SUMMARY OF PRODUCT CHARACTERISTICS

1 Name of the medicinal product

Depakote 250mg Tablets.
Depakote 500mg Tablets.

2 Qualitative and quantitative composition

Containing 269.10mg of valproate semisodium* per tablet (equivalent to 250mg of valproic acid).

Containing 538.20mg of valproate semisodium* per tablet (equivalent to 500mg of valproic acid).

*Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship. It is also known as divalproex sodium (USAN).

For a full list of excipients, see section 6.1

3 Pharmaceutical form

250mg: Oval, orange gastro-resistant tablets.
500mg: Oval, lilac pink gastro-resistant tablets

4 Clinical particulars

4.1 Therapeutic indications

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to Depakote for acute mania

4.2 Posology and method of administration

For oral administration. The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

The daily dosage should be established according to age and body weight. The wide variation in individual sensitivity to Depakote should also be considered.

Dosage

Manic episodes in bipolar disorder:

Adults
The daily dosage should be established and controlled individually by the treating physician. The initial recommended daily dose is 750 mg. In addition, in
clinical trials a starting dose of 20 mg valproate/kg body weight has also shown an acceptable safety profile. Prolonged-release formulations can be given once or twice daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adapted to the clinical response to establish the lowest effective dose for the individual patient. The mean daily dose usually ranges between 1000 and 2000 mg valproate. Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored. Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

**Elderly**
Although the pharmacokinetics of Depakote are modified in the elderly, they have limited clinical significance and dosage should be determined on the basis of clinical response.

**Children and adolescents**
The safety and effectiveness of Depakote for the treatment of manic episodes have not been studied in individuals below the age of 18 years.

**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 Depakote 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 Depakote, 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 Depakote in patients, already on anticonvulsants, these should be tapered slowly; if clinically possible; initiation of Depakote therapy should then be gradual, with target dose being reached after about 2 weeks. Faster titration may be permissible if plasma level monitoring is available. 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, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain control on a reduced dose of Depakote. When barbiturates are being administered concomitantly and particularly if sedation is observed the dosage of barbiturate should be reduced.
When using Depakote with other psychotropics, a reduced dose may be required, (see 4.5.1 Effects of Depakote on other drugs)
Optimum dosage is mainly determined by control. 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 Contra-indications

Active liver disease
Personal or family history of severe hepatic dysfunction, drug related
Hypersensitivity to valproate semisodium or any other ingredient of the preparation.
Porphyria

4.4 Special warnings and precautions for use

To ensure the correct medication is prescribed for the patient’s condition, care must be taken not to confuse Depakote with Epilim or sodium valproate. Patients with bipolar disorder and epilepsy are distinct populations. These differences are reflected in the patient information leaflets which clearly indicate specific indications for these differing medications.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

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

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. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Depakote should be discontinued.

**Women of childbearing potential:** This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). Women of child-bearing potential have to use effective contraception during treatment (see also section 4.6 Pregnancy and Lactation).
Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for valproate semisodium. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

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 Depakote, the potential benefit of Depakote 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 Depakote.

Weight gain: Depakote 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: See section 4.6 Pregnancy and Lactation.

Diabetic patients: Depakote 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 Depakote on other drugs
Clozapine, haloperidol, lithium
No significant interaction was observed when clozapine and haloperidol were administered concurrently with Depakote. Co-administration of Depakote and lithium does not appear to affect the steady state kinetics of lithium.

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

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

Phenobarbital
Depakote increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. 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
Depakote 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
Depakote decreases phenytoin total plasma concentration. Moreover Depakote 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 Depakote was administered with carbamazepine as Depakote may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine
The risk of rash associated with the use of Depakote may be increased if lamotrigine is also administered. Depakote may reduce the metabolism of lamotrigine and increase the mean half-life. Dose should be adjusted (lamotrigine dosage decreased) when appropriate.

Zidovudine
Depakote 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 Depakote 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 Depakote

Antiepileptics with enzyme inducing effects (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 Depakote may increase valproic acid plasma concentration. Depakote dosage should be monitored.

Mefloquine and Chloroquine increase valproic acid metabolism. Accordingly, the dosage of Depakote may need adjustment.

In case of concomitant use of Depakote 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 panipenem, imipenem and meropenem: Decrease in valproic acid blood level, sometimes associated with convulsions, has been observed when panipenem, imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood level is recommended.

Colestyramine may decrease the absorption of Depakote.

Rifampicin may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

4.5.3 Other interactions

Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring for signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

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

4.6 Pregnancy and lactation

This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). Women of child-bearing potential have to use effective contraception during treatment.
Adequate counselling should be made available to all women with bipolar disorder of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6.1).

Women who are taking Depakote and who may become pregnant should receive specialist psychiatric advice and the benefits of its use should be weighed against the risks.

If pregnancy is planned, consideration should be given to cessation of Depakote treatment.

When Depakote treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed. (See also section 4.6.1 paragraph entitled “In view of the above”)

In offspring born to mothers with epilepsy receiving any antiepileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations.

4.6.1 Pregnancy

- **Risk associated with bipolar therapy**
  This drug should be withdrawn under specialist supervision.

- **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: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with the greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs.

  Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a higher risk of abnormal pregnancy outcome than sodium valproate monotherapy.
Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.

Autism spectrum disorders have also been reported in children exposed to valproate in utero.

**- In view of the above data**

When a woman is planning pregnancy, this provides an opportunity to review the need for treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Depakote during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before Depakote is prescribed for the first time or a woman already treated with Depakote is planning a 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 Depakote, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.

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 is preferable in order to avoid high peak plasma levels.

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; a fibrinogenemia 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 phenobarbital and other 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 Depakote in breast milk is low, with a concentration between 1% to 10% of total maternal serum levels. Although there appears to be no contraindication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Depakote, specifically haematological disorders (see section 4.8 Undesirable Effects).

4.7 Effects on ability to drive and use machines
Patients should be warned of the risk of transient drowsiness, especially in cases of polytherapy or association with benzodiazepines (see section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

4.8 Undesirable effects
The following adverse events have been described from experience of sodium valproate in epilepsy; no other adverse event that could be specifically associated with the use of Depakote in the treatment of manic episodes have been identified.

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 Special 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 Special Warnings).

Gastrointestinal disorders: (nausea, gastalgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote Tablets with or after food.

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. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy 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 anticonvulsants, notably phenobarbital or topiramate. 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, but they 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 Depakote should be discontinued. Very rare cases of hyponatraemia have been reported.

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.

Bone marrow failure, including red cell aplasia.

Agranulocytosis.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Depakote 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:** Rash rarely occurs with Depakote. 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 more curly than previously. Hirsutism and acne have been very rarely reported.

**Reproductive system and breast disorders:** Amenorrhea 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 Depakote therapy, but the mode of action is as yet unclear. Very rare cases of enuresis have been reported.
Immune system disorders: Angioedema, Drug Rash with Eosinophilia, Systemic Symptoms (DRESS) syndrome, and 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

Signs of acute 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 functions and metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels in epileptic patients. Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic, including cardio-respiratogastric 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.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptic, ATC code: N03AG01
Depakote exerts its effects mainly on the central nervous system.

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

The effectiveness of Depakote in acute mania was demonstrated in two, 3-week, double-blind, placebo-controlled trials conducted in bipolar patients. Depakote was initiated at a dose of 250mg tid and subsequently titrated up to a maximum daily dose not exceeding 2500mg; the concomitant use of a benzodiazepine was allowed during the first 10 days of treatment to manage associated symptoms such as severe agitation.
Pharmacological studies have demonstrated activity in experimental models of animal behaviour in mania.

5.2 Pharmacokinetic properties

Following oral administration of Depakote the absolute bioavailability of valproic acid approaches 100%. Mean terminal half life is about 14 hours, steady state conditions usually being achieved within 3 to 4 days. Peak plasma concentrations are achieved within 3 to 5 hours. Administration with food increases $T_{max}$ by about 4 hours but does not modify the extent of absorption.

Depakote is extensively metabolised in the liver with less than 3% of an administered dose excreted unchanged in the urine. Principal metabolites found in urine are those originating from $\beta$-oxidation (up to 45% of the dose) and glucuronidation (up to 60% of the dose). Plasma clearance ranges from 0.4 to 0.6L/h and is independent of hepatic blood flow.

Plasma protein binding of Depakote ranges from 85 to 94% over plasma drug concentrations of 40 to 100 mcg/ml. It is concentration-dependent and the free fraction increases non-linearly with plasma drug concentration.

In elderly patients and those with liver cirrhosis (including alcoholic), acute hepatitis or renal failure the elimination of valproic acid is reduced. Reduction in intrinsic clearance and protein binding are reported. Thus, monitoring of total concentrations may be misleading and dosage adjustment may need to be considered according to clinical response.

Haemodialysis reduces serum valproic acid concentrations by about 20%.

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

Depakote 250mg:
Colloidal silica, hydrated, Starch pregelatinised, Povidone, Titanium dioxide (E171), Talc, Hypromellose phthalate, Diacetylated monoglycerides, Sunset yellow aluminium lake (E110), Vanillin.

Depakote 500mg:
Colloidal silica, hydrated, Starch pregelatinised, Povidone, Titanium dioxide (E171), Talc, Hypromellose phthalate, Diacetylated monoglycerides, Ponceau 4R aluminium lake (E124), Indigo carmine aluminium lake (E132), Vanillin.
6.2 **Major incompatibilities**

Not applicable.

6.3 **Shelf life**

3 years.

6.4 **Special precautions for storage**

None.

6.5 **Nature and contents of container**

Aluminium/aluminium blister packs containing 90 tablets.

6.6 **Special precautions for disposal**

No special requirements

7 **Marketing authorisation holder**

Sanofi-aventis
One Onslow Street
Guildford
Surrey
GU1 4YS

8 **Marketing authorisation holder**

Depakote 250 mg: 04425/0199
Depakote 500 mg: 04425/0200

9 **Date of the first authorisation or renewal**

Date of first authorisation:
Depakote 250mg and 500mg: 4 February 2009

Date of latest renewal:
Depakote 250mg: 1 June 2009
Depakote 500mg: 24 March 2009

10 **Date of revision of the text**

12 November 2010

**Legal status**

POM