

**Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 46 of Regulation (EC) No1901/2006, as  
amended**

Depakine Chronosphere, Depakine Chrono microgranules, Depakine depotrakeet, Micropakine LP, Valproate sodium/acide valproique, Ergenyl Chronosphere Retardgranulat, Valpro, Epillim Chronosphere, Depakin, Ergenyl retard, Epillim Chronosphere MR

Valproic Acid and Sodium Valproate

EL/W/0002/pdWS/001

**Marketing Authorisation Holder:**  
Sanofi-Aventis

<b>Rapporteur:</b>	EL
<b>Finalisation procedure (day 90):</b>	09 May 2010
<b>Date of finalisation of PAR</b>	20 September 2010

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Depakine Chronosphere, Depakine Chrono microgranules, Depakine depotrakeet, Micropakine LP, Valproate sodium/acide valproique, Ergenyl Chronosphere Retardgranulat, Valpro, Epillim Chronosphere, Depakin, Ergenyl retard, Epillim Chronosphere MR
INN (or common name) of the active substance(s):	Sodium Valproate – Valproic Acid
MAH:	Sanofi-Aventis
Currently approved Indication(s)	See Section VII
Pharmaco-therapeutic group (ATC Code):	NO3AG01
Pharmaceutical form(s) and strength(s):	Modified release granules 50,100,250,500,750,1000mg

## I. EXECUTIVE SUMMARY

In accordance with Article 46 of Regulation 1901/2006 the Marketing Authorisation Holder of Depakine Chronosphere (and associated names), Sanofi-Aventis, submitted information about paediatric studies. Altogether, one study has been submitted in epileptic children from 6 months to 15 years old. The pharmaceutical formulation used in this study is the latest developed, a modified-release granules formulation. This formulation was firstly registered in 22 July 2002 in France and has the advantage of having a neutral taste and, therefore, can be easily administered to children.

In the study, the safety and pharmacokinetics of this valproate formulation in children were assessed under the usual prescribing conditions.

The MAH stated that there are no new relevant data, which change or may result in a new risk/benefit evaluation. Consequently no SmPC and PL changes are deemed necessary resulting from this study outcome.

Based on the review of the presented paediatric data in the day 89 preliminary PdAR the rapporteur concluded that despite the small number of subjects, the data presented are considered satisfactory, supporting the usual prescribing administration of the medication at a dose of 20-30 mg/kg/day. It was also suggested that a referral could be considered appropriate since all the valproate containing products are registered via national procedures.

Comments were received from CMSs (HU, SE, UK) who fully endorsed the rapporteur's recommendations.

The results of the submitted study do not change the established benefit-risk profile of valproate in children when used under usual prescribing conditions, therefore no SmPC and PL changes are considered necessary.

## II. RECOMMENDATION<sup>1</sup>

No further action required with regards to adverse effects others to the already known. The target dose should be maintained 20-30 mg/kg/day.

## III. INTRODUCTION

Valproate was first approved as an antiepileptic drug in France on 23<sup>rd</sup> January 1967, where it was marketed in June 1967. The drug was first approved as a mood stabiliser for the treatment of bipolar disease in the USA in May 1995. Valproate is currently approved in more than 130 countries and marketed in more than 115 countries for one or both of these indications.

On 30 October 2009, Sanofi-Aventis has received the letter from EMEA/CMD(h) about the initiation of the worksharing procedure as per Article 46 of Regulation (EC) 1901/2006, as amended for valproate (sodium valproate / valproic acid) modified release granules. On April 20, 2009 the MAH had already submitted the cover letter and line-listing informing the authorities about completion of the VAPOR study (study L8971), in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use.

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<sup>1</sup> The recommendation from section V can be copied in this section

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for valproate and that there is no consequential regulatory action.

## IV. SCIENTIFIC DISCUSSION

### IV.1 Information on the pharmaceutical formulation used in the study(ies)

Valproate is available in Europe in various pharmaceutical forms such as tablets, film-coated tablets, oral solution, prolonged-release e.t.c. In the submitted study valproate was administered as a modified-release granule formulation (MICROPAKINE® SR 0.33mg).

### IV.2 Clinical aspects

#### 1. Introduction

The MAH submitted a final report for:

- STUDY NUMBER: L-8971

Therapeutic Follow-up observational study and population kinetics ancillary study of Valproate Microgranules (MICROPAKINE® SR) in patients aged between 6 months and 15 years suffering from epilepsy.

#### 2. Clinical study(ies)

##### ➤ Description

Study L-8971 was an open-label, single center, therapeutic follow-up observational study of Valproate microgranules (Micropakine SR) administered in paediatric patients with epilepsy, aged 6 months to 15 years. The study was conducted from 14/03/06 to 20/10/08.

##### ➤ Methods

- Objective(s)

The primary objective of the study was the evaluation of the clinical and biological safety of valproate in the form of microgranules, in epileptic children from 6 months to 15 years old, with clinical follow-up and individual dosage adjustment.

The secondary objective of the study was to estimate the population pharmacokinetic parameters of valproate.

The objectives of the study were clearly stated and the safety and pharmacokinetics of valproate formulation in children were assessed under the usual prescribing conditions 20 to 30 mg/kg/day.

- Study design

The study included 81 patients with various types of epilepsy treated with Micropakine SR under usual prescribing conditions (median dose 23.8 mg/kg/day). All patients but one were treated on a two doses/day regimen. The patients were followed for a minimum period of 2

months and a maximum period of 6 months. During the study the patients were assessed on three occasions:

- V0 (pre-inclusion visit and inclusion visit D0)

- V1 (1 to 3 months after inclusion)

- V2 (1 to 3 months after V1)

During these visits various clinical and biological parameters were evaluated. The time interval between assessments was considered appropriate.

<b>VISITS</b>	<b>V0 D30-D0</b>	<b>V1 M1 - M3</b>	<b>V2 M2 - M6</b>
Information / written consent	•		
Social and demographic data	•		
Disease history and other medical history	•		
Physical examination ( weight, height, neurological examination, mental state and behavior)	•	•	•
Seizures (number and types)	•	•	•
Inclusion / exclusion criteria	•		
Concomitant treatments	•	•	•
Adverse events collection	•	•	•
Plasma measurement of antiepileptic agents	•	•	•
Blood panel			
CBC, platelets	•		•
AST, ALT	•		•
Serum albumin	•		•
Serum creatinine	•		•
Serum electrolytes	•		•
βHCG for pubescent girls	•		•

The clinical and biological safety of valproate administered as microgranules was evaluated by the physician during visits V0, V1 and V2, and was also reported by parents with respect to the occurrence of any adverse events and/or a change in seizure frequency.

Emphasis was given to Treatment Emergent Adverse Events TEAE.

In order to determine the plasma concentrations of valproate and antiepileptic concomitant medications blood samples were collected on three occasions (one before the morning dose, one between one and 5 hours after the morning dose and one between 5 and 8 hours after the morning dose).

**Assessor's comment :This type of study is considered adequate for the above objectives. However the study is uncontrolled and therefore inferior to a double blind, placebo controlled study.**

- Study population /Sample size

A total of 81 patients aged from 6 months to 15 years were included in the study: 43 (53.1%) patients were male and 38 (46.9%) were female, the mean (SD) age was 5.9 (3.8) years, the mean (SD) weight was 22.6 (11.0) kg, the mean (SD) height was 113.5 (22.8) cm, the BMI was 16.6 (3.1) kg/m<sup>2</sup>. The first seizure took place 0.5 to 15 years before the inclusion, with a mean (SD) of 4.2 (3.9) years. The most frequent syndromes were generalized epilepsy (n=20, 24.7%), partial epilepsy (n=14, 17.3%) and severe myoclonic epilepsy in infancy (n=11, 13.6%). A total of 20 patients (24.7%) of the patients presented other types of syndromes. A majority of etiologies were idiopathic (n=38, 46.9% of the patients). 44.4% of the patients (n=36) presented other concomitant diseases.

Exclusion criteria were appropriate and were related to conditions where administration of Valproate would be dangerous on the basis of the known side effects (liver pathology, renal dysfunction, possible pregnancy, abnormal laboratory parameters), or would make the results difficult to interpret (unstable seizure frequency, evolving neurological disease, new antiepileptic medication).

**Assessor's comment: The sample size is considered adequate, although a bigger size would be more appropriate for evaluating rare adverse reactions**

- Treatments

The administration of Micropakine SR was under usual prescribing conditions of 20 to 30 mg/kg/day (median dosage of valproate was 23,8mg/kg/day) with daily dosage administered in 2 divided doses for all patients except for one who received valproate once daily.

Subjects received valproate alone or in combination with other antiepileptic drugs ( ≤ 4 AEDs) such as clobazam , lamotrigine , oxcarbamazepin , vigabatrin , ethosuximide , clonazepam , topiramate , stiripentol , levetiracetam , gabapentin and diazepam. Concomitant anti-epileptic medication is taken into account as this more likely represents a real-life like scenario.

- Outcomes/endpoints

Safety Evaluation: Safety was assessed through monitoring of Adverse Events reported by the patient or noted by the investigator; clinical, neurological, mental status assessments , behavioural disorders and number/type of seizures, hematology and blood chemistry.

Pharmacokinetic Evaluation: The objective was to study the pharmacokinetics of valproate administered in the form of Micropakine® SR 0.33 mg based on a population kinetic approach in order to assess the possible relationships between the pharmacokinetic parameters and the individual characteristics, or covariates, that could have an effect on them (including other antiepileptic drugs). Pharmacokinetic parameters and covariates able to explain the variability in the pharmacokinetic parameters of valproate were estimated and analyzed ( CL/F, V/F, Ka, Vc/F, Vp/F, Q/F).

- Statistical Methods

Clinical and biological safety was to be assessed using the following criteria:

- Overall incidence of events during treatment (new events or events that worsened during the treatment period), by System Organ Class and Preferred Term, coded using the validated MedDRA dictionary (Medical Dictionary for Regulatory Activities).

- Overall incidence of serious adverse events, by System and Preferred Term, coded using the validated MedDRA dictionary (Medical Dictionary for Regulatory Activities).

Furthermore, these incidences were to be calculated according to dosages, plasma concentrations or even concomitant antiepileptic medications.

Valproate concentration-time data were analyzed by use of the first-order conditional estimation with interaction method of the non-linear mixed effects modeling program NONMEM.

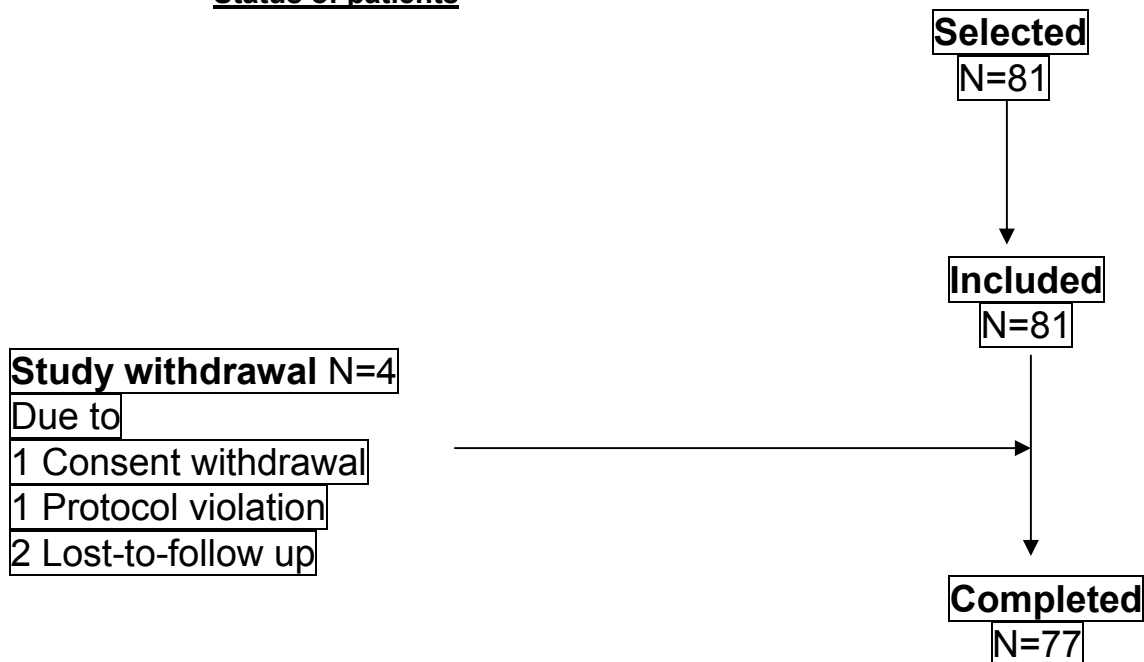
Monte Carlo simulations were used to estimate the VPA dosing regimen that achieves the target VPA concentration range of 50-100 mg/mL. These simulations were performed for different body weight (10-60 kg) and for 5 different dosing regimens (5 mg/kg b.i.d., 10 mg/kg b.i.d., 12.5mg/kg b.i.d., 15 mg/kg b.i.d., 20 mg/kg b.i.d.).

➤ **Results**

- Recruitment/ Number analysed

The percentage of subjects completed the study is considered satisfactory (77 of 81).

**Status of patients**



Four patients (n°17,32, 47 and 80) were withdrawn from the study:

One patient (n°17, male / 2 year-old) was excluded from the ITT and the PP population for protocol violation: a suspension of Micropakine® SR administration decided by the parents; the patient did not provided evaluable PK data.

One patient (n°80, male / 8 year-old) withdrew his consent.

Two patients (n°32, female / 6 year-old, and 47, male / 1 year-old) were lost to follow-up.

91.3% of the patients had three blood samples taken. Two hundred and thirty two concentration-time records were obtained from 80 patients.

- Efficacy results

Not applicable as this is not an efficacy study.

- Safety results

36 patients (44.4%) presented at least one AE during the study; the most frequent AE were not related to treatment, as they were infections. Only 11 patients (13.6%) presented AE considered related to treatment. The most frequent AE related to treatment (tremor and aggressive behavior) only affected 3 out of 81 patients (3.7%). The most frequently reported AEs were from the infections disorders and the psychiatric disorders SOC. The most frequently reported individual AEs (reported in more than 3 cases, > 3.7% of the patients) were varicella, tremor, aggression, cough and acute otitis media.

All AE were mild to moderate in intensity, except one severe AE: one subject (n°51) presented a severe prolonged epileptic seizure (30 minutes), which was not related to treatment. In all, 6 patients presented serious adverse events (SAE), none of which was related to treatment.

#### Adverse events by SOC and PT

Adverse events (AE)	N	81		AE considered related to treatment	
		N(%)		81	
<b>Total number of patients exposed</b>					
<b>Total number of patients exposed presenting at least one AE</b>	<b>N(%)</b>	<b>36</b>	<b>(44.4)</b>	<b>11</b>	<b>(13.6)</b>
<b>System Organ Class (SOC)</b>					
Preferred term					
<b>Ear and labyrinth disorders</b>	<b>N(%)</b>	<b>1</b>	<b>(1.2)</b>	<b>0</b>	<b>(0.0)</b>
Vertigo	N(%)	1	(1.2)	0	(0.0)
<b>Skin and subcutaneous tissue disorders</b>	<b>N(%)</b>	<b>3</b>	<b>(3.7)</b>	<b>0</b>	<b>(0.0)</b>
Varicella	N(%)	3	(3.7)	0	(0.0)
<b>Metabolism and nutrition disorders</b>	<b>N(%)</b>	<b>1</b>	<b>(1.2)</b>	<b>0</b>	<b>(0.0)</b>
Decreased appetite	N(%)	1	(1.2)	0	(0.0)
<b>Nervous system disorders</b>	<b>N(%)</b>	<b>7</b>	<b>(8.6)</b>	<b>4</b>	<b>(4.9)</b>
Convulsion	N(%)	2	(2.5)	0	(0.0)
Febrile convulsion	N(%)	1	(1.2)	0	(0.0)
Headache	N(%)	1	(1.2)	1	(1.2)
Tremor	N(%)	3	(3.7)	3	(3.7)
<b>Gastrointestinal disorders</b>	<b>N(%)</b>	<b>7</b>	<b>(8.6)</b>	<b>1</b>	<b>(1.2)</b>
Constipation	N(%)	1	(1.2)	0	(0.0)
Gastroenteritis	N(%)	2	(2.5)	0	(0.0)
Gastroenteritis viral	N(%)	1	(1.2)	0	(0.0)

Salivary hypersecretion	N(%)	1	(1.2)	0	(0.0)
Rectal haemorrhage	N(%)	1	(1.2)	1	(1.2)
Pharyngitis	N(%)	1	(1.2)	0	(0.0)
Vomiting	N(%)	1	(1.2)	0	(0.0)
<b>Psychiatric disorders</b>	<b>N(%)</b>	<b>8</b>	<b>(9.9)</b>	<b>5</b>	<b>(6.2)</b>
Agitation	N(%)	2	(2.5)	1	(1.2)
Aggression	N(%)	3	(3.7)	3	(3.7)
Psychomotor hyperactivity	N(%)	1	(1.2)	1	(1.2)
Middle insomnia	N(%)	1	(1.2)	0	(0.0)
Somnolence	N(%)	1	(1.2)	0	(0.0)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>N(%)</b>	<b>4</b>	<b>(4.9)</b>	<b>0</b>	<b>(0.0)</b>
Asthma	N(%)	1	(1.2)	0	(0.0)
Cough	N(%)	3	(3.7)	0	(0.0)
<b>Investigations</b>	<b>N(%)</b>	<b>1</b>	<b>(1.2)</b>	<b>1</b>	<b>(1.2)</b>
Weight increased	N(%)	1	(1.2)	1	(1.2)
<b>Infections and infestations</b>	<b>N(%)</b>	<b>14</b>	<b>(17.3)</b>	<b>0</b>	<b>(0.0)</b>
Tonsillitis	N(%)	2	(2.5)	0	(0.0)
Viral tonsillitis	N(%)	1	(1.2)	0	(0.0)
Bronchitis	N(%)	2	(2.5)	0	(0.0)
Exanthema subitum	N(%)	1	(1.2)	0	(0.0)
Infection	N(%)	1	(1.2)	0	(0.0)
Ear infection	N(%)	2	(2.5)	0	(0.0)
Febrile infection	N(%)	1	(1.2)	0	(0.0)
Viral infection	N(%)	2	(2.5)	0	(0.0)
Otitis media acute	N(%)	3	(3.7)	0	(0.0)
Rhinitis	N(%)	2	(2.5)	0	(0.0)
Viral rhinitis	N(%)	1	(1.2)	0	(0.0)

There is no difference between patients receiving Micropakine only and patients receiving Micropakine with at least one other antiepileptic treatment. There is the same number of patients with at least one AE, 45% (n=18) under Micropakine only, and 43.9% (n=18) under Micropakine and at least one another antiepileptic treatment. Furthermore the same kind of AE exists in both groups.

An increase was observed in the mean (SD) number of seizures per month: from 67,0 (99.1) to 82.1(134.9).As shown by the median value, actually decreasing from 30.0 to 10.0 seizures per month ,the increase of the mean (SD) value is likely to be due to subject n° 2,who presented an increase in the number of absence seizures from 300 to 450 seizures from V1 to V2.

With regards to clinical laboratory data there was no change in the parameters assessed between inclusion and last assessment. A mild lymphocytosis was recorded probably not related to the treatment.

There was no death, no adverse event that led to premature withdrawal from the study.

**Assessor's comment : Only 11 (13.6%) patients presented adverse effects related to the treatment. This is considered satisfactory and in accordance to the known safety profile of other Valproate formulations.**

- Pharmacokinetic results

Valproic Acid plasma concentrations were fit on a one compartmental model with first order absorption and elimination and an exponential residual error. Body weight was identified as the main covariate for interindividual variability on the valproate apparent plasma clearance and were related by an allometric model with an exponent 0.44. Other co-variables had no influence on the Valproate kinetics, although with regards to co-medication, it should be pointed that the antiepileptic drugs known to be enzyme inducers (carbamazepine, phenobarbital, phenytoin) are probably underrepresented. Mean population estimates were 0.25L/h (27.7%) for CL/F, 5.42 (77%) for V/F and  $0.44\text{h}^{-1}$  for  $k_a$ . Monte Carlo simulations showed that a 10mg/kg twice daily (BID) regimen would achieve the 50-100mg/L target concentration interval with a probability of 70%. PK data found to be similar with results from previous studies in children receiving a sustained release formulation of VPA (Bondavera IB, J Clin Pharm Ther, 29, 2004).

**Assessor's comment: Pharmacokinetics are similar with published data from previous studies in children receiving a sustained release formulation of VPA. PK findings support a dose of 20-30mg/kg/day.**

## V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

### ➤ Overall conclusion

This is a well designed study with no significant drawbacks which offers valuable information on the safety profile as well as the pharmacokinetic properties of Micropakine SR. However the number of subjects is small and relatively rare adverse effects may not be identified. The pharmacokinetic analysis is considered satisfactory supporting the twice-daily administration of the medication at a dose of 20-30 mg/kg/day.

### General points for consideration:

- considering the fact that these valproate containing products are registered via national procedures throughout the EU, a referral could be considered appropriate
- on the initiative of the European Committee for Medicinal Products for Human Use (CHMP), a procedure under Article 31 of Council Directive 2001/83/EC, as amended, has been initiated on 23 April 2009 because of concerns to efficacy of valproate-containing medicines when used in the treatment of manic episodes in patients with bipolar disorder. A positive CHMP Opinion was granted on 17 December 2009. The Committee concluded that the Product Information for all valproic acid/valproate containing medicinal products of the oral solid formulations should be amended throughout the EU to include information on the treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. In addition, some amendments are recommended in relation to the risk of suicidal ideation and behaviour, to the use in pregnancy and to the inclusion of nausea, sedation and extrapyramidal effects as undesirable effects.

➤ **Recommendation**

No further action required with regards to adverse effects others to the already known. The target dose should be maintained 20-30 mg/kg/day.

## **VI. CURRENTLY APPROVED INDICATIONS**

### Indications approved in Austria:

- Epilepsies:

For the treatment of generalised or partial epilepsies, in particular with the following seizure patterns: absences, myoclonic seizures, tonic-clonic seizures, atonic seizures, and mixed seizure types.

In case of partial epileptic seizures, such as simple or complex seizures, secondary generalised seizures, specific syndromes (West's syndrome, Lennox-Gastaut syndrome).

- Bipolar disorders:

Treatment and/or prevention of acute manic episodes within the scope of bipolar disorders.

### Indications approved in Belgium:

Monotherapy in:

- primary generalized seizures: Grand mal with or without myoclonia; Petit Mal; myoclonic epilepsy; Grand mal + Petit Mal association.
- benign partial seizures, in particular with rolandic points.

Monotherapy or polytherapy in:

- secondary generalized seizures,
- partial seizures with simple or complex symptomatology.

Note: in case of insufficient therapeutic effect by monotherapy, association of sodium valproate with other anticonvulsant drug is indicated.

In certain cases, Depakine may be a right choice for women of childbearing potential, provided that an informed choice has been made, based on a very careful evaluation, by the patient together with her treating physician, of all relevant elements (see sections 4.4.1 Warnings and 4.6 Pregnancy).

### Indications approved in Bulgaria:

In adults and children:

Either as single-drug therapy, or in combination with another antiepileptic therapy:

- treatment of generalized epilepsy: clonic seizures, tonic seizures, tonic-clonic seizures, absence attacks, myoclonic or atonic seizures and Lennox-Gestaut syndrome.
- treatment of partial epilepsy: partial seizures, with or without secondary generalization.

In children:

- prevention of febrile convulsions during a fever, when such prevention is deemed necessary or if there are risk factors of recurrence.

### Indications approved in Cyprus:

Treatment of generalized, partial or other epilepsy.

In certain cases Depakine Chronosphere may be an appropriate choice for women of childbearing potential, provided that an informed choice has been made, based on a

very careful evaluation, by the patient together with her treating physician, of all relevant elements (see Warnings and Pregnancy).

Indications approved in Estonia:

- Epilepsy.
- Treatment and prophylaxis of mania associated with bipolar disorder

Indications approved in Finland:

- Epilepsy. Generalized epileptic seizures like tonic clonic seizures (grand mal), absence seizures (petit mal), myoclonic seizures and atonic seizures. As second line treatment also in partial (focal) seizures.
- Treatment and prevention of mania in bipolar affective disorders. In infants, sodium valproate treatment is first-line treatment only in exceptional cases. It should be used with caution, after the risk-benefit ratio is considered, and if possible as a single antiepileptic medication.

Indications approved in France:

In adults and children:

Either as monotherapy or in combination with another antiepileptic treatment:

- Treatment of generalized seizures: clonic, tonic, tonic-clonic seizures, absences, myoclonic, atonic seizures ; Lennox-Gastaut syndrome.
- Treatment of partial seizures: partial seizures with or without secondary generalization.

In children:

Prevention of recurrence of seizures after one or more febrile convulsions meeting the criteria for complicated febrile convulsions, when intermittent benzodiazepine prophylaxis has failed.

Indications approved in Germany:

- Treatment of acute mania and prophylaxis of bipolar disorders
- Treatment of:
  - Generalised seizures in the form of absences, myoclonic seizures and tonic-clonic seizures
  - Partial and secondary generalised seizures and in combination treatment for other forms of seizure, e.g. partial seizures with simple and complex symptomatology, and partial seizures with secondary generalisation, if these forms of seizure do not respond to the usual anti-epileptic treatment.

Please note:

Please ensure adequate serum levels of valproic acid when switching from a previous (non-prolonged-release) pharmaceutical form to Ergenyl Chronosphere.

In infants, medicinal products containing valproic acid are only the first-choice treatment in exceptional cases. Ergenyl Chronosphere should be used with particular caution, only after a strict risk-benefit analysis and preferably as monotherapy.

In certain cases, Ergenyl Chronosphere can be the right choice for women of childbearing potential. Before making this choice, the treating doctor must provide comprehensive advice and carry out a very careful risk-benefit analysis (see sections on warnings and use during pregnancy).

Indications approved in Greece:

Depakine Chronosphere and Valpro: Generalized tonic clonic seizures, typical and atypical absence seizures, partial seizures, myoclonic epilepsy.

As adjuvant therapy to other antiepileptics in the management of various forms of refractory epilepsy.

Treatment of the manic episode associated with bipolar disorder.

Depakine Chronosphere: prevention of the manic episode associated with bipolar disorder

Indications approved in Hungary:

-It has proven effective in all forms of epilepsy, mainly as monotherapy in the generalized forms of primary (idiopathic) epilepsy.

*Generalized seizures:*

Absence seizures; pycnoleptic absence seizures; myoclonic seizures, (juvenile myoclonic generalised epilepsy); myoclonic astatic seizures (Lennox-Gastaut syndrome). Salaam-epilepsy, BNS seizures (West syndrome); grand mal; grand mal + absence seizures.

*Focal seizures:*

Simple and complex partial seizures; partial secondary generalised seizures.

-It is indicated for treatment and prevention of manic state in bipolar affective disorders.

Indications approved in Ireland:

-In the treatment of generalised, partial or other epilepsy.

-Treatment and prevention of mania associated with bipolar disorders

Indications approved in Italy:

-Treatment of generalized epilepsy, with the following types of seizures, in particular: Absence, myoclonic, tonic-clonic, atonic, mixed and partial epilepsy, simple or complex secondary generalized

- In the treatment of specific syndromes (West, Lennox Gastaut)

-In the treatment and in the prophylaxis of mania associated with bipolar disorder

Indications approved in Lithuania:

-Epilepsy. Generalized epileptic seizures such as tonic-clonic seizures (grand mal), absences (petit mal), myoclonic seizures and atonic seizures. Partial (focal) seizures.

- For the treatment and prevention of bipolar affective disorders.

In certain cases DEPAKINE CHRONOSPHERE may be an appropriate choice for women of childbearing potential, provided that an informed choice has been made, based on a very careful evaluation, by the patient together with her treating physician, of all relevant elements.

Indications approved in Malta:

Treatment of generalised, partial or other epilepsy.

Indications approved in Netherlands:

The primary form of generalised epilepsy typical and atypical absences (petit mal), myoclonia, tonic-clonic seizures (grand mal), mixed forms of tonic-clonic attacks and absences.

Can also be used to treat manifestations of epilepsy that don't adequately respond to other anti-epileptics, such as:

- The secondary form of generalised epilepsy, in particular akinetic and atonic seizures.
- Partial epilepsy, with both elementary (focal) and complex (psychomotory) symptoms.

Monotherapy is often possible for the primary form of generalised epilepsy. As a rule, polytherapy should be initiated in the case of partial epilepsy, the secondary form of generalised epilepsy and the mixed forms of primary, generalised and partial epilepsy.

Indications approved in Poland:

-Epilepsy,

generalized attacks: myoclonic attacks, tonic-clonic attacks, atonic attacks

complex attacks: partial seizures, simple or composed attacks, secondary generalized attacks, specific syndromes (West, Lennox-Gastaut)

- Prophylactic treatment of bipolar affective disorder in case the lithium salts and carbamazepine are not effective.

Indications approved in Portugal:

-Treatment of generalized or partial epileptic seizures

Primary generalized: convulsive (clonic, tonic, tonic-clonic, myoclonic) and non convulsive or absences.

Partial: simple or complex.

Partial secondary generalized.

In the treatment of mixed forms and idiopathic and/or symptomatic generalized epilepsies (West and Lennox-Gastaut)

-Treatment of mania associated with bipolar disorder.

Indications approved in Romania:

-Treatment of all forms of epilepsy (simple and composed partial seizures, with secondary generalized attacks or not, generalized epileptic seizures like tonic-clonic seizures (grand mal), absences (petit mal) myoclonic seizures and other mixed forms of epilepsy);

-Treatment and prevention of manic episodes in bipolar affective disorders.

Indications approved in Slovakia:

-The medication is applied in treatment of generalised and partial epilepsy, mainly in following types of seizures: absences, myoclonic seizures, tonic-clonic, atonic, mixed

as well as in partial epilepsy: simple or complex seizures, secondary generalised seizures, specific syndromes (West, Lennox-Gastaut)

-The medication is also used in treatment of manic phase of bipolar affective disorder I and bipolar affective disorder II.

In certain cases the medicinal product may be an appropriate choice for women of childbearing potential, provided that an informed choice has been made, based on a very careful evaluation, by the patient together with her treating physician, of all relevant elements (see section 4.4 Special warnings and precautions for use and section 4.6 Pregnancy and lactation).

Indications approved in Spain:

-Generalized or partial epilepsies.

Primary generalized: convulsive, non-convulsive or absence and myoclonus.

Partial: with elemental symptoms (including Bravais-Jackson's forms) or complex symptoms (psychosensory, psychomotor forms...).

Secondarily generalized partial.

Mixed forms and secondary generalized epilepsies (West and Lennox-Gastaut).

-Treatment of manic episodes associated with bipolar disorder.

Indications approved in Sweden:

-Epilepsy. Generalised epileptic seizures such as tonic-clonic seizures (grand mal), absences (petit mal), myoclonic seizures and atonic seizures. Partial (focal) seizures.

-Treatment of manic episodes, maintenance or prophylactic treatment of bipolar disease in patients who do not respond to or tolerate lithium.

Indications approved in United Kingdom:

Treatment of generalised, partial or other epilepsy.