- ANTIEPILEPTIC DRUG, DRUG FOR MANIA AND MANIC STATE, DRUG FOR MIGRAINE -

DEPAKENE®-R Tablets 100mg
DEPAKENE®-R Tablets 200mg

<Sodium valproate sustained-release product>

Prescription drug*

<table>
<thead>
<tr>
<th>Storage</th>
<th>100 mg Tablets</th>
<th>200 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store at room temperature.</td>
<td>Approval No. 22400AMX00869</td>
<td>Approval No. 22400AMX00870</td>
</tr>
<tr>
<td>Expiration date</td>
<td>Date of listing in the NHI reimbursement price June 2013</td>
<td>Date of listing in the NHI reimbursement price June 2013</td>
</tr>
<tr>
<td>Do not use after the expiration date indicated on the package.</td>
<td>Date of initial marketing in Japan January 1991</td>
<td>Date of initial marketing in Japan January 1991</td>
</tr>
<tr>
<td></td>
<td>Date of latest reexamination December 1996</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Additional indication Mania and manic phase of manic-depressive psychosis: September 2002</td>
<td>Prophylaxis of migraine attack: June 2011</td>
</tr>
</tbody>
</table>

* Caution: Use only pursuant to the prescription of a physician, etc.

CONTRAINDICATIONS (DEPAKENE-R is contraindicated in the following patients.)

1. Patients with serious hepatic disorder [Hepatic disorder may be intensified and become fatal.]
2. Patients receiving treatment with carbapenem antibiotics (panipenem/betamipron, meropenem hydrate, imipenem hydrate/cilastatin sodium, biapenem, doripenem hydrate, tebipenem pivoxil) [See Drug Interactions.]
3. Patients with urea cycle disorder [Serious hyperammonemia may occur.]

RELATIVE CONTRAINDICATIONS (As a general rule, DEPAKENE-R is contraindicated in the following patients. If the use of DEPAKENE-R is considered essential, it should be administered with care.)

Pregnant women, or women who may possibly be pregnant (See Use during Pregnancy, Delivery or Lactation.)

DESCRIPTION

1. Composition

<table>
<thead>
<tr>
<th>Brand name</th>
<th>DEPAKENE-R Tablets 100mg</th>
<th>DEPAKENE-R Tablets 200mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>100 mg of sodium valproate (JP) in one tablet</td>
<td>200 mg of sodium valproate (JP) in one tablet</td>
</tr>
</tbody>
</table>

2. Product description

DEPAKENE-R Tablets are sustained-release tablets composed of matrix as their core and of sustained-release film coating the matrix.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>DEPAKENE-R Tablets 100mg</th>
<th>DEPAKENE-R Tablets 200mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm)</td>
<td>8.3</td>
<td>10.6</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>5.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>0.26</td>
<td>0.52</td>
</tr>
<tr>
<td>Surface</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage form</td>
<td>White sugar-coated tablets</td>
<td>White sugar-coated tablets</td>
</tr>
<tr>
<td>ID code</td>
<td>KH113 (on tablets and PTP sheets)</td>
<td>KH114 (on tablets and PTP sheets)</td>
</tr>
</tbody>
</table>

Stability: DEPAKENE-R Tablets are sugar coated tablets, unlikely to suffer sudden deterioration of quality by absorption of moisture.

INDICATIONS

1. Treatment of various types of epilepsy (petit mal, focal seizure, psychomotor seizure and mixed seizure), and treatment of personality and behavior disorders resulting from epilepsy (moroseness, irascibility, etc.)
2. Treatment of mania and manic phase of manic-depressive psychosis
3. Prophylaxis of migraine attack
<Precautions>

[Prophylaxis of migraine attack]
In acute treatment, this drug should be administered only to patients who have migraine associated problems in their daily life.

DOSAGE AND ADMINISTRATION
1. Treatment of various types of epilepsy (petit mal, focal seizure, psychomotor seizure and mixed seizure), and treatment of personality and behavior disorders resulting from epilepsy (moroseness, irascibility, etc.)
2. Treatment of mania and manic phase of manic-depressive psychosis
   The usual dosage for oral use is 400 - 1,200 mg of sodium valproate daily in 1 - 2 divided doses. The dosage may be adjusted according to the patient's age and symptoms.
3. Prophylaxis of migraine attack
   The usual dosage for oral use is 400 - 800 mg of sodium valproate daily in 1 - 2 divided doses. The dosage may be adjusted according to the patient's age and symptoms provided that the daily dosage should not exceed 1,000mg of sodium valproate.

PRECAUTIONS
1. Careful Administration (DEPAKENE-R should be administered with care in the following patients.)
   (1) Patients with hepatic dysfunction or a history of impaired hepatic function [Hepatic dysfunction may be exacerbated by administration of this product.]
   (2) Patients with a history of hypersensitivity to drugs
   (3) Patients with mania or manic phase of manic-depressive psychosis who have attempted suicide or have suicidal thoughts [Symptom may be exacerbated.]
   (4) Patients with suspected urea cycle disorder [Serious hyperammonemia may occur.]
      1) Patients with a history of encephalopathy of unknown origin or coma of unknown origin.
      2) Patients with a family history of urea cycle disorder or infant death of unknown origin.

2. Important Precautions
   (1) Teratogenicity due to administration of this product has been shown. Therefore, in case of use in women of child-bearing potential, the teratogenicity should be explained to them, and the appropriateness for the use of this product should be judged carefully. (See Use during Pregnancy, Delivery or Lactation.)
   (2) In case of discontinuation of administration in patients with epilepsy, careful approach should be used, such as gradually reducing dosage, since radical reduction of the dosage or discontinuation of administration during treatment with this product may cause precipitated status of epilepticus. In addition, particular caution should be exercised in elderly or debilitated patients.
   (3) Since this product fails to remit headache attack, in case of the occurrence of migraine attack during administration of this product, drug for headache attack should be administered as needed. Patients should be fully informed on it prior to administration of this product.
   (4) During administration of this product, the patient’s condition should be closely monitored. In case problems in patient’s daily life were solved by disappearance/relief of the occurrence of headache attack, this product should be discontinued and the necessity for continuous administration of this product should be considered. If symptom of the patient is not improved, administration should not be continued aimlessly.
   (5) Since serious hepatic damage may occur (usually within the initial 6 months after the start of treatment), patients should be carefully observed by performing hepatic function test periodically in the initial 6 months. Even after that, it is recommended to perform hepatic function test periodically so long as the treatment is continued. Since consciousness disturbance may suddenly develop in association with hepatic damage, appropriate measures should be immediately taken if symptoms of that sort are found.
   (6) During treatment with this product, it is recommended to perform renal function test and hematological examination periodically.
   (7) For patients with suspected urea cycle disorder, it should be considered to perform examination such as amino acid analysis before administration of this product. Such patients should be carefully observed by paying attention to the fluctuation of ammonia value.
   (8) Since this product may induce drowsiness, lowering of attentiveness, mental concentration and reflex motor activities, patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as operating machinery or driving a car.
   (9) The sustained-release property of these preparations is produced by pharmaceutically regulating the rate of dissolution of sodium valproate, and this product should remain in the gastrointestinal tract for a certain time after administration. Therefore, it is necessary to observe patients with serious diarrhea, because blood concentration may not rise satisfactorily in those patients.
   (10)Cautions should be exercised in case of switching to this product in the patients on treatment with another sodium valproate product, because blood concentration of sodium valproate may fluctuate by the replacement.
3. Drug Interactions

(1) Contraindications for coadministration (DEPAKENE-R Tablets should not be coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem antibiotics</td>
<td>Epileptic seizure may recur.</td>
<td>Blood concentration of valproate is reduced.</td>
</tr>
<tr>
<td>Panipenem/betamipron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CARBENIN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem hydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem hydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>/cyrastatin sodium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(TIENTUM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biapenem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(OMEGACIN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doripenem hydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(FINIBAX)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tebipenem Pivoxil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ORAPENEM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>The effects of valproate may be potentiated.</td>
<td>These drugs inhibit the metabolism mediated by liver cytochrome P-450, resulting in the elevation of the blood concentration of valproate.</td>
</tr>
<tr>
<td>Cimetidine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(2) Precautions for coadministration (DEPAKENE-R Tablets should be administered with care when coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>The effects of valproate may be reduced, while the effects of barbiturates may be potentiated.</td>
<td>The blood concentration of valproate is reduced, and valproate causes elevation of the blood concentration of barbiturates.</td>
</tr>
<tr>
<td>Phenobarbital, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>The effects of valproate may be reduced, while the effects of these drugs may be potentiated or reduced.</td>
<td>The blood concentration of valproate is reduced, and valproate causes elevation or reduction of the blood concentration of these drugs.</td>
</tr>
<tr>
<td>Phenitoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>The effects of these drugs may be potentiated.</td>
<td>Valproate causes elevation of the blood concentration of these drugs.</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clobazam</td>
<td>The effects of valproate may be potentiated.</td>
<td>The blood concentration of valproate is elevated by unknown mechanism.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>It was reported that the elimination half-life of this drug was doubled.</td>
<td>The glucuronidation reactions of the drugs compete in the liver.</td>
</tr>
<tr>
<td>Salicylates</td>
<td>The effects of valproate may be potentiated.</td>
<td>The blood concentration of free valproate is elevated, and the metabolism of valproate is inhibited.</td>
</tr>
<tr>
<td>Aspirin, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>The effects of these drugs may be potentiated.</td>
<td>Valproate causes elevation of the blood concentration of free type of these drugs.</td>
</tr>
<tr>
<td>Diazepam, etc. Warfarin potassium</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Adverse Reactions

- Various types of epilepsy and personality and behavior disorder resulting from epilepsy

In the clinical studies before approval and in the post-marketing drug use surveillance, 341 adverse reactions including abnormalities in laboratory data were reported in 254 of 3,919 patients (6.5%).

The most frequently observed adverse reactions were hyperammonemia in 35 cases (0.9%), somnolence or sleepiness in 34 (0.9%), nausea or vomiting in 29 (0.7%), Al-P elevation in 14 (0.4%), leukopenia or neutropenia in 17 (0.4%), thrombocytopenia in 11 (0.3%), eosinophilia in 11 (0.3%), weight increase or obesity in 11 (0.3%) and ataxia in 10 (0.3%). (at the end of reexamination)

- Mania, manic phase of manic-depressive psychosis and prophylaxis of migraine attack

Since this product was approved for the indication of mania, manic phase of manic-depressive psychosis and prophylaxis of migraine attack as a prescription drug applicable to “Management of prescription drugs related to off-label use (Notification of MHLW)”, any investigation to show the incidence of adverse reactions was not performed in Japan.

(1) Clinically significant adverse reactions

1) Since serious hepatic disorder such as fulminant hepatitis, jaundice or fatty liver may occur, patients should be monitored carefully by periodical examination. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

2) Since consciousness disturbance associated with hyperammonemia may occur, patients should be monitored carefully by periodical examination of ammonia value. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

3) Since hemolytic anemia, pure red cell aplasia, pancytopenia, serious thrombocytopenia or granulocytopenia may occur, patients should be monitored carefully. If any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

4) Since acute pancreatitis may occur, administration of this drug should be discontinued and appropriate measures should be taken if symptoms such as drastic
abdominal pain, fever, nausea and vomiting develop or increases of pancreatic enzymes are recognized.

5) Since interstitial nephritis or Fanconi’s syndrome may occur, patients should be monitored carefully. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

6) Since toxic epidermal necrolysis (TEN) or oculomucocutaneous syndrome (Stevens-Johnson syndrome) may occur, patients should be monitored carefully. If any abnormalities are observed, administration should be discontinued, and appropriate measures should be taken.

7) Since hypersensitivity syndrome may occur, patients should be monitored carefully. If patients present with rash, pyrexia or other initial symptoms which are followed by swollen glands, hepatic function disorder, increased white blood cell count, increased eosinophil count, appearance of atypical lymphocytes or other abnormalities, administration should be discontinued, and appropriate measures should be taken. Precautions are required for potential relapse or protraction of symptoms including rash, pyrexia and hepatic function disorder.

8) Since cerebral atrophy, dementia-like symptoms (amnesia, disorientation, speech disorder, hypokinesia, reduced intelligence, apathy, etc.) or parkinsonian syndrome (resting tremor, rigidity, abnormal posture and gait, etc.) may occur, patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. Most patients can recover from these symptoms in one to two months by discontinuing administration.

9) Since rhabdomyolysis may occur, patients should be carefully monitored. If myalgia, weakness, increase of CK (CPK), increase of myoglobin in the blood and urine, etc. are recognized, administration should be discontinued and appropriate measures should be taken.

10) Since inappropriate antidiuretic hormone secretion (SIADH) may occur, patients should be carefully monitored. If hyponatraemia, blood hyposmosis, increased urine sodium, hyperthensuria, etc. occur, water restriction or other appropriate measures should be taken.

11) Since interstitial pneumonia or eosinophilic pneumonia may occur, immediately examinations such as chest X-ray and computed tomography should be conducted if coughing, dyspnoea and fever, etc. are recognized. If interstitial pneumonia or eosinophilic pneumonia is suspected, administration should be discontinued and appropriate measures such as treatment with adrenal corticosteroid should be taken.

(2) Other adverse reactions
Since the following adverse reactions may occur, the patients should be monitored carefully. If any of these signs is observed, appropriate measures, such as reducing the dose or withdrawing administration, should be taken.

5. Use in the Elderly
1. Valproate is highly bound to plasma albumin. Blood concentration of free drug may be increased in elderly patients due to a reduction in plasma albumin level, so this drug should be administered with care by paying special attention to the dosage.
2. Since radical reduction of the dosage or discontinuation of administration in patients with epilepsy during treatment with this product may cause precipitated status epilepticus, this drug should be administered cautiously in elderly patients with epilepsy.
3. No definitive evidences have been obtained for the safety and efficacy in elderly patients in clinical studies for the purpose of prophylaxis of migraine attack in Japan and abroad.

6. Use during Pregnancy, Delivery or Lactation
(1) DEPAKENE-R Tablets should be used in pregnant women and women who may possibly be pregnant, only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [An epidemiological study has found that women who received valproate during early pregnancy gave birth to a higher percentage of infants with spina bifida compared with the general population. In addition, it has been reported that women who had received valproate gave birth to infants with heart malformations such as ventricular septal defect, external malformations such as...]

Note) “Depression” is based on reports from abroad, and the other reactions are based on spontaneous reports in Japan.
polydactyly, cleft palate and hypospadias, and other malformations. It has been reported that women who had received valproate had neonates with peculiar features (frontal protrusion, dissociated eyes, flat nose, shallow and long philtrum, thin lips, etc.).]

(2) If use of this product during pregnancy is judged to be essential, coadministration with other drugs should be avoided as far as possible. [An epidemiological study has found that women who had received valproate concomitantly with other antiepileptics (particularly carbamazepine) gave birth to a higher percentage of deformed infants compared with the single use population.]

(3) Respiratory disorder, hepatic damage and hypofibrinogenemia may occur in neonates of women who received valproate during pregnancy.

(4) This product has been reported to cause hypoglycemia or withdrawal syndrome (nervousness, hypertonus, convulsions, vomiting) in neonates in association with administration during pregnancy.

(5) In an overseas observational study that enrolled pregnant women with epilepsy on antiepileptic drugs, intelligence quotient (IQ) scores of their children (n=224) at 6 years of age were compared by treatment. The IQ score (mean; 95% confidence interval) was reported to be lower after exposure to valproate (98; 95–102) compared with lamotrigine (108; 105–111), phenytoin (109, 105–113), and carbamazepine (106; 103–109). The mean IQ score in children exposed to valproate below 1,000 mg/day (median dose in the study) was 104 (99–109) and that in children exposed to valproate above 1,000 mg/day was 94 (90–99). 1)

(6) An overseas observational study reported that 508 children exposed to valproate during pregnancy had an increased risk for autism spectrum disorder compared with 655,107 children not exposed to valproate (adjusted hazard ratio, 2.9 [95% confidence interval, 1.7–4.9]). 2)

(7) Animal studies (in mice) have shown that valproate may contribute to congenital malformations in neonates by inhibiting metabolism of folic acid.

(8) Nursing mothers should discontinue breast feeding during treatment with this product. [Animal studies have shown that valproate is excreted in breast milk.]

7. Pediatric Use

1. The safety of this product in low-birth-weight babies, newborns has not been established. (There is insufficient clinical data.)

2. No definitive evidences have been obtained for the safety and efficacy in children in clinical studies for the purpose of prophylaxis of migraine attack in Japan and abroad.

8. Overdosage

Symptoms: It has been reported that overdosage of this drug by accidents or for suicide attempt caused consciousness disturbance (somnolence or coma), spasm, respiratory depression, hyperammonemia or cerebral edema. Deaths by overdose have been reported in other countries. In case of sustained-release drugs, onset of these symptoms may be delayed.

Treatment: If the patient has a clear consciousness and normal swallowing, rinse out the stomach as soon as possible. Give a cathartic and activated charcoal, promote urine excretion, and conduct usual supportive or palliative therapy. If necessary, perform direct blood perfusion or blood dialysis. Naroxon has been reported to be beneficial in this case.

9. Precautions concerning Use

(1) Patients should be instructed not to chew the tablet but to swallow it with water.

(2) White residue of this product is excreted in feces.

(3) Precautions regarding dispensing:

In the case of press-through packages (PTPs), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may penetrate the esophageal mucosa, leading to severe complications such as mediastinitis.]

10. Other Precautions

Pooled analyses of 199 placebo-controlled clinical trials of antiepileptic drugs (AEDs) including this drug for the patients with epilepsy, psychiatric diseases and other diseases in abroad showed that patients randomized to one of the AEDs had approximately twice the risk of suicidal thinking or behavior compared to patients randomized to placebo (AEDs group: 0.43%, placebo group: 0.24%), and the number of such patients in the AEDs group was larger by 1.9 per 1000 than placebo group (95% CI: 0.6 – 3.9). In addition, in the subgroup of patients with epilepsy, it was larger by 2.4 per 1000 than placebo group.

PHARMACOKINETICS

Pharmacokinetic characters of valproate

- Pharmacokinetic parameters (Referred to the data in foreign literature)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>About 100% (for all dosage forms)</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>&gt;90% (saturated binding at the concentrations more than about 100 μg/mL)</td>
</tr>
<tr>
<td>Distribution volume</td>
<td>0.1–0.4 L/kg (approximately equivalent to extracellular liquid)</td>
</tr>
<tr>
<td>Total clearance</td>
<td>6–8 mL/hr/kg (healthy adults: 16–60 years old)</td>
</tr>
<tr>
<td></td>
<td>13–18 mL/hr/kg (children with epilepsy: 3–16 years old, single-drug administration)</td>
</tr>
<tr>
<td>It was reported that the total clearance of the elderly is not different from that of adults, but the clearance of unbound drug of the elderly is lower than that of adults.</td>
<td></td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>1–3% (unchanged drug)</td>
</tr>
</tbody>
</table>

* *Absorption rate is assumed to be 100%.
Factors affecting total clearance

Total clearance of valproate is mainly affected by hepatic clearance and plasma unbinding rate. If a drug with a possible influence on main metabolic pathway is concomitantly used, administration should be carefully conducted. Since barbiturates, phenitoin, and carbamazepine are considered to promote the metabolism of valproate, careful attention is required for concomitant use (See Drug Interactions). When protein binding rate is decreased, it is considered to promote the metabolism of valproate, but concentration of the unbound drug is not decreased at steady state.

Effective blood concentration: 40–120 µg/mL

The effective blood concentration for various types of clearance and plasma unbinding rate. If a drug with a Total clearance of valproate is mainly affected by hepatic concentration at 6, 12 and 24 hrs after administration over a longer time owing to controlled dissolution (controlled dissolution tablets could maintain more stable blood concentration than conventional tablets) but concentration of the unbound drug is not decreased at steady state.

Table: Pharmacokinetic parameters of DEPAKENE R Tablets

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cmax (µg/mL)</th>
<th>Tmax (hr)</th>
<th>T1/2 (hr)</th>
<th>Vd (L)</th>
<th>AUCl∞(µg.hr/mL)</th>
<th>CL (L/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting dose</td>
<td>27.9 ± 5.3</td>
<td>10.26 ± 1.51</td>
<td>12.92 ± 3.34</td>
<td>14.00 ± 2.03</td>
<td>863 ± 271</td>
<td>0.79*</td>
</tr>
<tr>
<td>Post-meal dose</td>
<td>31.4 ± 5.3</td>
<td>8.95 ± 1.08</td>
<td>12.18 ± 4.03</td>
<td>12.84 ± 1.35</td>
<td>843 ± 262</td>
<td>0.83*</td>
</tr>
</tbody>
</table>

* CL was calculated from Vd and Kel. mean ± S.D., n=8

1. Absorption

(1) Single-dose administration

Changes with time of the serum concentration of valproate after DEPAKENE R Tablets (sustained-release; 200 mg) and DEPAKENE Tablets (not sustained-release; 200 mg) have been orally administered in a single dose of 3 tablets (total 600 mg) to 8 healthy adults, are shown in the following figure (measured by gas chromatography).

In comparison with DEPAKENE Tablets, DEPAKENE R Tablets could maintain more stable blood concentration over a longer time owing to controlled dissolution (concentration of valproate at 6, 12 and 24 hrs after administration was 28.0, 28.8 and 16.3 µg/mL respectively in the post-meal dose group, and 22.9, 27.4 and 16.8 µg/mL in the fasting dose group), and showed stable absorption unaffected by meals.

The pharmacokinetic parameters calculated by using 1-compartment model of DEPAKENE R Tablets are as follows.

(2) Repeated administration

The pattern of change in plasma concentration of valproate was studied with oral administration of three DEPAKENE R Tablets (600 mg) twice a day repeated 15 times and six tablets (1,200 mg) once a day repeated 8 times to 6 healthy adults each (measured by gas chromatography).

At the dose of 600 mg b.i.d., the plasma concentration reached a steady state in 6 to 7 days, and Cmax and Cmin after the final administration were 103.8 ± 10.9 and 85.4 ± 7.6 µg/mL respectively. Change with time in plasma concentration after 8-day repeated administration at 1,200 mg once daily is as shown below. It reached the steady state in 7 days, and Cmax and Cmin after the final administration were 103.9 ± 25.9 and 61.8 ± 15.7 µg/mL respectively.

2. Distribution

- Permeability and transfer

Blood-brain barrier permeability

Blood-placenta barrier permeability

Transfer into milk

Concentration in brain: 6.8–27.9% (vs concentration in plasma)

Concentration in umbilical blood: 1.7 times (vs concentration in maternal blood)

Concentration in milk: 3–6% (vs concentration in blood)
1. Results of Developmental Trials

• Protein binding rate

<table>
<thead>
<tr>
<th>Concentration (µg/mL)</th>
<th>Binding rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>91.39 ±0.72</td>
</tr>
<tr>
<td>50</td>
<td>91.36 ±0.20</td>
</tr>
<tr>
<td>100</td>
<td>88.63 ±0.72</td>
</tr>
<tr>
<td>150</td>
<td>85.52 ±0.74</td>
</tr>
<tr>
<td>200</td>
<td>80.03 ±0.37</td>
</tr>
</tbody>
</table>

By equilibrium dialysis method (at 37°C for 3 hours) mean±S.D.

3. Metabolism and Excretion

Valproate is almost entirely metabolized in the liver. After a single administration of DEPAKENE-R Tablets or DEPAKENE Tablets (600 mg) to 6 healthy adults, there was no difference between groups in the total amount of the drug excreted in urine, and the amount reached to about 60% (as valproate) of the dosage within 5 days. This drug was excreted in urine mainly as 3-keto-valproate, which was followed by glucuronide conjugate, 3-OH-valproate, PGA (2-propyl-glutaric acid), 4-OH-valproate, 5-OH-valproate, 4-keto-valproate, cis-2-en-valproate and then by trans-2-en-valproate. Practically no unchanged valproate, 3-en-valproate or 4-en-valproate was detected in urine. Pharmacologically, 2-en-valproate and 4-en-valproate are active, though less potent than the parent drug.

CLINICAL STUDIES

• Various types of epilepsy and personality and behavior disorders resulting from epilepsy

1. Results of Developmental Trials

(1) General clinical studies

The clinical efficacy of DEPAKENE-R Tablets (sustained-release preparation) was evaluated in 36 institutions in Japan by replacing DEPAKENE Tablets (conventional preparation) one to three times daily with DEPAKENE-R Tablets one to two times daily without change in the dosage.

The rate of overall improvement was 42.5% (171/402) for “markedly improved” and 45.0% (181/402) for “improved”; that is, 87.6% for “improved” or better evaluations.

In comparison of the two preparations, DEPAKENE-R Tablets was as good as or better than DEPAKENE Tablets in many cases (see the table below).

The reduction in dosing frequency in association with the switching from DEPAKENE Tablets to DEPAKENE-R Tablets was from twice daily to once daily in 217 cases, from three times daily to twice daily in 80 cases, from twice daily to twice daily in 52 cases, from three times daily to once daily in 44 cases and other changes in 9 cases.

(2) Crossover comparison trial

The equivalency in clinical efficacy between DEPAKENE Tablets given twice a day and DEPAKENE-R Tablets given once a day was evaluated in a group study of 30 institutions in Japan by the crossover method. DEPAKENE-R Tablets in respect to overall improvement and usefulness were judged to be equivalent to or better than DEPAKENE Tablets in 98.9% (94/95).

2. Post-marketing Drug Use Surveillance (See the table.)

Fresh cases (1,013 cases), which had not used sodium valproate preparation before DEPAKENE-R Tablets, were selected from a total of 3,035 cases enrolled in the post-marketing drug use surveillance (from September 28, 1990 to September 27, 1994) after the approval. Among these fresh cases, the types of seizure listed in the international classification of epileptic seizures of 1981 were picked up, and the improvement rate of them is shown below.

• Improvement rate by seizure type in fresh cases to DEPAKENE-R Tablets

<table>
<thead>
<tr>
<th>International Classification of Epileptic Seizures (1981)</th>
<th>Improvement rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[Improved or better cases/ Total cases]</td>
</tr>
<tr>
<td>Generalized seizures</td>
<td></td>
</tr>
<tr>
<td>Absence seizure</td>
<td>119/125 (95.2)</td>
</tr>
<tr>
<td>Myoclonic seizure</td>
<td>20/27 (74.1)</td>
</tr>
<tr>
<td>Complex partial seizure</td>
<td>29/36 (80.6)</td>
</tr>
<tr>
<td>Tonic seizure</td>
<td>98/109 (89.9)</td>
</tr>
<tr>
<td>Tonic-clonic seizure</td>
<td>340/393 (86.5)</td>
</tr>
<tr>
<td>Atonic seizure</td>
<td>13/19 (68.4)</td>
</tr>
<tr>
<td>Partial seizures</td>
<td></td>
</tr>
<tr>
<td>Simple partial seizure</td>
<td>55/71 (77.5)</td>
</tr>
<tr>
<td>Complex partial seizure</td>
<td>142/174 (81.6)</td>
</tr>
<tr>
<td>Secondly generalized seizure</td>
<td>135/181 (74.6)</td>
</tr>
</tbody>
</table>

• Mania and manic phase of manic-depressive psychosisis

Clinical studies for this indication have not been performed in Japan.

The outline of results of two double-blind studies that were assessed for the approval in the USA are as follows:

1) A double-blind study which compared valproate, lithium and placebo for 3 weeks was performed on 179 patients with bipolar affective disorder. As the results, the ratio of “markedly improved” (improvement of 50% or more on the mania rating scale) was 48% in valproate group and 49% in lithium group, and the results were significantly better than that of placebo group (25%). The common adverse events in valproate group were only vomiting and pain.
2) A double-blind placebo controlled study of valproate investigated the safety and efficacy in 36 patients with bipolar affective disorder who did not respond or were not tolerable to lithium. As the results, the change rate of median total score for the mania rating scale, the main efficacy assessment item, in valproate group (54%) was significantly higher than that in placebo group (5%). No adverse events in valproate group were significantly more frequent than those in placebo group.

Note) No definitive evidences have been obtained for long-term use more than 3 weeks of valproate in patients with mania or manic phase of manic-depressive psychosis in clinical studies in Japan and abroad.

PHARMACOLOGY

1. Pharmacological effects
(1) Valproate suppresses maximal electric shock (in mice, rats and rabbits), strychnine convulsion (in mice), picrotoxin convulsion (in mice), audiogenic seizure (in rats), anoxia seizure (in mice), pentetorasol seizure (in mice and rabbits) and bemegride convulsion (in mice).
(2) Valproate suppresses light sensitive convulsion (in baboons) and audiogenic seizure (in mice), which are the models of generalized epilepsy.
(3) Valproate suppresses cobalt focal epilepsy and Kinding convulsion (in cats), which are the models of partial epilepsy.
(4) Valproate suppresses discharge in the rear of hippocampus and convulsive discharge in the tonsillar nucleus (in rabbits).
(5) Valproate suppresses sensitively the potentiation of microfibrillation in the muscle elicited by stimulating the formatio reticularis of the mesencephalon (in rabbits).
(6) Valproate significantly suppresses excessive spontaneous motility caused by concomitantly administered chloridiazepoxide and dexamphetamine, which is considered the models of mania (in mice and rats).

2. Mechanism of action
It has been noted that the administration of valproate produces elevation of GABA and dopamin concentrations in the brain, as well as acceleration of serotonin metabolism. From these findings, it has been inferred that the efficacy of valproate originates in activation of the inhibitory systems in the brain through the action of neurotransmitter. The promotion of GABA neurotransmission is also considered to contribute to antimaniac effect and prophylaxis of migraine attack.

PHYSICOCHEMISTRY

Nonproprietary name: Sodium Valproate
Chemical name: Monosodium 2-propylpentanoate
Molecular formula: C₈H₁₅NaO₂ = 166.19

Chemical structure:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CO}_2\text{Na} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Description: Sodium valproate occurs as a white crystalline powder with a characteristic odor and a slight bitter taste. This product is hygroscopic (so much hygroscopic that it gradually deliquesces in the air)

Solubility: It is very soluble in water, freely soluble in ethanol (99.5) and in acetic acid (100).

Partition coefficient: \[\log P_{\text{OCT}} = 0.26\]

[measured by flask shaking method using n-octanol/pH7.4 buffered solution]

PACKAGING

DEPAKENE-R Tablets 100mg:
- Boxes of 100 (10 tablets × 10) and 1,000 (10 tablets × 100) tablets in press-through packages
- Bottles of 1,000 tablets

DEPAKENE-R Tablets 200mg:
- Boxes of 100 (10 tablets × 10), 1,000 (10 tablets × 100) and 3,000 (10 tablets × 300) tablets in press-through packages
- Bottles of 1,000 tablets

REFERENCES

REQUEST FOR LITERATURE OR INQUIRY ABOUT PRODUCT INFORMATION SHOULD BE MADE TO:
Medical Information Office
Kyowa Hakko Kirin Co., Ltd.
6-1, Ohtemachi 1-chome, Chiyoda-ku, Tokyo
100-8185 Japan
0120-850-150 (toll free)
Tel: 03-3282-0069, Fax: 03-3282-0102
Open: 9:00-17:30 (except Saturday, Sunday, national holidays and company holidays)

MANUFACTURED AND DISTRIBUTED BY:
Kyowa Hakko Kirin Co., Ltd.
1-6-1, Ohtemachi, Chiyoda-ku, Tokyo, Japan