# MAPHILEP 200MG MR TABLETS
# PL 17780/0239

# MAPHILEP 300MG MR TABLETS
# PL 17780/0240

# MAPHILEP 500MG MR TABLETS
# PL 17780/0241

## UKPAR

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## LAY SUMMARY

The MHRA granted Winthrop Pharmaceuticals UK Limited Marketing Authorisations (licences) for the medicinal products Maphilep 200mg MR Tablets (PL 17780/0239); Maphilep 300mg MR Tablets (PL 17780/0240) and Maphilep 500mg MR Tablets (PL 17780/0241) on 30th August 2007. This prescription-only medicine (POM) is used in the treatment of epilepsy (fits).

Maphilep MR Tablets contain the active ingredients valproic acid and its sodium salt (sodium valproate); both are used as anticonvulsants. The proposed mode of action is regulated through the concentrations of the inhibitory neurotransmitter, gamma amino butyric acid (GABA) in the brain.

These applications are identical to the previously granted applications for Epilim Chrono 200 (PL11723/0078), 300 (PL11723/0021) and 500 (PL11723/0079) Controlled Release Tablets, granted to Sanofi-Synthelabo Ltd on 31st August 1993 and, as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Maphilep 200mg, 300mg and 500mg MR Tablets outweigh the risks; hence Marketing Authorisations have been granted.

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## SCIENTIFIC DISCUSSION

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# INTRODUCTION

The UK granted marketing authorisations for the medicinal products Maphilep 200mg MR Tablets (PL 17780/0239); Maphilep 300mg MR Tablets (PL 17780/0240) and Maphilep 500mg MR Tablets (PL 17780/0241) to Winthrop Pharmaceuticals UK Limited on 30th August 2007. The products are prescription-only medicines.

The applications were submitted as simple abridged applications according to Article 10c of Directive 2001/83/EC, cross-referring to the original product Eplim Chrono 200, 300 and 500 Controlled Release Tablets (PL 11723/0078, PL 11723/0021 and PL 11723/0079) (Sanofi-Synthelabo Ltd), approved on 31st August 1993.

No new data were submitted nor was it necessary for these simple applications, as the data are identical to that of the previously granted cross-reference product. As the cross-reference products were granted prior to the introduction of current legislation, no Public Assessment Report (PAR) has been generated for them.

The product contains the active ingredients valproic acid and sodium valproate which are anticonvulsants used in the treatment of epilepsy.

These applications for Maphilep 200mg, 300mg and 500mg MR Tablets were submitted at the same time and were assessed concurrently. Consequently, all sections of this Scientific Discussion refer to all three strengths of the products.

# PHARMACEUTICAL ASSESSMENT

**LICENCE NO:** PL 17780/0239-0241
**PROPRIETARY NAME:** Maphilep 200mg, 300mg and 500mg MR Tablets
**ACTIVE(S):** Sodium valproate and valproic acid
**COMPANY NAME:** Winthrop Pharmaceuticals UK Ltd
**E.C. ARTICLE:** Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC
**LEGAL STATUS:** POM

## 1. INTRODUCTION

This is a simple, informed consent application for Maphilep 200mg, 300mg and 500mg MR Tablets submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Winthrop Pharmaceuticals UK Ltd, One Onslow Street, Guildford, Surrey, GU1 4YS, UK.

The application cross-refers to Eplim Chrono 200, 300 and 500 Controlled Release Tablets (PL 11723/0078, PL 11723/0021 and PL 11723/0079) approved on 31st August 1993 to the marketing authorisation holder Sanofi-Synthelabo Ltd which are currently registered in the UK. The current applications are considered valid.

## 2. MARKETING AUTHORISATION APPLICATION FORM

### 2.1 Name(s)

The proposed names of the products are Maphilep 200mg, 300mg and 500mg MR Tablets. The products have been named in line with current requirements.

### 2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains the active ingredients, valproic acid and sodium valproate equivalent to 200mg, 300mg and 500mg of sodium valproate respectively. It is to be stored in blisters composed of aluminium and polyvinyl chloride (PVC). The proposed shelf-life (36 months) and storage conditions ("Do not store above 30°C. Store in the original package") are consistent with the details registered for the cross-reference product.

### 2.3 Legal status

On approval, the products will be available as prescription-only medicines.

### 2.4 Marketing authorisation holder/Contact Persons/Company

Winthrop Pharmaceuticals UK Ltd, One Onslow Street, Guildford, Surrey, GU1 4YS, UK.

The QP responsible for pharmacovigilance is stated and his CV is included.

### 2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

### 2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

**2.7 Manufacturing process**
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

**2.8 Finished product/shelf-life specification**
The proposed finished product specification is in line with the details registered for the cross-reference product.

**2.9 Drug substance specification**
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

**2.10 TSE Compliance**
The finished product contains no starting material identified as being at risk under the scope of 'Note for Guidance on Minimising the Risk of Transmitting Animal Encephalopathy via Medicinal Products' CPMP/BWP1230/98.

## 3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

## 4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

## 5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summary is consistent with the details registered for the cross-reference product.

## 6. PATIENT INFORMATION LEAFLET/CARTON
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

## 7. CONCLUSIONS
The data submitted with the application are acceptable. Marketing Authorisations should be granted.

# PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

# CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.

## OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

### QUALITY
The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

### PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

### EFFICACY
Valproic acid and sodium valproate are well known drugs and have been used to treat epilepsy for many years. This application is identical to the innovator product Eplim Chrono 200mg, 300mg and 500mg Controlled Release Tablets.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

### RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product which, in turn, has been shown to be interchangeable with the innovator product. Extensive clinical experience with valproic acid and sodium valproate is considered to have demonstrated the therapeutic value of the compounds. The risk benefit is therefore considered to be positive.

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## STEPS TAKEN FOR ASSESMENT

| | |
|---|---|
| 1 | The MHRA received the marketing authorisation application on 17th August 2005. |
| 2 | Following standard checks and communication with the applicant the MHRA considered the application valid on 24th October 2005. |
| 3 | Following assessment of the application the MHRA requested further information relating to the quality dossier on 16th March 2006. |
| 4 | The applicant responded to the MHRA's requests, providing further information on 12th July 2007. |
| 5 | The application was determined on 30th August 2007 |

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## STEPS TAKEN AFTER ASSESSMENT

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| | | | |
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# MAPHILEP 200MG MR TABLETS
# PL 17780/0239

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT
Maphilep 200mg MR Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 133.2mg sodium valproate and 58.0mg valproic acid equivalent to 200mg sodium valproate.

For full list of excipients, see Section 6.1.

### 3 PHARMACEUTICAL FORM
Modified release tablet
Oblong violet film-coated tablet

### 4 CLINICAL PARTICULARS
#### 4.1 Therapeutic indications
Treatment of generalised, partial or other epilepsy.

#### 4.2 Posology and method of administration
For oral administration.

Maphilep 200mg MR Tablets is a prolonged release formulation of sodium valproate which reduces peak concentration and ensures more even plasma concentrations throughout the day.

Maphilep 200mg MR Tablets may be given once or twice daily. The tablets should be swallowed whole and not crushed or chewed.

Daily dosage requirements vary according to age and body weight.

In patients where adequate control has been achieved Maphilep MR formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

*Monotherapy*
Usual requirements are as follows:

<u>Adults</u>
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, i.e. 20-30mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg
An alternative formulation of sodium valproate should be used in this group of patients, due to the tablet size and need for dose titration. Sodium Valproate Liquid (sugar-free) is an alternative.

Elderly
Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see also sections 4.4 Special warnings and precautions for Use and 4.8 Undesirable effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with sodium valproate, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

*Combined Therapy*
When starting Maphilep MR in patients already on other anticonvulsants, these should be tapered slowly; initiation of Maphilep MR therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Maphilep MR. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.
NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic properties).

**4.3 Contraindications**

- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

**4.4 Special warnings and precautions for use**

**4.4.1 Special warnings**

***Liver dysfunction:***

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing sodium valproate, but the potential benefit of sodium valproate should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.

- in patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the drug.
Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Maphilep MR therapy.

As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

*Pancreatitis:* Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, valproate should be discontinued.

**4.4.2 Precautions**

***Haematological:*** Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8 Undesirable effects).

***Renal insufficiency:*** In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and method of administration and 5.2. Pharmacokinetic properties).

***Systemic lupus erythematosus:*** Although immune disorders have only rarely been noted during the use of sodium valproate, the potential benefit of sodium valproate should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable effects).

***Hyperammonaemia:*** When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate.

***Weight gain:*** Sodium valproate very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable effects).

***Pregnancy:*** Women of childbearing potential should not be started on sodium valproate without specialist neurological advice. Sodium valproate is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, sodium valproate should be used only in patients resistant to other treatment. Women who are likely to get pregnant, should receive specialist advice because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and lactation).

***Diabetic patients:*** Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

## 4.5 Interaction with other medicinal products and other forms of interaction

### 4.5.1 Effects of valproate on other drugs

- ***Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines***

Valproate may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and dosage should be adjusted when appropriate.

- ***Phenobarbital***

Valproate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***

Valproate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

Valproate decreases phenytoin total plasma concentration. Moreover valproate increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic

catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

**- *Carbamazepine***

Clinical toxicity has been reported when valproate was administered with carbamazepine as valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

**- *Lamotrigine***

Valproate may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and sodium valproate might increase the risk of rash.

**- *Zidovudine***

Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

**- *Vitamin K-dependent anticoagulants***

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

**- *Temozolomide***

Co-administration of temozolomide and valproate may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

**4.5.2 Effects of other drugs on Valproate**

Antiepileptics with enzyme inducing effect (including ***phenytoin, phenobarbital, carbamazepine***) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and Valproate may increase valproic acid plasma concentration. Valproate dosage should be monitored.

***Mefloquine*** and ***chloroquine*** increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy.

Accordingly, the dosage of Valproate may need adjustment.

In case of concomitant use of Valproate and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin.***

***Carbapenem antibiotics*** such as ***imipenem, panipenem and meropenem:*** Derease in valproic acid blood level, sometimes associated with convulsions, has been observed when imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood levels is recommended.

Colestyramine may decrease the absorption of Valproate.

**4.5.3 Other Interactions**

Caution is advised when using sodium valproate in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Valproate usually has no enzyme-inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

**4.6 Pregnancy and lactation**

**4.6.1 Pregnancy**

From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows:

***- Risk associated with epilepsy and antiepileptics***

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. Although an increased number of children with malformations have been reported in cases of multiple drug therapy, the respective role of treatments and disease in causing the malformations has not been formally established. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

***- Risk associated with valproate***

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit. There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.
In humans: an increased incidence of congenital abnormalities (including cases of facial dysmorphia, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy treated with valproate.
Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%.

***- In view of the above data***

When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy.

Folate supplementation, prior to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no

direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.
The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.
During pregnancy, valproate anti-epileptic treatment should not be discontinued if it has been effective.

Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special warnings and precautions for use).

***- Risk in the neonate***
Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone and other anti-epileptic enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

**4.6.2 Lactation**
Excretion of valproate in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels; up to now children breast fed that have been monitored during the neonatal period have not experienced clinical effects. There appears to be no contra-indication to breast feeding by patients on valproate.

**4.7 Effects on ability to drive and use machines**
Use of sodium valproate may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with other medicinal products and other forms of interaction).

**4.8 Undesirable effects**
Congenital and familial/genetic disorders: (see section 4.6 Pregnancy and lactation)

Hepato-biliary disorders: rare cases of liver dysfunction (see section 4.4.1 Warnings)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment. These problems can usually be overcome by taking Sodium valproate with or after food or by using enteric coated sodium valproate.
Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special warnings and precautions for use).

Nervous system disorders:
Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Metabolic disorders:
Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur sodium valproate should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Blood and lymphatic system disorders:
Frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.

Isolated reduction of fibrinogen or reversible increase in bleeding time have been reported, usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and lactation).

Skin and subcutaneous tissue disorders:
Cutaneous reactions such as exanthematous rash rarely occur with valproate. In very rare cases toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become curlier than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders:
Amenorrhoea and irregular periods have been reported. Very rarely gynaecomastia has occurred.

Vascular disorders:
The occurrence of vasculitis has occasionally been reported.

Ear disorders:
Hearing loss, either reversible or irreversible has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders:
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with valproate therapy, but the mode of action is as yet unclear.

Immune system disorders:
Allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

General disorders:
Very rare cases of non-severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special warnings and precautions for use).

**4.9 Overdose**

Cases of accidental and deliberate valproate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Clinical signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic properties). Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally. Deaths have occurred following massive overdose; nevertheless, a favourable outcome is usual.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, fatty acid derivatives
ATC Code: NO3A GO1

Sodium valproate is an anticonvulsant.

The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that sodium valproate could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that sodium valproate does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of sodium valproate on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

### 5.2 Pharmacokinetic properties

The half-life of sodium valproate is usually reported to be within the range of 8-20 hours. It is usually shorter in children.
In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Maphilep MR tablets may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Maphilep MR tablets are prolonged release formulations which demonstrate in pharmacokinetic studies less fluctuation in plasma concentration compared with other established conventional and modified release sodium valproate formulations.

In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of Maphilep MR make the measurement of plasma levels less dependent upon time of sampling.

The Maphilep MR formulations are bioequivalent to Sodium Valproate Liquid and enteric coated (EC) formulations with respect to the mean areas under the plasma concentration time curves. Steady-state pharmacokinetic data indicate that the peak concentration ($C_{max}$) and trough concentration ($C_{min}$) of Maphilep MR lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with sodium valproate EC.

**5.3 Preclinical safety data**

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

## 6 PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Hypromellose
Ethylcellulose
Hydrated Silica
Film Coat
Violet coat (Opadry 04-S-6705), containing:
Titanium dioxide (E171)
Erythrosine BS aluminium lake (E127)
Indigo carmine aluminium lake (E132)
Iron oxide black (E172)
Hypromellose
Macrogel 400

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Do not store above 30°C. Store in the original package.
Sodium valproate is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut.

**6.5 Nature and contents of container**

Maphilep 200mg MR Tablets are supplied in blister packs further packed into a cardboard carton. Pack size 100 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements

**7 MARKETING AUTHORISATION HOLDER**

Winthrop Pharmaceuticals UK Limited
One Onslow Street
Guildford
Surrey
GU1 4YS, UK
Trading as: Winthrop Pharmaceuticals, PO Box 611, Guildford, Surrey, GU1 4YS, UK

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 17780/0239

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

30/08/2007

**10 DATE OF REVISION OF THE TEXT**

30/08/2007

# MAPHILEP 300MG MR TABLETS
# PL 17780/0240

## SUMMARY OF PRODUCT CHARACTERISTICS

**1 NAME OF THE MEDICINAL PRODUCT**
Maphilep 300mg MR Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each tablet contains 199.8mg sodium valproate and 87.0mg valproic acid equivalent to 300mg sodium valproate.

For full list of excipients, see Section 6.1.

**3 PHARMACEUTICAL FORM**
Modified release tablet
Oblong violet film-coated tablet

**4 CLINICAL PARTICULARS**
**4.1 Therapeutic indications**
Treatment of generalised, partial or other epilepsy.

**4.2 Posology and method of administration**
For oral administration.

Maphilep 300mg MR Tablets is a prolonged release formulation of sodium valproate which reduces peak concentration and ensures more even plasma concentrations throughout the day.

Maphilep 300mg MR Tablets may be given once or twice daily. The tablets should be swallowed whole and not crushed or chewed.

Daily dosage requirements vary according to age and body weight.

In patients where adequate control has been achieved Maphilep MR formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

*Monotherapy*
Usual requirements are as follows:

Adults
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, i.e. 20-30mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight

per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg
An alternative formulation of sodium valproate should be used in this group of patients, due to the tablet size and need for dose titration. Sodium Valproate Liquid (sugar-free) is an alternative.

Elderly
Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see also sections 4.4 Special warnings and precautions for Use and 4.8 Undesirable effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with sodium valproate, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

*Combined Therapy*
When starting Maphilep MR in patients already on other anticonvulsants, these should be tapered slowly; initiation of Sodium Valproate and Valproic Acid therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Sodium Valproate and Valproic Acid. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic properties).

## 4.3 Contraindications

- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

## *4.4 Special warnings and precautions for use*

### 4.4.1 Special warnings

***Liver dysfunction:***

Conditions of occurrence:

Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.

After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing sodium valproate, but the potential benefit of sodium valproate should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:

Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the drug.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical

examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of MaphilepMR therapy.

As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

*Pancreatitis:* Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, valproate should be discontinued.

**4.4.2 Precautions**

***Haematological:*** Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8 Undesirable effects).

***Renal insufficiency:*** In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and method of administration and 5.2. Pharmacokinetic properties).

***Systemic lupus erythematosus:*** Although immune disorders have only rarely been noted during the use of sodium valproate, the potential benefit of sodium valproate should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable effects).

***Hyperammonaemia:*** When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate.

***Weight gain:*** Sodium valproate very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable effects).

***Pregnancy:*** Women of childbearing potential should not be started on sodium valproate without specialist neurological advice. Sodium valproate is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, sodium valproate should be used only in patients resistant to other treatment. Women who are likely to get pregnant, should receive specialist advice because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and lactation).

***Diabetic patients:*** Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

## *4.5 Interaction with other medicinal products and other forms of interaction*

### 4.5.1 Effects of valproate on other drugs

- ***Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines***

Valproate may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and dosage should be adjusted when appropriate.

- ***Phenobarbital***

Valproate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***

Valproate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

Valproate decreases phenytoin total plasma concentration. Moreover valproate increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
Clinical toxicity has been reported when valproate was administered with carbamazepine as valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
Valproate may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and sodium valproate might increase the risk of rash.

- ***Zidovudine***
Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
Co-administration of temozolomide and valproate may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

**4.5.2 Effects of other drugs on Valproate**

Antiepileptics with enzyme including effect (including ***phenytoin, phenobarbital, carbamazepine)*** decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and Valproate may increase valproic acid plasma concentration. Valproate dosage should be monitored.

***Mefloquine*** and ***chloroquine*** increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy.
Accordingly, the dosage of Valproate may need adjustment.
In case of concomitant use of Valproate and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin.***

***Carbapenem antibiotics*** such as ***imipenem, panipenem and meropenem***: Decrease in valproic acid blood level, sometimes associated with convulsions, has been observed when imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood levels is recommended.

Colestyramine may decrease the absorption of Valproate.

**4.5.3 Other Interactions**

Caution is advised when using sodium valproate in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Valproate usually has no enzyme-inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

***4.6 Pregnancy and lactation***

**4.6.1 Pregnancy**

From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows:

***- Risk associated with epilepsy and antiepileptics***

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. Although an increased number of children with malformations have been reported in cases of multiple drug therapy, the respective role of treatments and disease in causing the malformations has not been formally established. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

***- Risk associated with valproate***

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit. There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.
In humans: an increased incidence of congenital abnormalities (including cases of facial dysmorphia, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy treated with valproate.
Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%.

***- In view of the above data***

When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy.

Folate supplementation, prior to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs,

women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.
The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.
During pregnancy, valproate anti-epileptic treatment should not be discontinued if it has been effective.

Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special warnings and precautions for use).

***- Risk in the neonate***
Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone and other anti-epileptic enzyme inducing drugs. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

**4.6.2 Lactation**
Excretion of valproate in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels; up to now children breast fed that have been monitored during the neonatal period have not experienced clinical effects. There appears to be no contra-indication to breast feeding by patients on valproate.

**4.7 Effects on ability to drive and use machines**
Use of sodium valproate may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with other medicinal products and other forms of interaction).

**4.8 Undesirable effects**
Congenital and familial/genetic disorders: (see section 4.6 Pregnancy and lactation)

Hepato-biliary disorders: rare cases of liver dysfunction (see section 4.4.1 Warnings)
Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment. These problems can usually be overcome by taking Sodium valproate with or after food or by using enteric coated sodium valproate.
Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special warnings and precautions for use).

Nervous system disorders:
Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Metabolic disorders:
Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur sodium valproate should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Blood and lymphatic system disorders:
Frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.

Isolated reduction of fibrinogen or reversible increase in bleeding time have been reported, usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and lactation).

Skin and subcutaneous tissue disorders:
Cutaneous reactions such as exanthematous rash rarely occur with valproate. In very rare cases toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.
Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become curlier than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders:
Amenorrhoea and irregular periods have been reported. Very rarely gynaecomastia has occurred.

Vascular disorders:
The occurrence of vasculitis has occasionally been reported.

Ear disorders:
Hearing loss, either reversible or irreversible has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders:
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with valproate therapy, but the mode of action is as yet unclear.

Immune system disorders:
Allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

General disorders:
Very rare cases of non-severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special warnings and precautions for use).

**4.9 Overdose**

Cases of accidental and deliberate valproate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Clinical signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic properties). Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally. Deaths have occurred following massive overdose; nevertheless, a favourable outcome is usual.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, fatty acid derivatives
ATC Code: NO3A GO1

Sodium valproate is an anticonvulsant.

The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that sodium valproate could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that sodium valproate does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of sodium valproate on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

### 5.2 Pharmacokinetic properties

The half-life of sodium valproate is usually reported to be within the range of 8-20 hours. It is usually shorter in children.
In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Maphilep MR tablets may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Maphilep MR tablets are prolonged release formulations which demonstrate in pharmacokinetic studies less fluctuation in plasma concentration compared with other established conventional and modified release sodium valproate formulations.

In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of Maphilep MR make the measurement of plasma levels less dependent upon time of sampling.

The Maphilep MR formulations are bioequivalent to Sodium Valproate Liquid and enteric coated (EC) formulations with respect to the mean areas under the plasma concentration time curves. Steady-state pharmacokinetic data indicate that the peak concentration ($C_{max}$) and trough concentration ($C_{min}$) of Maphilep MR lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with sodium valproate EC.

**5.3 Preclinical safety data**

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

## 6 PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Hypromellose
Ethylcellulose
Hydrated Silica

Film Coat
Violet coat (Opadry 04-S-6705), containing:
Titanium dioxide (E171)
Erythrosine BS aluminium lake (E127)
Indigo carmine aluminium lake (E132)
Iron oxide black (E172)
Hypromellose
Macrogel 400

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Do not store above 30°C. Store in the original package.
Sodium valproate is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut.

**6.5 Nature and contents of container**

Maphilep 300mg MR Tablets are supplied in blister packs further packed into a cardboard carton. Pack size 100 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements

**7 MARKETING AUTHORISATION HOLDER**

Winthrop Pharmaceuticals UK Limited
One Onslow Street
Guildford
Surrey
GU1 4YS, UK
Trading as: Winthrop Pharmaceuticals, PO Box 611, Guildford, Surrey, GU1 4YS, UK

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 17780/0240

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

30/08/2007

**10 DATE OF REVISION OF THE TEXT**

30/08/2007

# MAPHILEP 500MG MR TABLETS
# PL 17780/0240
# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT
Maphilep 500mg MR Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 333mg sodium valproate and 145mg valproic acid equivalent to 500mg sodium valproate.

For full list of excipients, see Section 6.1.

## 3 PHARMACEUTICAL FORM
Modified release tablet
Oblong violet film-coated tablet

## 4 CLINICAL PARTICULARS
### 4.1 Therapeutic indications
Treatment of generalised, partial or other epilepsy.

### 4.2 Posology and method of administration
For oral administration.

Maphilep 500mg MR Tablets is a prolonged release formulation of sodium valproate which reduces peak concentration and ensures more even plasma concentrations throughout the day.

Maphilep 500mg MR Tablets may be given once or twice daily. The tablets should be swallowed whole and not crushed or chewed.

Daily dosage requirements vary according to age and body weight.

In patients where adequate control has been achieved Maphilep MR formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

*Monotherapy*
Usual requirements are as follows:

<u>Adults</u>
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, i.e. 20-30mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

<u>Children over 20kg</u>
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight

per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg
An alternative formulation of sodium valproate should be used in this group of patients, due to the tablet size and need for dose titration. Sodium Valproate Liquid (sugar-free) is an alternative.

Elderly
Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic properties).

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see also sections 4.4 Special warnings and precautions for Use and 4.8 Undesirable effects).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with sodium valproate, concomitant use in children under 3 years can increase the risk of liver toxicity (see section 4.4.1 Special warnings).

*Combined Therapy*
When starting Maphilep MR in patients already on other anticonvulsants, these should be tapered slowly; initiation of Maphilep MR therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Maphilep MR. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma

levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic properties).

**4.3 Contraindications**

- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

**4.4 Special warnings and precautions for use**

**4.4.1 Special warnings**

***Liver dysfunction:***

Conditions of occurrence:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.
After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing sodium valproate, but the potential benefit of sodium valproate should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy
In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:
Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the drug.
Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Maphilep MR therapy.

As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

*Pancreatitis:* Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, valproate should be discontinued.

### 4.4.2 Precautions

***Haematological:*** Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8 Undesirable effects).

***Renal insufficiency:*** In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 Posology and method of administration and 5.2. Pharmacokinetic properties).

***Systemic lupus erythematosus:*** Although immune disorders have only rarely been noted during the use of sodium valproate, the potential benefit of sodium valproate should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8 Undesirable effects).

***Hyperammonaemia:*** When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate.

***Weight gain:*** Sodium valproate very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8 Undesirable effects).

***Pregnancy:*** Women of childbearing potential should not be started on sodium valproate without specialist neurological advice. Sodium valproate is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, sodium valproate should be used only in patients resistant to other treatment. Women who are likely to get pregnant, should receive specialist advice because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and lactation).

***Diabetic patients:*** Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

## 4.5 Interaction with other medicinal products and other forms of interaction

### 4.5.1 Effects of valproate on other drugs

- ***Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines***
Valproate may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and dosage should be adjusted when appropriate.

- ***Phenobarbital***
Valproate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***
Valproate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***
Valproate decreases phenytoin total plasma concentration. Moreover valproate increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- ***Carbamazepine***
Clinical toxicity has been reported when valproate was administered with carbamazepine as valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***
Valproate may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and sodium valproate might increase the risk of rash.

- ***Zidovudine***
Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- ***Temozolomide***
Co-administration of temozolomide and valproate may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

**4.5.2 Effects of other drugs on Valproate**
Antiepileptics with enzyme including effect (including ***phenytoin, phenobarbital, carbamazepine)*** decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of ***felbamate*** and Valproate may increase valproic acid plasma concentration. Valproate dosage should be monitored.

***Mefloquine*** and ***chloroquine*** increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy.
Accordingly, the dosage of Valproate may need adjustment.
In case of concomitant use of Valproate and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin.***

***Carbapenem antibiotics*** such as ***imipenem, panipenem and meropenem***: Decrease in valproic acid blood level, sometimes associated with convulsions, has been observed when imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood levels is recommended.

Colestyramine may decrease the absorption of Valproate.

**4.5.3 Other Interactions**

Caution is advised when using sodium valproate in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Valproate usually has no enzyme-inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

**4.6 Pregnancy and lactation**

**4.6.1 Pregnancy**

From experience in treating mothers with epilepsy, the risk associated with the use of valproate during pregnancy has been described as follows:

***- Risk associated with epilepsy and antiepileptics***

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. Although an increased number of children with malformations have been reported in cases of multiple drug therapy, the respective role of treatments and disease in causing the malformations has not been formally established. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

Epidemiological studies have suggested an association between in-utero exposure to sodium valproate and a risk of developmental delay. Many factors including maternal epilepsy may also contribute to this risk but it is difficult to quantify the relative contributions of these or of maternal anti-epileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.

***- Risk associated with valproate***

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit. There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.
In humans: an increased incidence of congenital abnormalities (including cases of facial dysmorphia, hypospadias and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy treated with valproate.
Valproate use is associated with neural tube defects such as myelomeningocele and spina bifida. The frequency of this effect is estimated to be 1 to 2%.

***- In view of the above data***

When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy.

Folate supplementation, prior to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs,

women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.
The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels.
During pregnancy, valproate anti-epileptic treatment should not be discontinued if it has been effective.
Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special warnings and precautions for use).

***- Risk in the neonate***
Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone and other anti-epileptic enzyme inducing drugs.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

**4.6.3 Lactation**
Excretion of valproate in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels; up to now children breast fed that have been monitored during the neonatal period have not experienced clinical effects. There appears to be no contra-indication to breast feeding by patients on valproate.

**4.7 Effects on ability to drive and use machines**
Use of sodium valproate may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5 Interactions with other medicinal products and other forms of interaction).

**4.8 Undesirable effects**
Congenital and familial/genetic disorders: (see section 4.6 Pregnancy and lactation)

Hepato-biliary disorders: rare cases of liver dysfunction (see section 4.4.1 Warnings)
Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment. These problems can usually be overcome by taking Sodium valproate with or after food or by using enteric coated sodium valproate.
Very rare cases of pancreatitis, sometimes lethal, have been reported (see section 4.4 Special warnings and precautions for use).

Nervous system disorders:
Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Metabolic disorders:
Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur sodium valproate should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2 Precautions). In such cases further investigations should be considered.

Blood and lymphatic system disorders:
Frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued.

Isolated reduction of fibrinogen or reversible increase in bleeding time have been reported, usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6 Pregnancy and lactation).

Skin and subcutaneous tissue disorders:
Cutaneous reactions such as exanthematous rash rarely occur with valproate. In very rare cases toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become curlier than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders:
Amenorrhoea and irregular periods have been reported. Very rarely gynaecomastia has occurred.

Vascular disorders:
The occurrence of vasculitis has occasionally been reported.

Ear disorders:
Hearing loss, either reversible or irreversible has been reported rarely; however a cause and effect relationship has not been established.

Renal and urinary disorders:
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with valproate therapy, but the mode of action is as yet unclear.

Immune system disorders:
Allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

General disorders:
Very rare cases of non-severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see section 4.4 Special warnings and precautions for use).

**4.9 Overdose**

Cases of accidental and deliberate valproate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Clinical signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic properties). Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.
Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally. Deaths have occurred following massive overdose; nevertheless, a favourable outcome is usual.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, fatty acid derivatives
ATC Code: NO3A GO1

Sodium valproate is an anticonvulsant.

The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in-vitro* studies it was reported that sodium valproate could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that sodium valproate does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of sodium valproate on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

### 5.2 Pharmacokinetic properties

The half-life of sodium valproate is usually reported to be within the range of 8-20 hours. It is usually shorter in children.
In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Maphilep MR tablets may not be clearly correlated with the total or free (unbound) plasma valproic acid levels. Maphilep MR tablets are prolonged release formulations which demonstrate in pharmacokinetic studies less fluctuation in plasma concentration compared with other established conventional and modified release sodium valproate formulations.

In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of Maphilep MR make the measurement of plasma levels less dependent upon time of sampling.

The Maphilep MR formulations are bioequivalent to Sodium Valproate Liquid and enteric coated (EC) formulations with respect to the mean areas under the plasma concentration time curves. Steady-state pharmacokinetic data indicate that the peak concentration ($C_{max}$) and trough concentration ($C_{min}$) of Sodium Valproate and Valproic Acid lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with sodium valproate EC.

**5.3 Preclinical safety data**

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

## 6 PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Hypromellose
Ethylcellulose
Hydrated Silica

Film Coat
Violet coat (Opadry 04-S-6705), containing:
Titanium dioxide (E171)
Erythrosine BS aluminium lake (E127)
Indigo carmine aluminium lake (E132)
Iron oxide black (E172)
Hypromellose
Macrogel 400

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Do not store above 30°C. Store in the original package.
Sodium valproate is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut.

**6.5 Nature and contents of container**

Maphilep 500mg MR Tablets are supplied in blister packs further packed into a cardboard carton. Pack size 100 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements

**7 MARKETING AUTHORISATION HOLDER**

Winthrop Pharmaceuticals UK Limited
One Onslow Street
Guildford
Surrey
GU1 4YS, UK
Trading as: Winthrop Pharmaceuticals, PO Box 611, Guildford, Surrey, GU1 4YS, UK

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 17780/0241

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

30/08/2007

**10 DATE OF REVISION OF THE TEXT**

30/08/2007

# MAPHILEP 200MG, 300MG AND 500MG MR TABLETS
# PL 17780/0239-0241

# PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

## MAPHILEP 200MG, 300MG AND 500MG MR TABLETS
(sodium valproate/valproic acid)

**Read all of this leaflet carefully before you start taking this medicine.**
- Keep this leaflet. You may need to read it again.
- It is essential that you follow your doctor's advice. If you have further questions, please ask your doctor or your pharmacist.
- If you are helping someone else to take Maphilep MR, read this leaflet carefully before you give them the first dose.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- Your doctor may have given you this medicine before from another company and it may have looked slightly different. Either brand will have the same effect.

**In this leaflet:**


### 1. WHAT MAPHILEP MR IS AND WHAT IT IS USED FOR

The name of this medicine is Maphilep 200mg, 300mg or 500mg MR Tablets (referred to as Maphilep MR throughout this leaflet).

Maphilep MR is an antiepileptic, which is used to treat epilepsy (fits). Maphilep MR is made so that the medicine in the tablets is released slowly over a long period of time.

### 2. BEFORE YOU TAKE MAPHILEP MR

**Do not take Maphilep MR if you have:**
- liver problems
- a family history of liver problems
- a known allergy to sodium valproate and valproic acid or any of the other ingredients
- porphyria (a rare metabolic condition).

**Check with your doctor before you take Maphilep MR if you:**
- have lupus (an immune system condition affecting skin, bones and joints, lungs, kidneys)
- are diabetic - sodium valproate may give an indication that ketones are present in the urine when this is not the case
- have kidney problems - you may need a lower dose.

You should talk to your doctor or pharmacist even if you no longer have these conditions, but have had them in the past. Your doctor may wish to do tests before you start and during the first six months of treatment.

**Taking Maphilep MR with food and drink**
Swallow the tablets whole, (do not crush or chew them), with a drink of water, usually after meals.

**Pregnancy**
Ask your doctor or pharmacist for advice before taking any medicine. It is essential that you discuss your epilepsy treatment with your doctor well before you become pregnant. If at any time you suspect that you might already be pregnant you must tell your doctor immediately.

Women who take these tablets during the first month of pregnancy to control their epilepsy have a small risk (1-2%) of having a baby with spina bifida, an abnormality of the spinal cord. Taking folic acid 5mg daily as soon as you stop contraception may lower the risk of having a baby with spina bifida. There is also an increased risk of other birth defects. These can usually be detected in the first part of the pregnancy using routine antenatal screening blood tests and ultrasound scans. Rarely there may also be bleeding problems in the new born if the mother has taken this medicine during pregnancy.

Infants born to mothers who took Maphilep MR during pregnancy may develop less quickly than normal. This may also be because of the mother's epilepsy but the exact cause is not known.

It is important not to stop taking your tablets suddenly as this is likely to result in you having fits which may harm both you and your baby.

**Breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. Very little sodium valproate and valproic acid gets into the breast milk but you should discuss with your doctor whether you should breast feed your baby.

**Driving and using machines**
When you first start taking these tablets, or if you are taking it with other medicines, you may notice some drowsiness. If affected you should not drive or operate machinery.

**Taking other medicines**
If taken with some other medicines the effects of Maphilep MR or the effects of the other medicines may be changed. Please check with your doctor if you are taking any of the following:
- cholestyramine - used to treat high blood lipid (fat) levels
- antidepressant therapy - including monoamine oxidase inhibitors
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- other antiepileptic therapy e.g. phenytoin, carbamazepine, phenobarbitone, lamotrigine, primidone, felbamate.
- cimetidine - used to treat stomach ulcers
- salicylates e.g. aspirin
- erythromycin, imipenem and meropenem - antibiotics
- mefloquine and chloroquine - used to prevent and treat malaria - may increase the likelihood of a fit. Before travelling to a malaria area, you should get advice from your doctor or pharmacist on the most appropriate prevention tablets.
- benzodiazepines - used as sleeping tablets and to treat anxiety
- zidovudine - used to treat HIV and AIDS
- temozolomide - used to treat cancer

The effects of these tablets may also be changed by medicines taken some time ago, or it may change the effects of medicines you may take in the future. Please inform your doctor or pharmacist if you are taking, or have recently taken any other medicine - even those which your doctor has was not prescribed for you, but which you have brought yourself from your chemist/pharmacy.

### 3. HOW TO TAKE MAPHILEP MR

**How much you take is decided by your doctor.**
Swallow the tablets whole, (do not crush or chew them), with a drink of water, usually after meals.

Adults: The usual dose of Maphilep MR is between 1000mg and 2000mg per day but may be increased to 2500mg per day. This quantity may be given in one dose or can be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

Elderly: The usual dose will be determined by the doctor.

Children over 20kg:- The usual dose of Maphilep MR is based on the child's weight as an amount of Maphilep MR for each kg of body weight. The usual dose is between 20 and 30mg for each kg of body weight but may be increased to 35mg for each kg of body weight per day. This quantity may be given in one dose or can be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

Maphilep MR are not suitable for use in children under 20kg.

When treatment is first started you may be prescribed a lower dose. This is because some patients need less Maphilep MR than others to control their fits. Your doctor will increase the dosage until your condition is controlled. Because of this it is very important that you follow the instructions your doctor has given you about how much to take. Blood tests may be needed.

If you are taking other medicines to control your epilepsy at the same time as Maphilep MR your doctor may increase the dose of Maphilep MR by 5 to 10mg for each kg of body weight per day. If you have kidney disease your doctor may prescribe a lower dose.

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**If you take more Maphilep MR than you should:**
An overdose of this medicine may be dangerous. If you think you or someone else may have taken too many tablets than you should, talk to a doctor, pharmacist or go to the nearest hospital casualty department immediately.

**If you forget to take Maphilep MR:**
If you forget to take a dose at the right time, take it as soon as you remember, then go on as before. However, you must take care not to take two doses at the same time.

Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.
Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed. If you go into hospital or visit another doctor or a dentist tell them you are taking Maphilep MR.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Maphilep MR can have side-effects. Maphilep MR tablets can affect the liver (and rarely the pancreas) in a very small number of patients. You should tell your doctor **IMMEDIATELY** if you develop a sudden illness, especially if it is within the first six months of treatment, and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs or worsening of your epilepsy or a general feeling of being unwell.

Particular care is needed in the case of children under 3 or those with other nervous system disease.

Whilst taking your tablets your appetite may be increased and you must take care to avoid weight gain.

Maphilep MR sometimes cause the following: nausea (usually relieved by taking tablets with or after food); vomiting; diarrhoea; changes in the amount of ammonia in the blood (which may cause vomiting, unsteady movements and an unawareness of your surroundings); vasculitis (inflammation of the blood vessels, you may notice pain, redness or itching).

Maphilep MR sometimes causes changes in the blood; you may notice abnormal bleeding or a tendency to bruise more easily; severe stomach pains; shakiness or problems with balance. Rarely may it cause tiredness; confusion; hallucinations; seizures; change in mood, jerky muscle movements and loss of consciousness.

Occasionally Maphilep MR can affect the hair. Any loss of hair is usually temporary but when it grows back it may be curlier than before.

Rashes, sometimes severe, occur rarely but patients who are also taking lamotrigine may be more at risk.

If you experience any of these effects or if you get any unusual symptoms you should tell your doctor as soon as possible as you may have to stop taking the tablets. These effects usually reverse on stopping these tablets.

Rarely an increase in alertness may occur, sometimes with aggression, hyperactivity and behavioural deterioration. Also, immune disorders have occurred rarely.

Very rarely it may also cause a change in women's periods, hearing problems, kidney problems, acne, increased hair growth or increased breast growth in men.

If you experience any of these effects you need not worry but you should discuss with your doctor any which become troublesome. If you notice any side effects not mentioned in this leaflet, please inform you doctor or pharmacist.

## 5. HOW TO STORE MAPHILEP MR

Keep your medicine in a safe place, out of the reach and sight of children.
Do not store above 30°C. Store in the original package in order to keep them dry.

Maphilep MR may spoil if not stored properly. It is very important to keep them in the foil until just before you take them.

Do not use this medicine after the expiry date printed on the packaging.

## 6. FURTHER INFORMATION

Maphilep MR are oval shaped, lilac coloured tablets and are supplied in cartons of 100.

Maphilep 200mg, 300mg or 500mg MR tablets contains a mixture of sodium valproate and valproic acid equivalent to 200mg, 300mg or 500mg sodium valproate respectively.

They also contain hypromellose, hydrated silica, ethylcellulose, titanium dioxide (E171), erythrosine (E127), indigo carmine (E132), black iron oxide (E172) and macrogol 400.

**The Marketing Authorisation holder is**: Winthrop Pharmaceuticals, PO Box 611, Guildford, Surrey, GU1 4YS, UK.
**The Manufacturer is**: Fawdon Manufacturing Centre, Edgefield Avenue, Fawdon, Newcastle-upon-Tyne, Tyne & Wear, NE3 3TT.

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

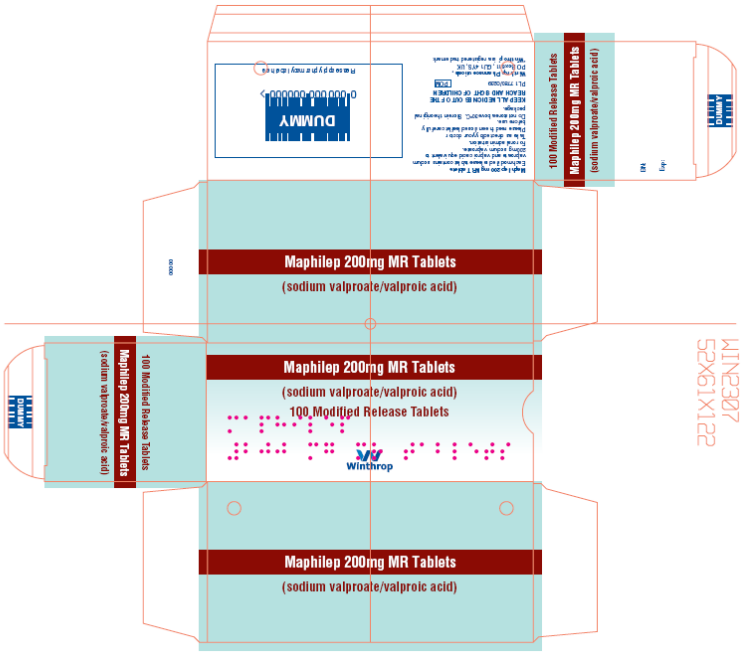
The British Epilepsy Association (telephone: 0808 800 5050) will also be happy to try and answer any general questions on epilepsy.

Date of revision of leaflet: July 2007

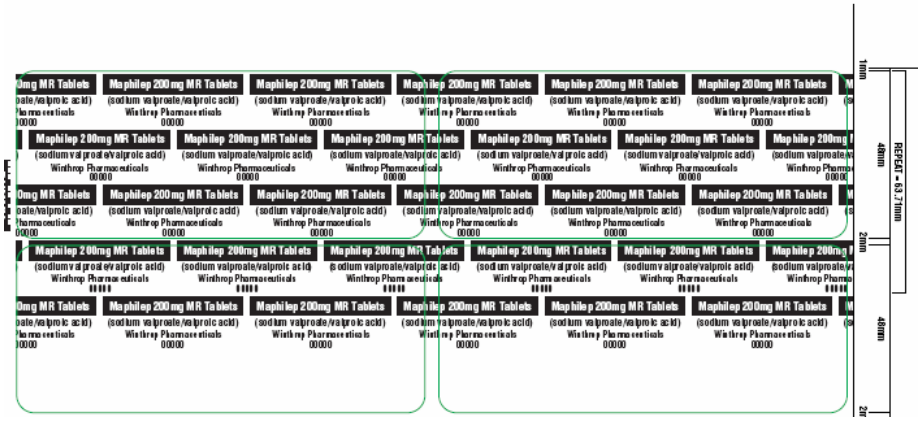
# MAPHILEP 200MG MR TABLETS
# PL 17780/0239

## LABELLING

## CARTON

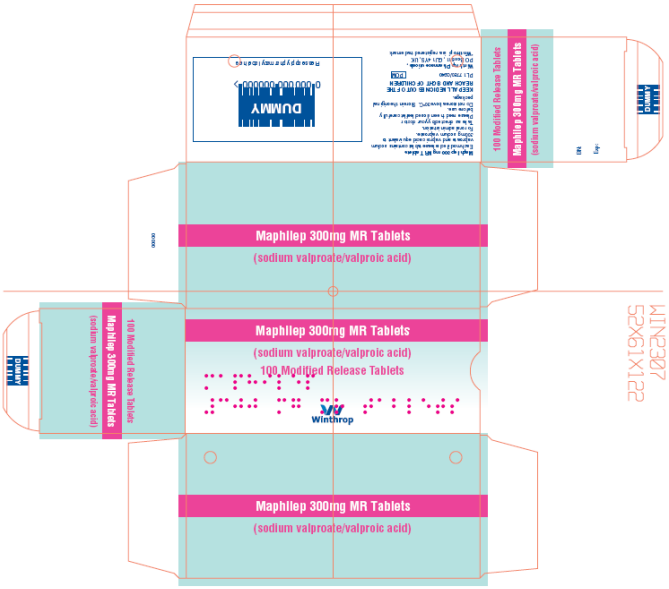



## BLISTER FOIL



# MAPHILEP 200MG MR TABLETS
# PL 17780/0240

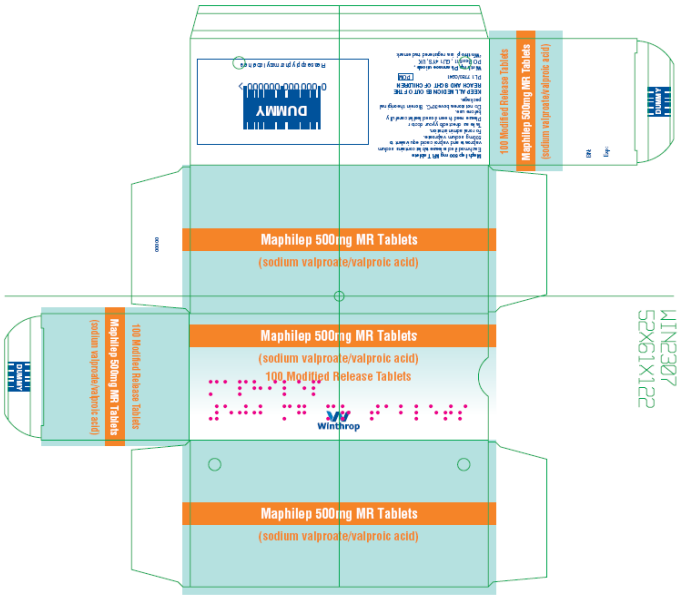
## CARTON




## BLISTER FOIL

# MAPHILEP 200MG MR TABLETS
# PL 17780/0241

## CARTON




## BLISTER FOIL