

**EPISENTA<sup>®</sup> 150 AND 300 MG PROLONGED-RELEASE CAPSULE  
EPISENTA<sup>®</sup> 500 AND 1000 MG PROLONGED-RELEASE GRANULES**

**(Sodium valproate)**

**PL 14040/0024-0027**

**UKPAR**

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**LAY SUMMARY**

This is a summary of the Public Assessment Report (PAR) for Episenta<sup>®</sup> 150 mg and 300 mg Prolonged-release Capsule and Episenta<sup>®</sup> 500 mg and 1000 mg Prolonged-release Granules (PL 14040/0024-0027). These medicinal products will be referred to as Episenta<sup>®</sup> Prolonged-release Capsule/Granules in the remainder of this report.

This summary explains how Episenta<sup>®</sup> Prolonged-release Capsule/Granules were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Episenta<sup>®</sup> Prolonged-release Capsule/Granules.

For practical information about using Episenta<sup>®</sup> Prolonged-release Capsule/Granules, patients should read the package leaflet or contact their doctor or pharmacist.

**What are Episenta<sup>®</sup> Prolonged-release Capsule/Granules and what are they used for?**

Episenta<sup>®</sup> Prolonged-release Capsule/Granules are hybrid applications. This means that Episenta<sup>®</sup> Prolonged-release Capsule/Granules are similar to reference medicines, Depakine Chrono 500 mg authorised in France and registered in the UK as Epilim Chrono 200 mg, 300 mg and 500 mg Controlled release Tablets (Sanofi Aventis, PL 11723/0078, 0079 & PL 11723/0021). Furthermore, reference was made to the Marketing Authorisations Orlept Tablets 200 mg or Sodium Valproate Tablets BP 200 mg and Orlept Tablets 500 mg or Sodium valproate Tablets BP 500 mg (PL 04543/0283-0284; CP Pharmaceuticals Ltd) authorised in UK. The reference products are available as tablets whilst Episenta<sup>®</sup> Prolonged-release Capsule/Granules are available as prolonged release capsule/granules.

Episenta<sup>®</sup> Prolonged-release Capsule/Granules are used to control epileptic seizures and mania. Episenta is used in the treatment of

- various types of epilepsy (seizures)
- mania, where a patient may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called “bipolar disorder”. Episenta can be used when lithium cannot be used.

**How are Episenta<sup>®</sup> Prolonged-release Capsule/Granules used?**

Episenta<sup>®</sup> Prolonged-release Capsule/Granules are taken by mouth. The daily dosage may be taken as one single or two divided doses (half in the morning and half in the evening) before, with or after meals. Patients are dosed according to their age and weight and the dosage will be adjusted to achieve adequate control of the seizures.

These medicines can only be obtained on prescription from a doctor.

For further information on how Episenta<sup>®</sup> Prolonged-release Capsule/Granules are used, please see the Summaries of Product Characteristics or Package Leaflet available on the MHRA website.

### **How do Episenta® Prolonged-release Capsule/Granules work?**

Episenta® Prolonged-release Capsule/Granules contain the active substance sodium valproate, which belongs to a group of medicines called antiepileptics. Sodium valproate prevents epileptic fits by preventing the excessive electrical activity in the brain.

### **How have Episenta® Prolonged-release Capsule/Granules been studied?**

As Episenta® Prolonged-release Capsule/Granules are hybrid applications, studies in patients have been limited to tests to determine that they are therapeutically equivalent to the reference medicine, Ergenyl chrono 300 mg sustained release matrix tablets (equivalent to the UK product, Epilim Chrono 300 mg controlled release tablets). Two medicines are therapeutically equivalent when they produce the same measure of therapeutic effect in the body.

The Marketing Authorisation holder has provided data from the published literature on sodium valproate. In addition studies were provided to compare the bioavailability of different sodium valproate formulations and the influence of food on the rate and extent of absorption.

### **What are the benefits of Episenta® Prolonged-release Capsule/Granules?**

Because Episenta® Prolonged-release Capsule/Granules are hybrid applications and are considered to be therapeutically equivalent, to the reference product Ergenyl chrono 300 mg sustained release matrix tablet, their benefits and risks are taken as being the same as those of the reference medicine.

### **What is the risk associated with Episenta® Prolonged-release Capsule/Granules?**

The common side effects with Episenta Prolonged-release Capsule/Granules are decreased number of blood platelets (thrombocytopenia), weight gain (risk factor for polycystic ovary syndrome (state leading to the formation of cysts of different sizes in the ovaries)) as appetite may be increased, weight loss, decreased appetite, tiredness and confusion which may rarely progress to hallucinations and loss of consciousness, headache, bleeding (haemorrhage), nausea, stomach ache or diarrhoea, especially when starting the treatment, increased liver functional parameters, temporary hair loss, which may be more curly on re-growth, hair fading and painful menstrual periods (dysmenorrhoea).

For the full list of all side effects reported with Episenta® Prolonged-release Capsule/Granules, see section 4 of the package leaflets.

### **Why are Episenta® Prolonged-release Capsule/Granules approved?**

No new or unexpected safety concerns arose from these applications. It was, therefore, considered that the benefits of taking Episenta Prolonged-release Capsule/Granules outweigh the risks; and the grant of Marketing Authorisations were recommended.

### **What measures are being taken to ensure the safe and effective use of Episenta® Prolonged-release Capsule/Granules?**

A satisfactory pharmacovigilance system has been provided, which 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.

Safety information has also been included in the summary of product characteristics and the package leaflet for Episenta® Prolonged-release Capsule/Granules, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Episenta<sup>®</sup> Prolonged-release Capsule/Granules**

Marketing Authorisations for Episenta<sup>®</sup> Prolonged-release Capsule/Granules were granted on 1<sup>st</sup> August 2006.

The full PAR for Episenta<sup>®</sup> Prolonged-release Capsule/Granules follows this summary.

For more information about treatment with Episenta<sup>®</sup> Prolonged-release Capsule/Granules, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in July 2014.

**EPISENTA<sup>®</sup> 150 AND 300 MG PROLONGED-RELEASE CAPSULE  
EPISENTA<sup>®</sup> 500 AND 1000 MG PROLONGED-RELEASE GRANULES**

**(Sodium valproate)**

**PL 14040/0024-0027**

**SCIENTIFIC DISCUSSION**

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## INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Desitin Arzneimittel GmbH Marketing Authorisations (licences) for the medicinal products Episenta® 150 mg and 300 mg Prolonged-release Capsule and Episenta® 500 mg and 1000 mg Prolonged-release Granules (PL 14040/0024-0027) on 23<sup>rd</sup> March 2012. These medicinal products were originally authorised to Desitin Arzneimittel GmbH (PL 14040/0012-0015) on 1<sup>st</sup> August 2006. The licenses have undergone Change of Ownership procedures to Beacon Pharmaceuticals Limited (PL 18157/0021-0024) on 11<sup>th</sup> October 2006. The names of the products were changed from Orlept LA 150 mg and 300 mg prolonged-release capsule and Orlept LA 500 mg and 1000 mg prolonged-release granules to Episenta® 150 mg and 300 mg Prolonged-release Capsule and Episenta® 500 mg and 1000 mg Prolonged-release Granules via a variation that was approved on 29<sup>th</sup> November 2006. These products have been authorised to the current Marketing Authorisation Holder, Desitin Arzneimittel GmbH (PL 14040/0024-0027) since 28<sup>th</sup> March 2012. These medicinal products will be referred to as Episenta® Prolonged-release Capsule/Granules throughout this report.

The applications for Episenta® Prolonged-release Capsule/Granules were submitted as abridged hybrid applications according to Article 10.3 of Directive 2001/83/EC, as amended. The applicant has cross-referred to Depakine Chrono 500 mg, authorised in France and registered in the UK as Epilim Chrono 200 mg, 300 mg and 500 mg Controlled release Tablets (Sanofi Aventis, PL 11723/0078 & 0079 & PL 11723/0021). Furthermore, reference was made to the Marketing Authorisations Orlept Tablets 200 mg or Sodium Valproate Tablets BP 200 mg and Orlept Tablets 500 mg or Sodium valproate Tablets BP 500 mg (PL 04543/0283-0284; CP Pharmaceuticals Ltd) authorised in UK.

Episenta® Prolonged-release Capsule/Granules are prescription only medicines (POM) and are indicated for the treatment of all forms of epilepsy.

Episenta® Prolonged-release Capsule/Granules contain the active ingredient sodium valproate, which can control epilepsy by reducing the over-activity in the brain that can cause epileptic seizures in some people.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Episenta® Prolonged-release Capsule/Granules outweigh the risks, hence Marketing Authorisations have been granted.

## PHARMACEUTICAL ASSESSMENT

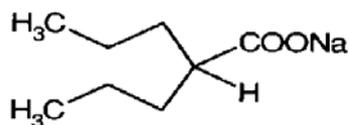
### 1. INTRODUCTION

These are national abridged applications for Marketing Authorisation in the UK submitted under Article 10.3 of Directive 2001/83/EC; hybrid for four strengths of new modified release dosage forms of authorised medicinal products. Each preparation is composed of identical modified release white, or almost white, film-coated minitables filled in hard-shell capsules (Episenta<sup>®</sup> 150 mg and 300 mg) or aluminium sachets (Episenta<sup>®</sup> 500 mg and 1000 mg). The proposed products all contain Sodium Valproate Ph Eur as a multiple unit modified release formulation. Cross-reference has been made to Depakine Chrono 500 mg, authorised in France, (registered in the UK as Epilim Chrono 200 mg, 300 mg and 500 mg Controlled release Tablets (Sanofi Aventis, PL 11723/0078 & 0079 & PL 11723/0021)) and to Orlept 200 mg and 500 mg gastro-resistant tablets, PL 04543/0283 and 0284, granted to CP Pharmaceuticals in May 1991 and December 1989, respectively.

### 2. DRUG SUBSTANCE

#### STRUCTURE/NOMENCLATURE

Sodium valproate is sodium 2-propylvalerate.



$C_8H_{15}NaO_2$

M wt = 166.2

CAS No: 1069-66-5

The sodium valproate supplied to the drug product manufacturer has been previously authorised for use in UK licensed products for oral administration. Current Ph Eur Certificates of Suitability are available.

#### SPECIFICATION

The proposed specification complies with the Ph Eur monograph for Sodium Valproate and some additional tests.

#### BATCH ANALYSES

Batch analyses data for three batches of sodium valproate from the first supplier and a single batch of sodium valproate obtained from the second have been presented. The reported results are acceptable and comparable.

Details of the control test methods routinely carried out on incoming batches of bulk drug material by the product manufacturer have been provided.

### 3. DOSAGE FORM

#### FORMULATION

The modified release minitables contain Sodium Valproate Ph Eur. The UK brand leaders, PL 11723/0078, 0021 and 0079: Epilim Chrono 200 mg, 300 mg & 500 mg controlled release tablets (Sanofi Winthrop) contain a mixture of sodium valproate Ph Eur and valproic acid FP, equivalent to 200 mg, 300 mg and 500 mg sodium valproate, respectively.

The qualitative formulation for the Episenta<sup>®</sup> Prolonged-release Capsule/Granules are given as follows:

**Qualitative Composition of Orlept prolonged-release products**

<b>Ingredient</b>	<b>Function</b>
Sodium valproate Ph Eur	Active
Calcium stearate Ph Eur	Lubricant
Colloidal silicon dioxide Methylated	Glidant
Ammonio methacrylate copolymer, type B USP/NF	Binder
Ethylcellulose Ph Eur	Coating agent
Dibutyl sebacate USP/NF	Plasticiser
Oleic acid USP/NF	Stabiliser/co-plasticiser
Gelatin Ph Eur	Hard shell capsule
Indigo carmine E132	Hard shell capsule -colourant
Quinoline yellow E104	Hard shell capsule - colourant
Sodium lauryl sulphate Ph Eur	Hard shell capsule

The various presentations contain identical modified release minitables and differ only in the amount of minitables included in the corresponding capsule size or aluminium sachet.

**CLINICAL TRIAL FORMULA**

Bioavailability/bioequivalence studies were performed using two clinical trial (CT) batches of Orfiril 300 retard modified release capsules. Both CT batches were manufactured by the specified finished product manufacturer. The formulation is identical to the Orlept LA 300 mg prolonged-release capsule proposed for marketing, except that the hard gelatin capsules are white. The difference in colour is unlikely to have any clinical impact.

Batch details, including the batch numbers and source of active ingredient used to manufacture both CT batches, the batch size of the batches, the date of manufacture and expiry date of both CT batches of the proposed finished product have been provided. Satisfactory batch analytical and stability data have been provided.

**PHARMACEUTICAL DEVELOPMENT**

The objective of development work was to produce a prolonged release multiple unit formulation of sodium valproate for long-term treatment, since constant plasma levels in a therapeutic range with reduced peak-trough fluctuation are required for clinical efficacy and tolerance. Single unit modified release formulations of sodium valproate generally produce considerable variance of plasma profiles after food intake due to high individual variation in gastric emptying times.

A brief summary was provided on the development of a multiple unit dose formulation for prolonged release of sodium valproate. During pre-formulation studies the solubility of the active ingredient was characterised and the compatibility between the active and other constituents established. Sodium valproate is hygroscopic and reportedly stable to heat, light and strong aqueous alkali. The aim was to produce extremely small minitables with the minimal amount of non-active excipients to achieve high drug loading. Relatively high drug

loading was considered necessary for multiple unit dosing without affecting compliance. Dosage form size was therefore limited. Since the small particles have a short retention time in the stomach, an enteric coated formulation was not considered necessary, because no increased risk of gastro-intestinal adverse events was expected. Ammonio methacrylate copolymer, type B, was chosen as the granulation agent in order to decrease sensitivity of the uncoated minitables against a water-based coating because of the lipophilic behaviour of the polymer. Since sodium valproate is known to be highly soluble, ethylcellulose and other additives with lipophilic characteristics were used to form a sufficient slow release film at a reasonable concentration level.

Development of an *in vitro* drug release test with discriminatory capability in relation to differences in drug release rates was reported. Development of the test included consideration of the physicochemical behaviour of sodium valproate. At pH values greater than 6.0, sodium valproate is very soluble in water, but under acidic conditions, valproic acid with a low solubility in water, is available. To evaluate the most suitable test method, separate development batches with different drug release profiles were tested and *in vitro* drug release results reported. Data presented satisfactorily demonstrated the delayed release of sodium valproate from the proposed modified-release minitables.

The proposed drug release specification was stated as  $\pm 10\%$  of the drug release profile of the test product, Orfiril Retard MUD 300 mg sustained release capsules, compared against the reference product, Ergenyl Chrono 300, in the bioequivalence studies carried out. Confidence limits were included in the calculation.

A preliminary investigation of the pharmacokinetic parameters and an evaluation of bioavailability were carried out using a sodium valproate oral solution, 300 mg/5 ml, as a reference. Multiple dose bioavailability studies carried out with Orfiril Retard MUD 300 mg sustained release capsules, Orfiril 300 enteric coated tablets and Ergenyl chrono 300 sustained release matrix tablet (claimed to be equivalent to the UK product, Epilim Chrono tablets) demonstrated that, although the extent of absorption of the active was similar for Orfiril retard 300 mg sustained release capsules and Orfiril 300 enteric coated tablets, the rate of absorption and fluctuation of plasma levels demonstrated the superiority of the modified release product. Orfiril retard 300 mg sustained release capsules were reportedly bioequivalent to Ergenyl chrono 300. A food interaction study under single dose conditions has shown that concomitant food intake exerts no influence on the pharmacokinetic behaviour of Orfiril retard 300 mg sustained release capsules.

The suitability of the proposed primary packaging with respect to protection of the modified-release minitables from moisture has been investigated as part of the stability study of the products. Photostability in the proposed commercial packaging has been satisfactorily addressed. The recommended storage conditions ensure that photostability of the four strengths of product is maintained.

#### MANUFACTURE/PROCESS VALIDATION

Typical production batch sizes have been stated as:

- 221.660 kg for Episenta® Prolonged-release Capsule 150 mg (equivalent to 560,000 prolonged-release capsules)
- 218.300 kg for Episenta® Prolonged-release Capsule 300 mg (equivalent to 280,000 prolonged-release capsules)

- 114.8 kg for Episenta® Prolonged-release Granules 500 mg and 1000 mg (equivalent to 168,000 sachets of Episenta® Prolonged-release Granules 500 mg and 84,000 sachets of Episenta® Prolonged-release Granules 1000 mg prolonged-release granules).

The manufacturing process involves: Wet granulation, drying, mixing with further excipients, compression using a rotary press, spray coating and packaging. For Episenta® Prolonged-release Capsule 150 mg and 300 mg prolonged-release capsules, the minitablets are filled into hard shell capsules prior to packaging.

In-process controls include:

*Wet granulation* - Mixing time; power consumption.

*Drying* - Temperature; time; loss on drying.

*Mixing with further excipients* - Mixing time.

*Tabletting* - Visual inspection; weight; uniformity of weight.

*Coating* - Visual inspection; process parameters; weight of film-coated minitablets.

*Hard shell capsule filling* - Visual inspection; weight; uniformity of weight; yield.

*Packaging* - Filling control; label; packaging material; batch number and expiry date; visual inspection of finished pack; yield.

Satisfactory validation plan and reports have been submitted for three consecutive production batches of the four strengths of product.

#### **EXCIPIENTS**

Calcium Stearate, Ethylcellulose and Oleic Acid are specified as complying with current Ph Eur monographs. The Calcium Stearate used is of vegetable origin. The current EDQM certificate of suitability was provided to confirm the satisfactory TSE status of the Oleic Acid used. Ammonio methacrylate copolymer type B and dibutyl sebacate are specified as complying with current USP/NF monographs. Recent Certificates of Analysis have been provided for all excipients as evidence of their full compliance with their corresponding pharmacopoeial monographs.

Colloidal silicon dioxide, methylated, complies with an 'in house' specification based on the Ph Eur monograph for colloidal anhydrous silica. The individual components of the hard gelatin capsule cap and body are specified as complying with published Ph Eur monographs. Satisfactory specifications and relevant test methods for the capsule shells have been provided by the supplier. Confirmation has been provided that the gelatin used in the capsule manufacture has been obtained wholly from recognised BSE-free sources.

#### **IMMEDIATE PACKAGING**

##### Episenta® 150 mg and 300 mg prolonged-release capsule

Packed in white polypropylene containers with white polyethylene stoppers, with a bellow. The PE stopper is filled with a drying agent. Specifications have been supplied. The plastic container and stopper comply with the Ph Eur requirements for plastic containers and closures.

##### Episenta® 500 mg and 1000 mg, prolonged-release granules

Filled into PET/Al/PE sachets. After filling the packs are closed by heat sealing. Specifications have been supplied. It has been stated that the PE component in contact with the granules complies with EU food contact regulations. Compatibility has been demonstrated by available stability data.

#### **CONTROL TESTS ON THE INTERMEDIATE PRODUCT**

In-process controls are applied to the uncoated granulecores and coated prolonged-release granules. It has been stated that the finished product specifications for appearance and active ingredient release rates are applied, if necessary, to the prolonged-release granules. Appropriate batch analytical data have been reported that demonstrate compliance with the specified controls.

#### **CONTROL TESTS ON THE FINISHED PRODUCT**

The routine finished product specifications at release and end of shelf life have been summarised. Satisfactory control tests are applied.

Satisfactory batch analytical data are available for production batches of all four strengths of product manufactured at the proposed manufacturing site. The reported results show full compliance with the specifications proposed for each product.

#### **ANALYTICAL METHODS**

The HPLC identification, assay and release rate quantification method has been adequately validated with respect to linearity, accuracy and precision. The method has been shown to be stability-indicating.

The GC related substances quantitative determination has been adequately validated with respect to linearity, accuracy, repeatability, limits of detection/quantification of named related substances.

The sodium valproate working standard used for analysis was standardised against the Ph Eur Reference Standard.

#### **STABILITY**

Stability of the prolonged-release granules over the proposed 36-month shelf lives of the four strengths of product has been satisfactorily demonstrated. The prolonged-release granules were tested for appearance, disintegration, loss on drying, identification and assay of sodium valproate (HPLC), active ingredient release, related substances (GC) and microbial contamination. Reported results do not indicate any significant degradation of sodium valproate and generally comply with the stated quality specifications.

#### **BIOAVAILABILITY**

Three studies were performed to compare the bioavailability of different sodium valproate formulations and the influence of food on the rate and extent of absorption. The first study (VPA-11/K), a single dose randomised, two-way cross-over study was carried out to compare the pharmacokinetic profile and determine the relative bioavailability of Orfiril Retard 300 mg and sodium valproate oral solution 300 mg/5 ml (Orfiril Saft) as the reference formulation. Both formulations were manufactured by Desitin.

The study was carried out by administering 300 mg doses of sodium valproate, either as a single modified release capsule of the test formulation or as 5 ml of the reference oral solution, to six healthy male volunteers (aged 28-44 years), under fasting conditions with a washout period of 7 days. Blood samples were taken prior to dosing and at specified periods up to 72 hours after administration. Plasma concentrations were assayed by a validated GC-FID system with 2-butyl hexanoic acid as internal standard, to determine  $AUC_{\infty}$ ,  $AUC_T$ ,  $C_{max}$  and  $T_{max}$  values. These are summarised as follows:

**Summary of pharmacokinetic data for sodium valproate following single dose administration**

Parameter		Test	Ref	90% Confidence Intervals (%) ANOVA	Ratio of GeoM (%)	90% Confidence Intervals (%) Non-parametric	Rnpar (%)
C <sub>max</sub> (µg/ml)	Mean	12.49	24.26	44.3-58.2	50.8	43.8-58.0	51.7
	S Dev	2.65	2.71				
	% CV	21.2	11.2				
	GeoM	12.26	24.14				
T <sub>max</sub> (hours)	Mean	9.33	0.58			6.25h-10.50	Dnpar 8.50
	S Dev	2.42	0.20				
	% CV	726.0	35.0				
	GeoM	9.00	0.50				
AUC <sub>0-t</sub> (µg-hr/ml)	Mean	351.8	325.6	95.1-122.2	107.8	94.9-124.6	105.9
	S Dev	87.7	74.8				
	% CV	24.9	23.0				
	GeoM	343.1	318.3				
AUC <sub>0-∞</sub> (µg-hr/ml)	Mean	369.0	339.5	96.6-121.9	108.5	96.5-124.0	106.8
	S Dev	88.9	76.2				
	% CV	24.1	22.4				
	GeoM	360.6	332.3				
t <sub>½e</sub> (hours)	Mean	14.52	14.34	91.8-111.8	101.3	89.7-111.5	100.2
	S Dev	1.93	1.99				
	% CV	13.3	13.9				
	GeoM	14.41	14.22				

Rpar : Parametric ratio, ratio of geometric means of test and reference formulation

Rnpar : Non-parametric point estimator for the ratio of the expected medians of test and reference formulation

Dnpar : Non-parametric point estimator for the difference of the expected medians of test and reference formulation

Significant differences in the rate characteristics, C<sub>max</sub> and T<sub>max</sub>, confirm the delayed release characteristics of the test formulation with C<sub>max</sub> occurring approximately 9 hours after administration of the modified release test formulation and 0.58 hours after administration of the reference oral solution. The extent of absorption was equivalent.

The second study (VPA-15/K) was performed as an open three-period, randomised, cross-over, multiple dose study to determine the steady state pharmacokinetics and compare bioavailability after multiple dosing with three different preparations. The three preparations were, [a] Orfiril Retard MUD, sustained release capsules containing 300 mg sodium valproate, [b] Orfiril Dragees, enteric coated tablets containing 300 mg sodium valproate and [c] Ergenyl Chrono 300, a sustained release matrix tablet containing 200 mg sodium valproate and 87 mg valproic acid equivalent to a total of 300 mg sodium valproate. Formulations [a] and [b] were manufactured by Desitin. Formulation [c] was manufactured by Sanofi Winthrop GmbH. The study consisted of three periods of 6 days each. In each period, one of the treatments was applied for nine intervals of 12 hours each. A 300 mg dose of sodium valproate was administered twice daily to 18 healthy male volunteers (aged 22-44 years),

randomly assigned to one of the treatment sequences, under fasting conditions and with a washout period of 10 days between administrations. Blood samples were taken prior to dosing and at specified periods up to 24 hours after administration eight. Plasma concentrations of valproic acid were assayed by the same validated GC-FID system as used in the first study. The pharmacokinetic profile of formulation [a] differed from that of [b] with respect to the rate characteristics Peak Trough Fluctuation (PTF) and AUC Fluctuation (AUCF). Data indicates that formulation [b] has a fluctuation which is more than twice as high as that of [a], probably due to changes in the gastric emptying times. The extent of absorption was equivalent for formulations [a] and [b]. The pharmacokinetic profiles of formulations [a] and [c] did not differ with respect to rate or extent of absorption characteristics.

The third study (VPA-17/K) was performed as an open 4-period, randomised, cross-over, single dose study to compare the relative bioavailability of three different preparations as four treatments after single dosing. The influence of concomitant food was investigated. The four treatments were, [a] Orfiril Retard MUD, sustained release capsules containing 300 mg sodium valproate fasted, [b] Orfiril Retard MUD, sustained release capsules containing 300 mg sodium valproate with breakfast, [c] Orfiril Dragees, enteric coated tablets containing 300 mg sodium valproate fasted, and [d] Ergenyl Chrono 300, a sustained release matrix tablet containing 200 mg sodium valproate and 87 mg valproic acid equivalent to a total of 300 mg sodium valproate fasted. Formulations [a], [b] and [c] were manufactured by Desitin. Formulation [d] was manufactured by Sanofi Winthrop GmbH. The study was carried out by administering 300 mg doses of sodium valproate as a single dose to 16 healthy male volunteers (aged 18-45 years), under fasting conditions for treatments [a], [c] and [d], and with a standardised breakfast high in calories and with a high fat content for treatment [b], each with a washout period of at least 7 days. Blood samples were taken prior to dosing and at specified periods up to 72 hours after administration. Plasma concentrations were assayed by the validated GC-FID system used in the other studies, to determine AUC,  $C_{max}$ ,  $t_{max}$  and  $t_{1/2}$  values. These are summarised as follows:

**Summary of pharmacokinetic data for sodium valproate following single dose administration of Orfiril Retard MUD [a], Orfiril Retard Dragees [c] and Ergenyl Chrono 300 [d]**

Parameter	90% Confidence Intervals(%) ANOVA	$R_{par}$ (%)	90% Confidence Intervals (%) Non-parametric	$R_{npar}$ (%)
<b>Orfiril retard MUD vs Orfiril retard dragees [a/c]</b>				
AUC <sub>0-tz</sub>	97.3-113.1	104.9	96.9-112.4	104.8
AUC <sub>0-∞</sub>	94.7-110.5	102.3	94.8-110.8	102.5
$C_{max}$	110.6-124.7	117.5	111.2-124.4	118.7
$t_{1/2}$	85.7-98.1	91.7	84.0-101.3	91.7
$t_{max}$ /hours			-3.5-0.0	$D_{npar}$ -0.5
<b>Orfiril retard MUD vs Ergenyl Chrono 300 [a/d]</b>				
AUC <sub>0-tz</sub>	98.6-114.7	106.3	97.7-113.3	104.4
AUC <sub>0-∞</sub>	97.9-114.2	105.8	96.9-112.7	103.6
$C_{max}$	100.7-113.6	107.0	100.0-114.1	108.4
$t_{1/2}$	90.6-103.8	97.0	91.0-102.1	96.7

t <sub>max</sub> /hours			-1.5-2.0	D <sub>npar</sub> 0.5
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R<sub>par</sub> : Parametric ratio, ratio of geometric means of test and reference formulation

R<sub>npar</sub> : Non-parametric point estimator for the ratio of the expected medians of test and reference formulation

D<sub>npar</sub> : Non-parametric point estimator for the difference of the expected medians of test and reference formulation

The time concentration profiles were very similar. No statistical difference was seen with the test Orfiril retard MUD product and the reference Orfiril Dragees and Ergenyl Chrono with respect to AUC, C<sub>max</sub> and t<sub>1/2</sub>. The results presented lie within the accepted range of 80-125% for the rate and extent of absorption required to demonstrate bioequivalence.

**Summary of pharmacokinetic data for sodium valproate following single dose administration of Orfiril Retard MUD [a] fasting and Orfiril Retard MUD [b] with breakfast**

Parameter	90% Confidence Intervals (%) ANOVA	R <sub>par</sub> (%)
<b>Orfiril retard MUD (with breakfast) vs Orfiril retard MUD (fasting) [b/a]</b>		
AUC <sub>0-tz</sub>	90.0-104.7	97.1
AUC <sub>0-∞</sub>	90.1-105.2	97.4
C <sub>max</sub>	93.2-105.1	99.0
t <sub>1/2</sub>	93.8-107.4	100.4

R<sub>par</sub> : Parametric ratio, ratio of geometric means of test and reference formulation

No statistical difference was seen with treatments [a] and [b] with respect to AUC, C<sub>max</sub> and t<sub>1/2</sub>. The bioavailability of Orfiril retard MUD 300 mg is not significantly influenced by the intake of standardised, high energy, high fat food.

The medical assessor has also assessed these studies and supports the claims that the pharmacokinetic profile of Orfiril retard MUD is comparable to that of the reference formulation, Ergenyl Chrono, and that food intake does not significantly alter the absorption kinetics of the test formulation.

#### 4. ADMINISTRATIVE DETAILS

##### PRODUCT LABELLING

Colour mock-ups have been provided for each strength of the proposed product. These are all satisfactory.

##### PATIENT INFORMATION LEAFLET

Full mock-ups for each strength of proposed product have been provided and are satisfactory.

##### MAA FORM

##### Section 2 - Structured Marketing Authorisation Information

All structured MA information is satisfactory.

##### Section 3 - Summary of Product Characteristics

The SPCs for all strengths are satisfactory.

#### **Section 4 - Additional Data Requirements**

##### **Expert Report**

Satisfactory, individual Expert Reports were prepared by a suitably qualified expert at Desitin Arzneimittel GmbH (Germany).

#### **5. PHARMACEUTICAL RECOMMENDATION**

Granting of Marketing Authorisations is recommended.

## **NON-CLINICAL ASSESSMENT**

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

## CLINICAL ASSESSMENT

### 1. INDICATIONS

Treatment of all forms of epilepsy.

### 2. DOSE & DOSE SCHEDULE

Dose recommendations are detailed in the SPC. They are quite similar to those stated for the X-reference, and nearly identical in wording to those for the currently approved range of Orlept.

### 3. TOXICOLOGY

Bibliographic documentation and a separate expert report on the pharmaco-toxicology have been made available.

No novel toxicological data have been submitted. None were required. The applicant cross-refers to Epilim Chrono 300 (PL 11723/0021).

### 4. CLINICAL PHARMACOLOGY

#### 4.1 PHARMACODYNAMICS

No new pharmacodynamic data have been presented. Reference is made to the published literature.

Valproate is mainly known for its anticonvulsant activity. Much attention has been focused on its effect on the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and on membrane ion channels. Valproate increases CNS concentrations of GABA by activating its synthesis, inhibiting its catabolism and enhancing its post-synaptic effects.

#### 4.2 PHARMACOKINETICS

The kinetic properties of valproate have been well described in the past. The Clinical Expert refers to the published literature. A summary is provided in Section 5.2 of the SmPC and the following table:

#### Pharmacokinetic properties of valproate

Process	Properties
Absorption	rapid, nearly complete after ingestion
Time to peak plasma level	1 - 4 h (dependent on formulation)
Distribution	rapid, reaches CNS within minutes
Protein binding	highly bound to proteins, mainly albumin
CSF concentration	suggest equilibration with free drug in plasma
Half-life	6 - 16 h, shortened by concomitant intake of enzyme-inducing drugs
Metabolism	liver, primarily conjugation, also $\beta$ -, omega-oxidation
Excretion	urine, faeces, 97% as metabolites, less than 3% unchanged

In brief, bioavailability is close to 100% and the volume of distribution is mainly confined to blood and rapid exchange extra-cellular liquid. Valproate concentrations in cerebrospinal fluid are close to free plasma concentrations. Valproate is highly bound to plasma proteins (90%). Mean terminal life is about 15 hours. Valproate is mainly excreted in urine following hepatic metabolism via glucuro-conjugation and  $\beta$ -oxidation.

### 4.3 BIOAVAILABILITY/BIOEQUIVALENCE

Original data on the pharmacokinetics have been provided by the applicant. These are three Phase I studies examining the bioavailability of different formulations and the influence of food on the rate and extent of absorption. All studies included Orfiril retard MUD 300 mg, which is confirmed to be identical to Episenta® 300 mg Prolonged-release Capsule. Likewise, Ergenyl chrono 300 mg is identical to the reference product, Epilim chrono 300 mg. A summary table outlining the major studies is given below:

Orfiril Long (Orlept Long) phase I studies						
Study	Study design	Rte	Dosage form	Dose (mg)	N° Subj	Results
VPA-013/K	Bioavailability crossover, SD	PO	Orfiril Retard	300	6	The regimens produced equiv. AUCs (CI:0.951 -1.222) but lower C <sub>max</sub> for Retard capsules
			Orfiril Saft	300		
VPA-015/K	Bioavailability, crossover, MD	PO	Orfiril Retard	300 bd	18	Orfiril Retard vs. Orfiril enteric: bioequivalent for extent of absorption AUC (CI: 0.981-1.057).  Orfiril retard vs. Ergenyl Chrono: Regimens were equivalent for extent and rate of absorption.
			Orfiril Enteric	300 bd		
			Ergenyl Chrono	300 bd (9 doses)		
VPA-017/K	Bioavailability Effect of food, crossover, SD	PO	Orfiril Retard (fasted)	300	16	No effect of food intake on rate and extent of absorption.  All formulations equivalent for rate and extent of absorption.
			Orfiril Retard (fed)	300		
			Orfiril Enteric SR (fasted)	300		
			Ergenyl Chrono (fasted)	300		
Abbreviations: CI=confidence interval, SD=single dose, MD=multidose N° Subj=subjects evaluable for complete PK workup						

#### 4.3.1 Pilot study on the pharmacokinetics of a new sustained release formulation compared with a valproate solution (VPA-013/K)

This is a two period, single-dose crossover study comparing the pharmacokinetic profile of Orfiril retard MUD 300mg with the profile obtained for Orfiril Saft oral solution administered at an identical dosage (300mg/5ml).

The study was in accordance with GCP.

For the ratio of the main parameters, the parametric point estimator ( $R_{par}$ ) and 90% confidence interval limits are shown:

Parametric from Ln-transformed 90% Confidence Intervals		
Parameter	Confidence Interval (%)	$R_{par}$ (%)
AUC <sub>0-t</sub>	95.1 - 122.2	107.8
AUC <sub>0-∞</sub>	96.6 - 121.9	108.5
C <sub>max</sub>	44.3-58.2	50.8
t <sub>1/2</sub>	91.8-111.8	101.3
Nonparametric linear 90% Confidence Intervals (MANN/WHITNEY)		
t <sub>max</sub>	6.25 h - 10.50 h	8.5 h

Statistically significant differences were found for the rate characteristics C<sub>max</sub> and t<sub>max</sub>. Following intake of the test formulations, the C<sub>max</sub> occurred 9.33 h after administration of the tablet formulation, and 0.58 h after the intake of the solution.

On the other hand, there was no significant difference between the two formulations in terms of extent of the absorption.

#### 4.3.2 Steady state pharmacokinetics of valproate after multiple dosing of three different preparations (VPA -015/K).

An overview of the study is given in the clinical dossier.

The objective of this study was to assess the relative bioavailability of a new test formulation a (Orfiril retard MUD sustained release capsule containing 300 mg sodium valproate) as compared with reference formulation b (Orfiril Dragees, an enteric coated tablet containing 300 mg sodium valproate) and with formulation c (Ergenyl Chrono 300, also called Epilim Chrono 300, a matrix tablet containing 200mg sodium valproate and 87mg valproic acid, corresponding to 300 mg sodium valproate).

Formulations a and b are produced by Desitin, while the reference formulation c is a product of Sanofi Winthrop GmbH. This was a three period, six sequence crossover study, with study periods separated by a wash out phase of at least 10 days. In each period, one of the treatments was applied for nine intervals of 12 hours each. Blood samples were drawn at adequate intervals post-dosing (eighth and ninth dosing interval), and serum was analysed for valproic acid concentrations.

The study complied with GCP guidelines. A full report has been submitted.

Eighteen healthy male subjects took part, aged 22-44 years.

Results indicate that the pharmacokinetic profile of formulation a differed from that of formulation b with respect to the rate characteristics PTF and AUCF, but not to the extent characteristics. The fluctuation of formulation b is more than twice as high as that of formulation a.

<b>Parametric 90% Confidence Intervals from Ln-transformed Data (ANOVA)</b>		
	<b>a vs. b</b>	
Parameter	Confidence Interval (%)	R <sub>par</sub> (%)
AUC <sub>(8r, 9r)</sub>	98.1 - 105.7	101.8
C <sub>max(9r)</sub>	82.1 - 91.8	86.8
PTF <sub>(8r, 9r)</sub>	32.1 - 43.8	37.5
AUCF <sub>8r, 9r)</sub>	32.6 - 46.9	39.1

On the other hand, the pharmacokinetic profiles of formulations a and c do not differ with respect to rate nor to extent characteristics.

<b>Parametric 90% Confidence Intervals from Ln-transformed Data (ANOVA)</b>		
	<b>a vs. b</b>	
Parameter	Confidence Interval (%)	R <sub>par</sub> (%)
AUC <sub>(8r, 9r)</sub>	98.7- 106.4	102.5
C <sub>max(9r)</sub>	93.3 - 104.4	98.7
PTF <sub>(8r, 9r)</sub>	84.9 - 115.9	99.2
AUCF <sub>8r, 9r)</sub>	88.3 - 127.1	105.9

In addition, as a separate study part, the pharmacokinetic profile of Orfiril enteric coated dragees after a dosage regimen of 300 mg t.i.d was predicted from the results measured after the twice daily dosing and the simulated profile (t.i.d) was compared with the profile of the new retard formulation. Orfiril retard MUD given b.i.d. It concluded that the rate characteristics did not considerably improve with addition of a third daily tablet. The Orfiril retard MUD formulation given b.i.d, showed lower fluctuation than the enteric coated tablets, administered t.i.d.

#### 4.3.3 Single dose bioavailability and food interaction study on Orfiril retard MUD, a new formulation of sodium valproate

In this single dose, four period, crossover study, the relative bioavailability of a Orfiril retard MUD 300mg capsules (fasting) was compared with two reference formulations: c Orfiril 300 retard enteric coated dragees (fasting) and d Ergenyl Chrono 300 sustained release tablet (fasting). In addition, the administration of formulation a under non-fasting conditions was assessed in order to examine the influence of the food effect (denoted as treatment b).

Treatment periods were separated by a washout phase of at least 7 days.

The study was conducted according GCP standards and a full report has been made available.

The results indicate that, apart from proving bioequivalence between the sponsor's treatment a and reference formulations c and d, the bioavailability of Orfiril retard MUD 300 mg is not significantly influenced by the intake of a standardised, high energy, high fat diet:

Parametric 90% Confidence Intervals from LN-transformed Data (ANOVA)		
Food/Non-Food (b/a)		
Parameter	Confidence Interval (%)	R <sub>par</sub> (%)
AUC <sub>0-t</sub>	90.0 - 104.7	97.1
AUC <sub>0-∞</sub>	90.1 - 105.2	97.4
C <sub>max</sub>	93.2 - 105.1	99.0
t <sub>1/2</sub>	93.8 - 107.4	100.4

#### Conclusions

The overall conclusions derived from these three well designed studies are that:

1. As expected, the release of sodium valproate from the multiple unit capsule was retarded. This was not achieved at the expense of the extent of the absorption.
2. The kinetic profile of Orfiril retard MUD is comparable to that of the reference formulation, Ergenyl chrono.
3. Orfiril retard MUD maintains valproate concentrations with a lower fluctuation than the Orfiril enteric coated tablets, making them suitable for twice daily or even once daily dosing.
4. Food intake does not significantly alter the absorption kinetics of the new formulation. In addition to the aforementioned studies, the applicant provided reviews from the published literature. From a reappraisal of the pharmacokinetic properties (Davis et al.), it appears that there is a clear dose dependent linear increase in mean plasma level of valproate. Also, the applicant states that the kinetic characteristics of the different Orfiril long preparations are not influenced whatsoever by the disintegration of the hard gelatine capsules, but only depend on the release characteristics of sodium valproate from the sustained release pellets (see also

Pharmaceutical Assessment). Hence, it is accepted that the principle of dose proportionality can be applied, and therefore the conclusions from the above bioequivalence studies with the 300 mg hard capsule formulation can be extended as well to the other Orfiril long dosage forms.

## **5. CLINICAL EFFICACY**

No novel data have been supplied; none would be required. A recent review on valproic acid (Davis R et al.), Valproic Acid. A reappraisal of its pharmacological properties and clinical efficacy in epilepsy. *Drugs* 1994; 47(2): 332-372) indicates a wide spectrum of anticonvulsant activity, either as monotherapy or as part of a combination therapy in adults (including the elderly) as well as in children.

## **6. CLINICAL SAFETY**

The clinical safety of valproate has been well summarised by the expert. Valproate has a well established safety profile. Most commonly reported are mild to moderately severe gastrointestinal disturbances, weight gain, transient hair loss and neurological effects. Rare valproic acid induced fatal hepatotoxicity occurs more frequently in patients <2 years of age receiving polytherapy. Increased incidence of congenital abnormalities has been demonstrated in offspring born to both treated and untreated mothers with epilepsy. An estimated risk of 1% to 2% for neural tube defects is reported for infants born to women treated with valproic acid during pregnancy. Post-marketing experience for the epilepsy indication with Orfiril formulations (>55,000,000 defined daily doses [1500 mg] sold in Germany during the time period 1988-1996) re-enforces the view that valproate is safe, with 1 reported adverse event/2528 patient treatment years.

### **6.1 SUMMARY OF ADVERSE REACTIONS – VOLUNTEERS**

Main adverse events reported during the conduct of the Phase I trials were mainly confined to headache and gastro-intestinal disturbances (nausea; abdominal pain).

### **6.2 OVERALL COMMENT ON SAFETY**

In the clinical studies, the safety profile was consistent with the known safety pattern observed during treatment for epilepsy. Published literature draws attention to possibility of fatal hepatotoxicity (especially in the very young), rare occurrence of blood dyscrasia and acute pancreatitis. Teratogenicity of divalproex is another well known feature. Concomitant administration of valproic acid can affect the plasma concentrations of other drugs by displacement from plasma proteins and/or inhibition of hepatic metabolism. Appropriate warnings occur in the SmPC and PIL.

## **7. EXPERT REPORTS**

An appropriate expert report on the pharmaco-toxicological documentation has been provided. It has been signed by a veterinary doctor, professor in pharmacology and toxicology. The report briefly reviews the pre-clinical data on valproate.

A satisfactory clinical expert report has been provided.

## **8. PATIENT INFORMATION LEAFLET**

The patient information leaflet is satisfactory.

## **9. LABELLING**

All labelling is satisfactory.

## **10. APPLICATION FORM**

A proper application form for each individual strength has been submitted. The administrative details are duly completed.

## **11. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

The SmPCs for these products are satisfactory.

## **13. CONCLUSION**

The efficacy and safety of these products are satisfactory for the grant of product licences (for each strength) with respect to the epilepsy indication. The Committee may wish to consider that there is insufficient evidence of efficacy related to the treatment of a manic episode in patients with bipolar disorder.

**COMMITTEE ON SAFETY OF MEDICINES RECOMMENDATION – 9  
DECEMBER 1998**

The UK Advisory Committee considered the licence application on 9 December 1998 and reported that, on the evidence before them, the Committee could not recommend the granting of Marketing Authorisation on the grounds of quality, safety and efficacy.

The main clinical objections related to insufficient evidence of efficacy related to the treatment of a manic episode in patients with bipolar disorder.

On 14 December 1998 the applicant responded to this point and agreed that the indications could be restricted, as proposed by the MHRA, to all forms of epilepsy and that these products should not be indicated for manic episodes in patients with bipolar disorder.

On 11 May 1999 the MHRA accepted this revision.

## **OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT**

### **QUALITY**

The important quality characteristics of Episenta<sup>®</sup> 150 and 300 mg, prolonged-release capsule and Episenta<sup>®</sup> 500 and 1000 mg, prolonged-release granules (PL14040/0024-0027) are well defined and controlled. The specifications and batch analysis results confirm consistancy 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 application of these type.

### **EFFICACY**

No new or unexpected safety concerns arose from these applications.

The SmPCs, PILs and labelling are satisfactory.

### **BENEFIT RISK ASSESSMENT**

The quality of the products is acceptable and no new non-clinical or clinical concerns have been identified. The benefit risk ratio is considered to be positive.

**EPISENTA® 150 AND 300 MG PROLONGED-RELEASE CAPSULE**  
**EPISENTA® 500 AND 1000 MG PROLONGED-RELEASE GRANULES**

**(Sodium valproate)**

**PL 14040/0024-0027**

**STEPS TAKEN FOR ASSESSMENT**

<b>1</b>	The MHRA received the Marketing Authorisation application on 20 July 1998
<b>2</b>	Following assessment of the application the MHRA requested further information relating to the quality dossier on 16 November 1998
<b>3</b>	As a result of issues raised during assessment, the application went to CPS sub-committee on 3 December 1998 and CSM on 9 December 1998. A decision notification was sent to the applicant on 14 December 1998
<b>4</b>	The applicant responded to the committee, accepting their decision on 29 April 1999
<b>5</b>	Following assessment of the revised application the MHRA requested further information relating to the quality dossier on 30 May 2002 and 11 December 2003
<b>6</b>	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 5 April 2004
<b>7</b>	Following assessment of the application the MHRA requested further information relating to the quality dossier on 13 July 2004
<b>8</b>	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 14 July 2004
<b>9</b>	Following assessment of the application the MHRA requested further information relating to the quality dossier on 28 July 2004
<b>10</b>	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 5 January 2005
<b>11</b>	Following assessment of the application the MHRA requested further information relating to the quality dossier on 16 May 2005
<b>12</b>	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 1 June 2005
<b>13</b>	Following assessment of the response the MHRA requested further information relating to the quality dossier on 10 August 2005
<b>14</b>	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 23 September 2005 and 16 March 2006 and 29 March 2006
<b>15</b>	Following assessment of the response the MHRA requested further information

	relating to the quality dossier on 30 March 2006 and 1 June 2006
<b>16</b>	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 2 June 2006
<b>17</b>	Following assessment of the response the MHRA requested further information relating to the quality dossier on 2 June 2006 and 20 June 2006
<b>18</b>	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 5 June 2006 and 22 June 2006
<b>21</b>	The application was determined on 2 August 2006

## **SUMMARY OF PRODUCT CHARACTERISTICS**

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

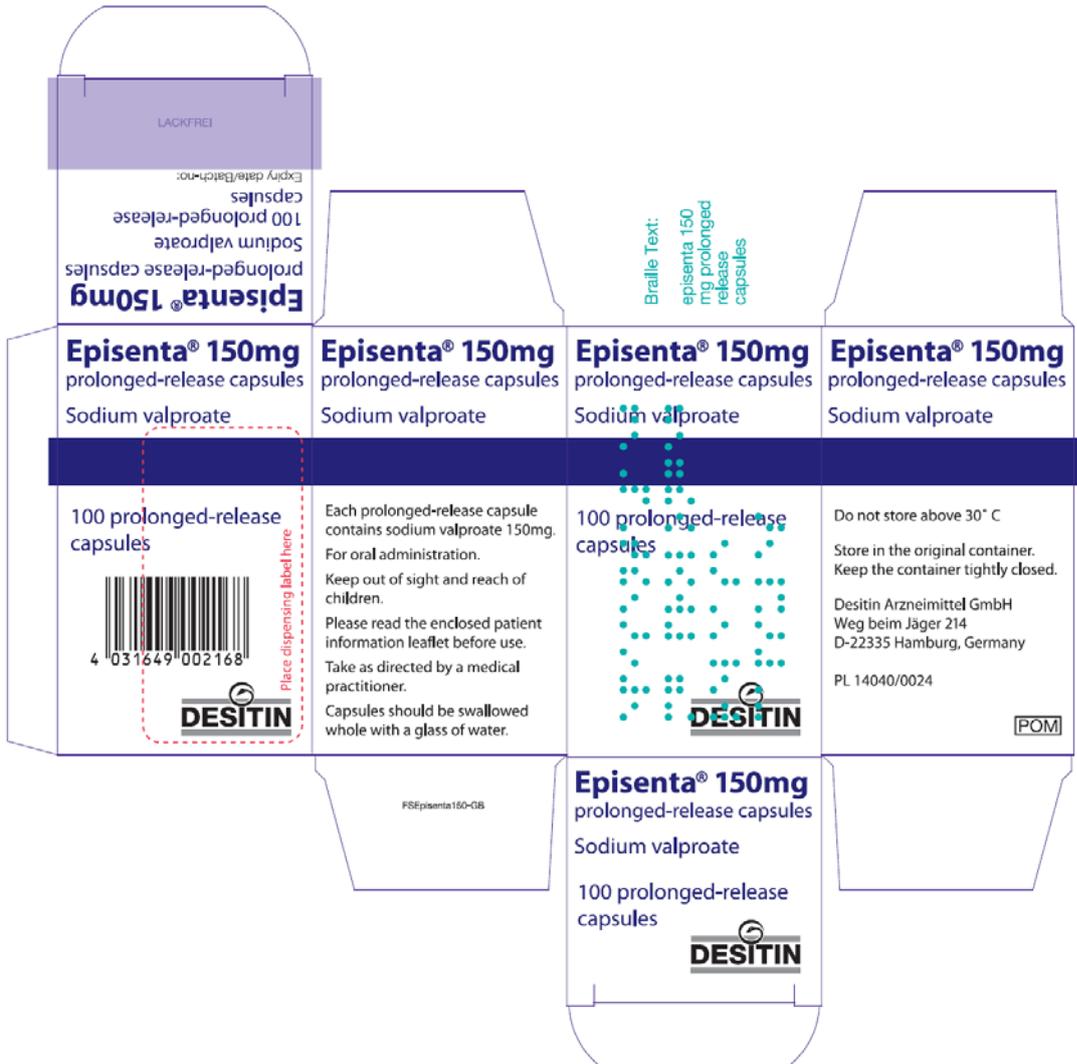
## **PATIENT INFORMATION LEAFLET (PIL)**

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

## LABELLING

**150 mg:**

<p><b>Episenta® 150mg</b> prolonged-release capsules</p> <hr style="border: 2px solid black;"/> <p>Sodium valproate</p> <p>100 prolonged release capsules</p> <div style="text-align: center; margin-top: 20px;">  </div>	<p>Each prolonged-release capsule contains sodium valproate 150mg. For oral administration, Keep out of sight and reach of children Please read the enclosed patient information leaflet before use. Take as directed by a medical practitioner. Do not store above 30°C. Store in the original container. Keep the container tightly closed. Capsules should be swallowed whole with a glass of water. PL 14040/0024 Desitin Arzneimittel GmbH Weg beim Jäger 214 D-22335 Hamburg, Germany</p>	<p style="writing-mode: vertical-rl; transform: rotate(180deg);"><b>HEEepisenta150-GB</b></p> <p style="writing-mode: vertical-rl; transform: rotate(180deg);">Expiry date</p> <p style="writing-mode: vertical-rl; transform: rotate(180deg);">Batch no</p> <div style="text-align: center; margin-top: 20px;"> <div style="border: 2px solid black; padding: 5px; display: inline-block;"><b>POM</b></div> </div>
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The flat layout shows the following panels and text:

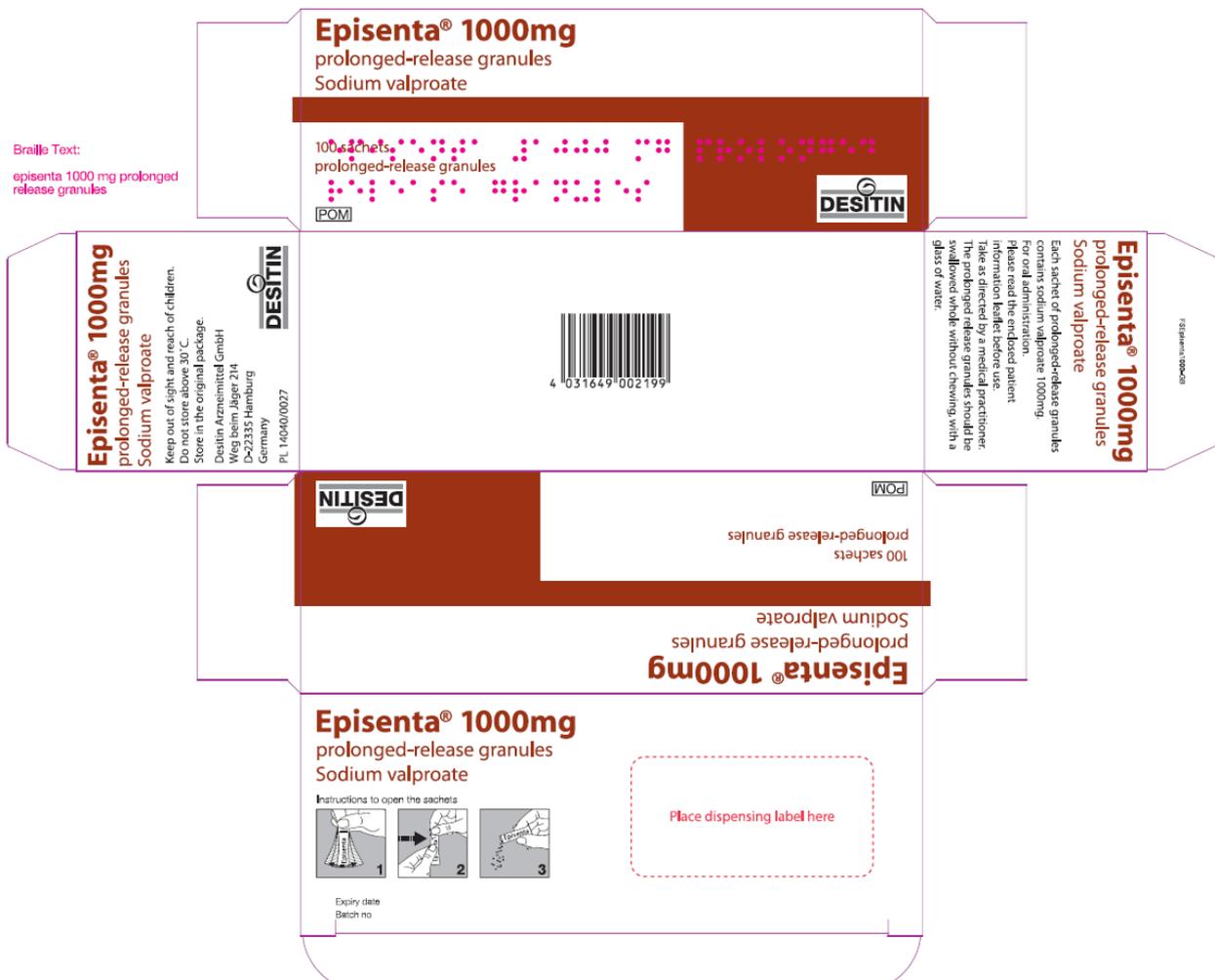
- Top Panel:** LACHTFREI
- Back Panel:** Expiry date/Batch no: 100 prolonged-release capsules Sodium valproate prolonged-release capsules **Episenta® 150mg**
- Front Panel (Left):** **Episenta® 150mg** prolonged-release capsules Sodium valproate 100 prolonged-release capsules. Includes barcode (4 031649 002168) and **DESITIN** logo. A red dashed box indicates "Place dispensing label here".
- Front Panel (Middle):** **Episenta® 150mg** prolonged-release capsules Sodium valproate. Includes Braille text: episenta 150 mg prolonged release capsules and **DESITIN** logo.
- Front Panel (Right):** **Episenta® 150mg** prolonged-release capsules Sodium valproate. Includes storage instructions: "Do not store above 30° C. Store in the original container. Keep the container tightly closed." and manufacturer info: "Desitin Arzneimittel GmbH Weg beim Jäger 214 D-22335 Hamburg, Germany PL 14040/0024". Includes **POM** logo.
- Bottom Panel:** **Episenta® 150mg** prolonged-release capsules Sodium valproate 100 prolonged-release capsules. Includes **DESITIN** logo.
- Internal Panel:** FSEepisenta150-GB





1000 mg:

	Batch no	Expiry date
FOEpisenta1000-GB	<p><b>Episenta® 1000mg</b>                  prolonged-release granules</p> <p>1000 mg sodium valproate Ph. Eur.                  For oral administration                  Desitin Arzneimittel GmbH</p> <p>Open here </p>	



**EPISENTA® 150 AND 300 MG PROLONGED-RELEASE CAPSULE  
EPISENTA® 500 AND 1000 MG PROLONGED-RELEASE GRANULES**

**(Sodium valproate)**

**PL 14040/0024-0027**

**STEPS TAKEN AFTER ASSESSMENT**

The following table lists some non-safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<b>Date submitted</b>	<b>Application type</b>	<b>Description</b>	<b>Outcome</b>
24/04/2014	VAR Medical Type II	To update section 5 (Pharmacological properties) of the SmPCs and consequentially the leaflet with safety information.	Variation granted 01/07/2014

## **ANNEX 1 – CLINICAL VARIATION ASSESSMENT REPORT**

### **Reason:**

To update section 5 (Pharmacological properties) of the SmPC and consequentially the leaflet with safety information.

Linked/Related Variation(s) or Case(s):

The Assessment Report also refers to the following submissions: PL 14040/0025 - 0016, PL 14040/0027 – 0016 and PL 14040/0026 - 0017.

### **Supporting Evidence**

In support of this variation the Marketing Authorisation holder provided literature references and justifications. Revised SmPCs and PILs have been provided. The currently approved labelling is acceptable and needs no further revisions.

### **Evaluation**

Some changes have been added to the PILs which include warning on hypoproteinaemia, possible skeletal deformities, mental retardation and other congenital malformations in babies, abnormal sperm production and infertility in males.

The Marketing Authorisation holder has provided supporting evidence for the changes requested. Sodium valproate and related substances have been referred under Article 31 in October 2013 and the referral is still on-going.

Evidence has been found that children born to women who were treated with valproate medicines during pregnancy have an increased risk of birth defect, mental retardation and autism. It was noted that there was a need to update the product information of these medicines to bring them in line with current evidence.

The literature reference submitted support the changes related to decrease male fertility, protein binding and hypoproteinaemia. The amended sections of the SmPCs and the amended PILs are satisfactory.

### **Conclusion**

There are no objections for the approval of the above variation.

### **Decision - Approved**

## **SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) Updated**

Following approval of the variations on 1<sup>st</sup> July 2014 the SmPCs were updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

**PATIENT INFORMATION LEAFLET (PIL) Updated**

Following approval of the variations on 1<sup>st</sup> July 2014 the PILs were updated. In accordance with Directive 2010/84/EU the Patient Information Leaflet (PILs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.