on the carton box and blister after EXP.
The expiry date refers to the last day of the month.
Do not store above 25°C.

6. FURTHER INFORMATION
What Levetiracetam Tablets contain
The active substance is (called) levetiracetam.
Each Levetiracetam 250 mg Tablet contains 250 mg of levetiracetam.
Each Levetiracetam 500 mg Tablet contains 500 mg of levetiracetam.
Each Levetiracetam 750 mg Tablet contains 750 mg of levetiracetam.
Each Levetiracetam 1000 mg Tablet contains 1000 mg of levetiracetam.

The other ingredients are:
Tablet core: microcrystalline cellulose, povidone, silica colloidal anhydrous, croscarmellose sodium and glacial acetic acid.
Film-coating: Polyvinyl alcohol partially hydrolyzed, macrogol 3350, talc, titanium dioxide (E171) and carnauba wax.

Levetiracetam 250 mg film-coated tablets also contain: indigo carmine lake (E132).

Levetiracetam 500 mg film-coated tablets also contain: yellow iron oxide (E172).

Levetiracetam 750 mg film-coated tablets also contain: sunset yellow (E110) and red iron oxide (E172).

What Levetiracetam Tablets looks like and contents of the pack
Levetiracetam 250 mg film-coated tablets are blue, oblong, biconvex tablets, scored on one side.
Levetiracetam 500 mg film-coated tablets are yellow, oblong, biconvex tablets, scored on one side.
Levetiracetam 750 mg film-coated tablets are orange, oblong, biconvex tablets, scored on one side.
Levetiracetam 1000 mg film-coated tablets are white, oblong, biconvex tablets, scored on one side.
The tablets can be divided into equal halves.
Levetiracetam tablets are available in packs containing 80 tablets.

Marketing Authorisation Holder and Manufacturer
Dexcel®-Pharma Ltd. 7 Stowpath Way, Drayton Fields, Daventry, Northamptonshire, NN11 8PB, UK.
This leaflet was last revised in March 2012.
LEVETIRACETAM 250 MG, 500 MG, 750 MG AND 1000 MG FILM COATED TABLETS

PL 14017/0228-0231

LABELLING

PLEASE NOTE: Other labels for this strength are identical apart from the number of tablets.

CARTON

BLISTER FOIL