

## **Public Assessment Report**

**EPILIM CHRONOSPHERE MR 50 MG MODIFIED  
RELEASE GRANULES (PL 04425/0310)**

**EPILIM CHRONOSPHERE MR 100 MG MODIFIED  
RELEASE GRANULES (PL 04425/0312)**

**EPILIM CHRONOSPHERE MR 250 MG MODIFIED  
RELEASE GRANULES (PL 04425/0313)**

**EPILIM CHRONOSPHERE MR 500 MG MODIFIED  
RELEASE GRANULES (PL 04425/0314)**

**EPILIM CHRONOSPHERE MR 750 MG MODIFIED  
RELEASE GRANULES (PL 04425/0315)**

**EPILIM CHRONOSPHERE MR 1000 MG MODIFIED  
RELEASE GRANULES (PL 04425/0316)**

**(Sodium valproate and valproic acid)**

**Aventis Pharma Limited**

## LAY SUMMARY

### **EPIILIM CHRONOSPHERE MR 50 MG MODIFIED RELEASE GRANULES (PL 04425/0310)**

### **EPIILIM CHRONOSPHERE MR 100 MG MODIFIED RELEASE GRANULES (PL 04425/0312)**

### **EPIILIM CHRONOSPHERE MR 250 MG MODIFIED RELEASE GRANULES (PL 04425/0313)**

### **EPIILIM CHRONOSPHERE MR 500 MG MODIFIED RELEASE GRANULES (PL 04425/0314)**

### **EPIILIM CHRONOSPHERE MR 750 MG MODIFIED RELEASE GRANULES (PL 04425/0315)**

### **EPIILIM CHRONOSPHERE MR 1000 MG MODIFIED RELEASE GRANULES (PL 04425/0316)**

#### **(Sodium valproate and valproic acid)**

This is a summary of the public assessment report (PAR) for applications for Epilim Chronosphere MR 50 mg, 100 mg, 250 mg, 500 mg, 750 mg and 1000 mg Modified Release Granules (PL 04425/0310, 0312-0316). These medicinal products will be referred to as Epilim Chronosphere MR Modified Release Granules in the remainder of the report.

This summary explains how Epilim Chronosphere MR Modified Release 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 these products.

For practical information about Epilim Chronosphere MR Modified Release Granules, patients should read the package leaflets or contact their doctor or pharmacist.

#### **What are Epilim Chronosphere MR Modified Release Granules and what are they used for?**

Epilim Chronosphere MR Modified Release Granules are 'hybrid medicines'. This means that Epilim Chronosphere MR Modified Release Granules are similar to a reference medicine containing the same active substance, but these medicines are available as a multiple unit modified release granules in sachets.

The different presentations contain identical modified –release granules and differ only in the amount of granules included in the sachets.

**PAR Epilim Chronosphere MR 50, 100, 250, 500, 750 and 1000 mg Modified Release Granules  
PL 04425/0310, 0312-0316**

The reference medicine already authorised in the UK is Epilim Chrono 500 Controlled Release Tablets (Aventis Pharma Limited; PL 04425/0309).

Epilim Chronosphere MR Modified Release Granules are used to treat epilepsy (fits) in adults and children.

**How are Epilim Chronosphere MR Modified Release Granules used?**

Epilim Chronosphere MR Modified Release Granules are taken by mouth once or twice daily. The granules (full contents of each sachet) can be mixed with small amount of food or drink without crushing or chewing.

Epilim Chronosphere treatment must be started and supervised by a doctor specialised in the treatment of epilepsy. A doctor will decide how much Epilim Chronosphere to give to a patient depending on the body weight.

The starting dose in adults is 600 mg daily. A doctor will gradually increase this dose by 200 mg every 3 days depending on their condition. The usual dose is generally between 1000 mg and 2000 mg (20-30 mg per kilogram of body weight) each day. This may be increased to 2500 mg each day depending on a patient's illness.

The starting dose in children over 20 kilograms should be 400 mg daily. A doctor should increase this dose depending on the child's illness. The usual dose is usually between 20 and 30 mg for each kilogram of body weight each day (to the nearest whole 50mg sachet). This may be increased to 35 mg for each kilogram of body weight each day depending on the child's illness.

The usual dose in children under 20 kilograms is 20 mg for each kilogram of body weight each day. Depending on the child's condition a doctor may decide to increase this dose. These granules should not be given in babies' bottles as they can block the nipple.

Patients may be taking other medicines for epilepsy at the same time as Epilim Chronosphere. If so, a doctor should gradually initiate treatment depending on the patient's condition. A doctor may also increase the dose of Epilim Chronosphere by 5 to 10 mg for each kilogram of body weight each day depending on which other medicines the patient is taking.

These medicinal products must not be given with hot meals or drinks.

Epilim Chronosphere MR Modified Release Granules can only be obtained on prescription from a doctor.

For further information on how Epilim Chronosphere MR Modified Release Granules are used, refer to the Summaries of Product Characteristics or package leaflets available on the MHRA website.

**How do Epilim Chronosphere MR Modified Release Granules work?**

Epilim Chronosphere MR Modified Release Granules contain the active substances, sodium valproate and valproic acid. Both belong to a group of medicines called anti-convulsants or anti-epileptic agents. They work by helping to calm the brain down.

**What benefits of Epilim Chronosphere MR Modified Release Granules have been shown in studies?**

Studies in patients have been limited to tests to determine that Epilim Chronosphere MR Modified Release Granules are bioequivalent to the reference medicine, Epilim Chrono 500 Controlled Release Tablets (Aventis Pharma Limited; PL 04425/0309). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects from Epilim Chronosphere MR Modified Release Granules?**

Like all medicines, Epilim Chronosphere can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Epilim Chronosphere MR Modified Release Granules, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why are Epilim Chronosphere MR Modified Release Granules approved?**

It was concluded that, in accordance with EU requirements, Epilim Chronosphere MR Modified Release Granules have been shown to have comparable quality and to be bioequivalent to Epilim Chrono 500 Controlled Release Tablets (Aventis Pharma Limited). Therefore, the view was that, as for Epilim Chrono 500 Controlled Release Tablets (Aventis Pharma Limited) the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Epilim Chronosphere MR Modified Release Granules?**

A satisfactory pharmacovigilance system has been provided to ensure that Epilim Chronosphere MR Modified Release Granules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Epilim Chronosphere MR Modified Release Granules, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Epilim Chronosphere MR Modified Release Granules**

Marketing Authorisations were granted in the UK on 11<sup>th</sup> July 2006.

For more information about taking Epilim Chronosphere MR Modified Release Granules, read the Patient Information Leaflet (PIL), or contact your doctor or pharmacist.

The full PAR for Epilim Chronosphere MR Modified Release Granules follows this summary.

This summary was last updated in April 2015.

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## **I INTRODUCTION**

Based on the review of the data on quality, safety and efficacy the UK granted Marketing Authorisations for the medicinal products Epilim Chronosphere MR 50 mg, 100 mg, 250 mg, 500 mg, 750 mg and 1000 mg Modified Release Granules to Sanofi-Synthelabo Limited (PL 11723/0399, 0412-416) on 11<sup>th</sup> July 2006. These medicinal products underwent change of ownership procedures to the current Marketing Authorisation holder, Aventis Pharma Limited (PL 04425/0310, 0312-0316) on 5<sup>th</sup> February 2009. The products are prescription-only medicines for the treatment of generalised, partial or other epilepsy.

These are abridged applications for Epilim Chronosphere MR Modified Release Granules, submitted under Article 10.3 Directive 2001/83/EC, as amended, so-called hybrid applications. The proposed products are line-extensions of the UK brand leader Epilim Chrono 500 Controlled Release Tablets, first granted to Sanofi-Synthelabo Limited (PL 11723/0079) on 31<sup>st</sup> August 1993. This reference licence underwent a change of ownership procedure to the currently Marketing Authorisation Holder, Aventis Pharma Limited (PL 04425/0309), on 14<sup>th</sup> October 2010.

The products contain the active substances sodium valproate and valproic acid. Valproic acid and its sodium salt (sodium valproate) are anticonvulsants with a broad spectrum of antiepileptic activity. They are widely used as first-line and adjunctive therapy in generalised seizures (including absences, myoclonic and tonic-clonic seizures), and simple and complex partial seizures. At present, it is considered the drug of first choice in the syndrome of primary generalised epilepsy.

A prolonged-release formulation of sodium valproate allows considerable simplification of the dosage regimen. Better patient compliance can be attained with a once or twice daily regimen. In patients with epilepsy, such a regimen has been associated with maintained efficacy and an improved tolerability profile compared with oral immediate release dosage forms. In addition, a prolonged-release formulation leads to less fluctuation in drug plasma levels. Lower peak plasma levels are thought to result in fewer adverse reactions. On these grounds, a number of modified-release tablet formulations of sodium valproate have been developed.

These applications for Epilim Chronosphere MR 50 mg, 100 mg, 250 mg, 500 mg, 750 mg and 1000 mg Modified Release Granules were submitted at the same time. Consequently, all sections of this Scientific Discussion refer to all products.

## II QUALITY ASPECTS

### DRUG SUBSTANCE

#### Sodium Valproate

INN: Sodium valproate  
Chemical Name: Sodium-2-propylpentanoate  
Molecular Formula:  $C_8H_{15}NaO_2$

Structure:



Molecular Weight: 166.2  
CAS Number: 1069-66-5  
Appearance: White to almost white, hygroscopic crystalline powder

Sodium valproate is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance sodium valproate. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of analysis have been provided for any working standards used.

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

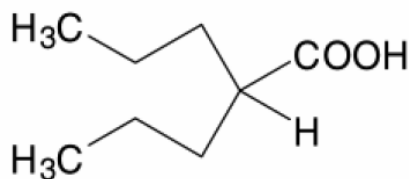
Sodium valproate is stored in double polyethylene bags, which are then placed in a cardboard drum with a desiccant and stored at room temperature (20-25°C). Specifications for all packaging have been provided and all are suitable for use in storing pharmaceutical products. All packaging that comes into contact with the drug substance complies with European directives regarding suitability for contact with food.

Appropriate stability data have been generated supporting a retest period of 12 months.

#### Valproic Acid

INN: Valproic acid  
Chemical Name: 2-propylpentanoic acid  
Molecular Formula:  $C_8H_{16}O_2$

Structure:



Molecular Weight: 144.2  
CAS Number: 99-66-1  
Appearance: Clear, colourless to slightly yellow, slightly viscous liquid

Valproic acid is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance valproic acid. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of analysis have been provided for any working standards used.

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

Valproic acid is stored in polyethylene bottles with a stopper. Specifications for all packaging have been provided and all are suitable for use in storing pharmaceutical products. All packaging that comes into contact with the drug substance complies with European directives regarding suitability for contact with food.

Appropriate stability data have been generated supporting a retest period of 24 months.

## **DRUG PRODUCT**

### **Other ingredients**

Other ingredients consist of the excipients hard paraffin, glycerol dibehenate and colloidal hydrated silica. All excipients comply with their respective European Pharmacopoeia monographs.

Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.



### **Pharmaceutical development**

The main development objective was to produce additional medicinal products to the Epilim Chrono Controlled Release Tablet range which were easier to administer to patients that have difficulty swallowing, as alternative single-dose pharmaceutical presentations containing granules.

A satisfactory development rationale has been provided for these products.

Comparative dissolution profiles were shown for the proposed products versus the comparator products.

### **Manufacture**

A description and flow-chart of the manufacturing method have been provided and are satisfactory.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on pilot-scale batches of each strength. The results appear satisfactory.

### **Finished product specifications**

The finished product specifications are satisfactory. The test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

### **Container Closure System**

All strengths of the finished product are stored in paper/aluminium/ionomer resin sachets. These are stored in boxes in pack sizes of 30 or 50 sachets. Not all pack sizes are to be marketed. The Marketing Authorisation holder has committed to submitting packaging to the MHRA before marketing any pack size of the product.

Specifications and certificates of analysis for all packaging materials have been provided. These are satisfactory.

The applicant has confirmed that all packaging that comes into direct contact with the drug product complies with the current regulations with respect to their contact with food.

### **Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Batches of all strengths of product manufactured by the finished product manufacturer, using active substance from the active substance manufacturer and in the packaging proposed for marketing were placed on stability at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH.

Based on the results, a shelf-life of 24 months with the conditions 'Store in original packaging', 'Do not store above 25°C' and 'Do not refrigerate or freeze' has been proposed for all strengths. These are satisfactory.

Suitable post approval stability commitments have been provided by the applicant.

**Bioequivalence**

See clinical assessment

**Expert Report**

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the applicant's dossier.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**

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

**Conclusion**

It is recommended that Marketing Authorisations are granted for these applications.

### **III NON-CLINICAL ASPECTS**

The pharmacodynamic, pharmacokinetic and toxicological properties of sodium valproate and valproic acid are well-known. Therefore, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

There are no objections to the approval of Epilim Chronosphere MR Modified Release Granules from a non-clinical point of view.

#### IV CLINICAL ASPECTS CLINICAL PHARMACOLOGY

##### Pharmacodynamics and Pharmacokinetics

With the exception of the bioequivalence studies, no new data on the pharmacodynamics or pharmacokinetics of sodium valproate or valproic acid are provided and none are required for these applications.

##### Bioequivalence

The bioequivalence data consisted of two bioequivalence studies performed in healthy volunteers. All studies were performed in accordance with Good Clinical Practice and according to the principles of the Declaration of Helsinki and its amendments.

##### BDR7481

###### *Method:*

This was an open-label, randomised, two-period, combined single- and repeat-dose crossover study in healthy male volunteers to determine the relative bioavailability of valproic acid after a single dose and at steady state of two preparations, Epilim Chronosphere MR 1000 mg Modified Release Granules versus two Epilim Chrono 500 mg Controlled Release Tablets.

The study period comprised a single-dose phase followed by an 8-day repeat-dose phase separated from the first phase by a 7-day washout interval. All volunteers received the study medication in a fasted state with 200 ml water. Blood samples were collected pre-dose and up to 96 hours post dose for the single-dose phase and 24 hours post dose for the repeat-dose phase.

###### *Results:*

##### Single-dose pharmacokinetic parameters for valproic acid (mean $\pm$ SD, median (range) for $t_{max}$ )

	Epilim Chronosphere	Epilim Chrono
AUC <sub>t</sub> (mg.h/L)	1594 $\pm$ 430	1529 $\pm$ 369
AUC <sub><math>\infty</math></sub> (mg.h/L)	1664 $\pm$ 481	1588 $\pm$ 418
C <sub>max</sub> (mg/L)	48.6 $\pm$ 6.9	48.0 $\pm$ 6.6
t <sub>max</sub> (h)	6.00 (3.00 - 15.00)	10.00 (6.00 - 15.00)
MRT (h)	27.1 $\pm$ 5.5	27.0 $\pm$ 5.0

##### Statistical analysis of single-dose pharmacokinetic parameters (Chronosphere vs. Chrono)

	Lower bound	Point estimate	Upper bound
AUC <sub>t</sub>	0.99	1.04	1.09
AUC <sub><math>\infty</math></sub>	1.01	1.06	1.11
C <sub>max</sub>	0.97	1.01	1.06
t <sub>max</sub>	-4.00	-3.25	-2.50

##### Repeat-dose pharmacokinetic parameters for valproic acid (mean $\pm$ SD, median (range) for $t_{max}$ )

	Epilim Chronosphere	Epilim Chrono
AUC <sub><math>\tau</math></sub> (mg.h/L)	1714 $\pm$ 372	1603 $\pm$ 332
C <sub>max</sub> (mg/L)	89.8 $\pm$ 18.5	83.6 $\pm$ 16.5
C <sub>min</sub> (mg/L)	48.5 $\pm$ 14.0	47.8 $\pm$ 11.1
t <sub>max</sub> (h)	4.00 (3.00 - 11.00)	6.50 (3.00 - 12.00)
FR	0.59 $\pm$ 0.11	0.54 $\pm$ 0.11

**Statistical analysis of repeat dose pharmacokinetic parameters (Chronosphere vs. Chrono)**

	<b>Lower bound</b>	<b>Point estimate</b>	<b>Upper bound</b>
AUC <sub>t</sub>	1.01	1.07	1.13
C <sub>max</sub>	1.01	1.07	1.14
C <sub>min</sub>	0.95	1.00	1.06
t <sub>max</sub>	-2.50	-1.00	-0.46

**Conclusions:**

Bioequivalence between the Epilim Chronosphere and Epilim Chrono formulations can be concluded, as the 90% confidence intervals for the test/reference geometric mean ratios of the pharmacokinetic parameters of interest are within the 0.80-1.25 range for both single- and repeat-dose administrations.

After administration of a single dose, the time to reach peak plasma concentrations is significantly shorter for Epilim Chronosphere Modified Release Granules than for Epilim Chrono Controlled Release Tablets. This statistically significant difference in t<sub>max</sub> is not associated with a difference in C<sub>max</sub>. In addition, the difference in t<sub>max</sub> between the two formulations is not so significant on repeated-dose administration.

ALI7122

*Method:*

This was an open-label, randomised, three-period, single-dose crossover study in healthy male volunteers to assess the effect of food on the bioavailability of valproic acid from Epilim Chronosphere MR 500 mg Modified Release Granules.

The three study periods were conducted under identical conditions, with a 7-day washout between treatments. All volunteers received the study medication with 200ml water in a fasted state, 30 minutes after the start of a high-fat meal or 30 minutes after eating yoghurt. Blood samples were collected pre-dose and up to 96 hours post dose.

*Results:*

**Pharmacokinetic parameters for valproic acid (mean ± SD, median (range) for t<sub>max</sub>)**

	<b>Water</b>	<b>High-Fat meal</b>	<b>Yoghurt</b>
AUC <sub>t</sub> (mg.h/L)	680 ± 179	701 ± 178	645 ± 189
AUC <sub>∞</sub> (mg.h/L)	712 ± 190	742 ± 194	674 ± 200
C <sub>max</sub> (mg/L)	21.4 ± 2.9	23.3 ± 3.5	20.0 ± 2.8
t <sub>max</sub> (h)	7.00 (4.00 - 12.00)	7.00 (4.00 - 15.00)	5.00 (3.00 - 12.00)

**Statistical analysis of pharmacokinetic parameters (ratio of high-fat meal/water)**

	<b>Lower bound</b>	<b>Point estimate</b>	<b>Upper bound</b>
AUC <sub>t</sub>	0.99	1.03	1.07
AUC <sub>∞</sub>	0.99	1.03	1.07
C <sub>max</sub>	1.04	1.09	1.13

**Statistical analysis of pharmacokinetic parameters (ratio yoghurt / water)**

	<b>Lower bound</b>	<b>Point estimate</b>	<b>Upper bound</b>
AUC <sub>t</sub>	0.90	0.94	0.98
AUC <sub>∞</sub>	0.91	0.95	0.98
C <sub>max</sub>	0.90	0.94	0.98

*Conclusions:*

The absence of an effect of food on the bioavailability of valproic acid from the Epilim Chronosphere MR 500 mg Modified Release Granules can be concluded, as the 90% confidence intervals for the high-fat meal/water and yoghurt/water geometric

mean ratios of the pharmacokinetic parameters of interest all fall within the 0.80-1.25 range.

**EFFICACY**

No new data were submitted for these applications and none are required for applications of this type.

**EXPERT REPORT**

The clinical expert report is written by an appropriately qualified physician and is a satisfactory summary of the clinical aspects of the dossier.

**SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs)**

The SmPCs for all strengths of the proposed product are consistent with the SmPC for the reference product and are medically satisfactory.

**PATIENT INFORMATION LEAFLET (PIL)**

The PIL is consistent with the information stated in the SmPC and is medically satisfactory.

**LABELLING**

The labelling is medically satisfactory.

**APPLICATION FORM (MAA)**

The MAA forms are medically satisfactory.

**CONCLUSION**

The grant of Marketing Authorisations is recommended.

## **V. User consultation**

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the patient information leaflet (PIL) was English.

The results show that the package leaflet meets the criteria for readability as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use*.

## **VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION**

### **Quality**

The important quality characteristics of Epilim Chronosphere MR 50 mg, 100 mg, 250 mg, 500 mg, 750 mg and 1000 mg Modified Release Granules 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.

### **Clinical**

Bioequivalence has been demonstrated between the applicant's Epilim Chronosphere MR 1000 mg Modified Release Granules and two Epilim Chrono 500 mg Controlled Release Tablets. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 1000 mg strength can be extrapolated to the 50 mg, 100 mg, 250 mg, 500 mg and 750 mg.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products, where necessary.

### **BENEFIT/RISK ASSESSMENT**

The quality of the products is acceptable and no new non-clinical or clinical 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 sodium valproate and valproic acid is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**

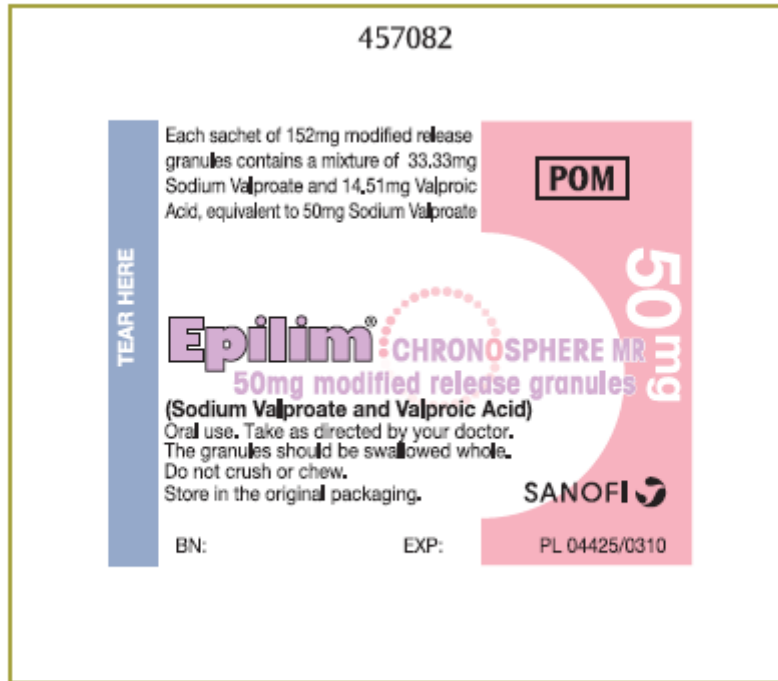
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

**LABELLING**



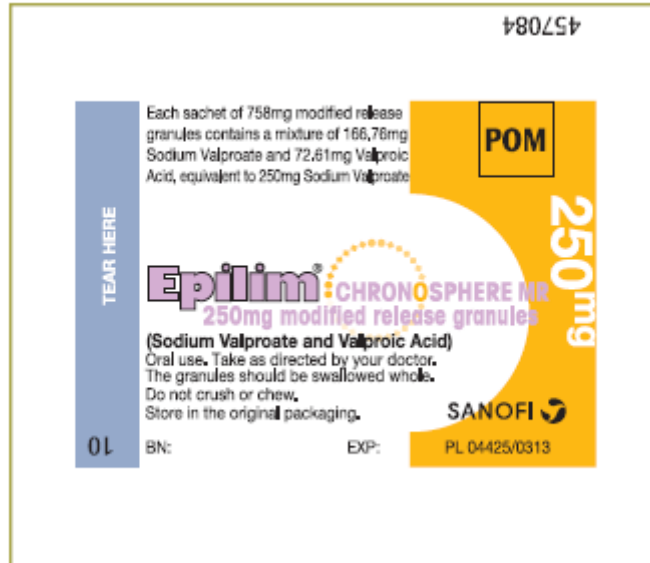


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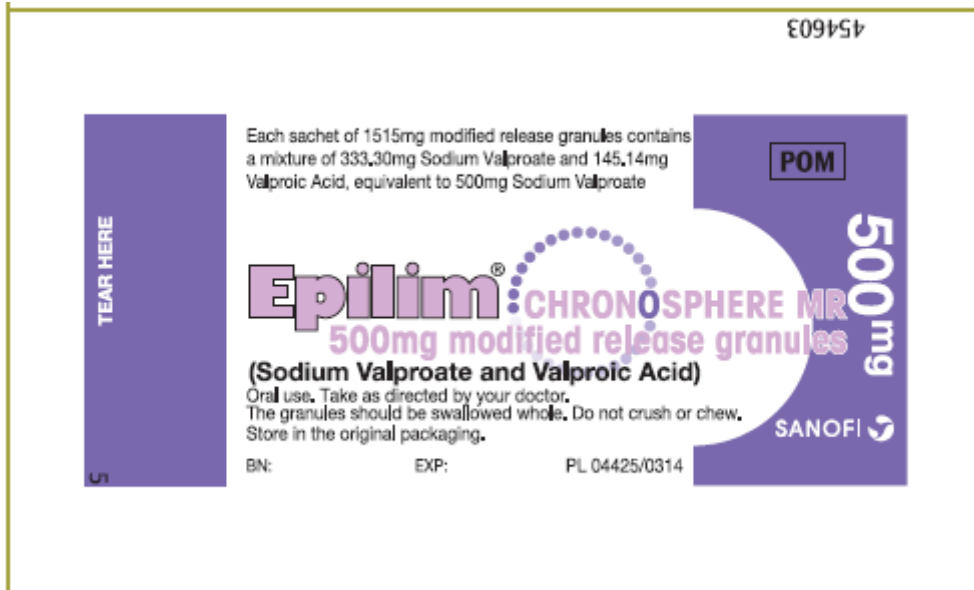
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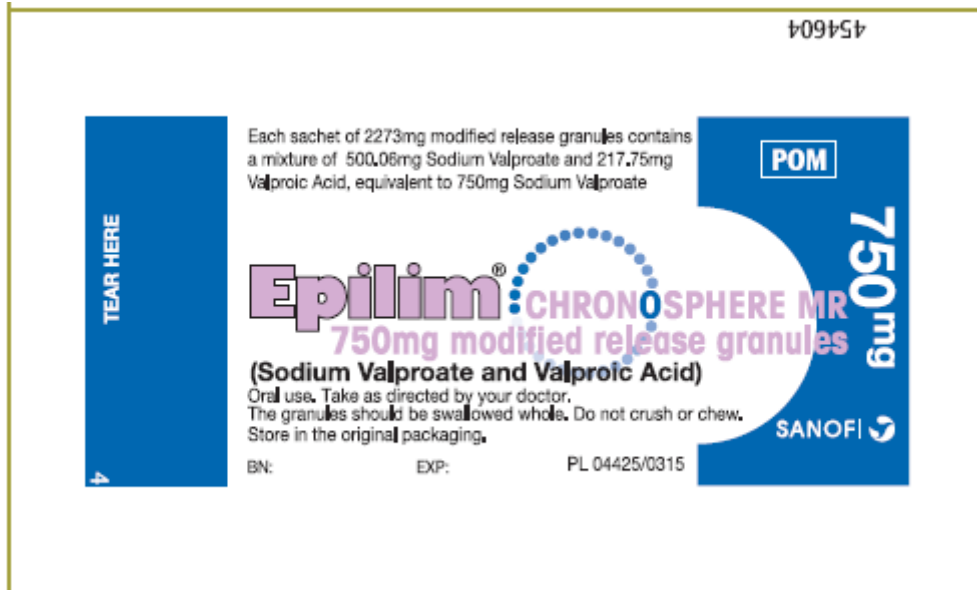
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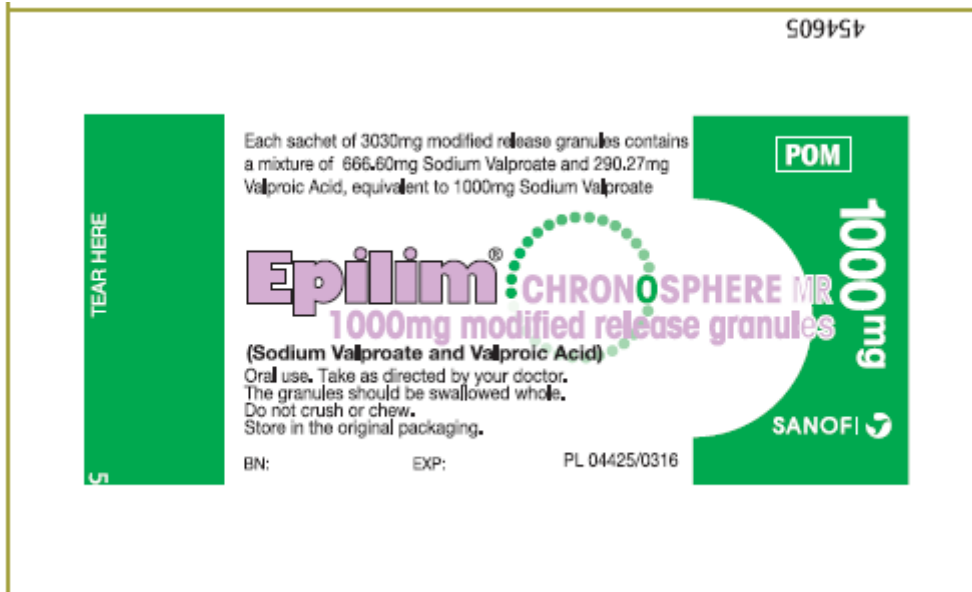


**PAR Epilim Chronosphere MR 50, 100, 250, 500, 750 and 1000 mg Modified Release Granules  
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PAR Epilim Chronosphere MR 50, 100, 250, 500, 750 and 1000 mg Modified Release Granules  
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## Table of content of the PAR update

### Steps taken after the initial procedure with an influence on the Public Assessment Report

The following table lists some non-safety updates to the Marketing Authorisation 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>Scope</b>	<b>Outcome</b>
7 <sup>th</sup> July 2014	Type II	To update section 4.2 (Posology and method of administration) of the SmPC and consequentially the leaflet in line with the company core data sheet, (CCDS) version 15.	Approved on 26 <sup>th</sup> February 2015

## Annex 1

**Reference:** PL 04425/0310-0052; PL 04425/0312-0053; PL 04425/0313-0051; PL 04425/0314-0052; PL 04425/0315-0050 and PL 04425/0316-0050

**Product:** Epilim Chronosphere MR 50, 100, 250, 500, 750 and 1000 mg modified release granules

**MAH:** Aventis Pharma Limited

**Active Ingredient:** Sodium valproate and valproic acid

### Reason:

To update section 4.2 (Posology and method of administration) of the SmPCs and consequentially the leaflet in line with the company core data sheet, (CCDS) version 15.

### Supporting Evidence

In January 2014, the MHRA requested the company to update the SmPC and patient information leaflet (PIL) for Epilim Chronosphere to include a statement regarding residue from the granules being visible in stools since there had been eight UK spontaneous reports.

The proposed statement (see below) by the Marketing Authorisation holder was agreed by the MHRA.

The MHRA suggested a more friendly explanation for the PIL as follow:

*“You may see what appears to be complete granules in the patients stools. This is normal as the matrix of the chromosphere granules is not digested by the body. It does not mean that the medicine is not working”.*

### Evaluation

The following sentence has been added to section 4.2 of the SmPC:

*In view of the sustained release process and the nature of the excipients in the formula, the inert matrix of the granules is not absorbed by the digestive tract; it is eliminated in the stools after the active substances have been released.*

### PIL

#### Section 3

*“You may see what appears to be complete granules in the patients stools. This is normal as the matrix of the chromosphere granules is not digested by the body. It does not mean that the medicine is not working”.*

### Conclusion

The Marketing Authorisation holder has amended the SmPC and PIL as requested by the MHRA. There are no objections to the approval of this variation. However, the sentence regarding the stool residua was already approved by the vigilance and risk

**PAR Epilim Chronosphere MR 50, 100, 250, 500, 750 and 1000 mg Modified Release Granules  
PL 04425/0310, 0312-0316**

Management of Medicines (VRMM) on 10<sup>th</sup> February 2015 during submissions 0053-0056.

**Decision**

The variation was approved on 26<sup>th</sup> February 2015.

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

Following approval of the variation on 26<sup>th</sup> February 2015 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 variation on 26<sup>th</sup> February 2015 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.