

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use divalproex sodium extended-release tablets safely and effectively. See full prescribing information for divalproex sodium extended-release tablets for oral administration.

Divalproex Sodium Extended-Release Tablets

Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

- Hepatotoxicity, including fatalities, usually during first 6 months of treatment. Children under the age of 2 years are at considerably higher risk of fatal hepatotoxicity. Monitor patients closely, and perform liver function tests prior to therapy and at frequent intervals thereafter (5.1).
- Teratogenicity, including neural tube defects (5.2)
- Pancreatitis, including fatal hemorrhagic cases (5.3)

RECENT MAJOR CHANGES

Warnings and Precautions (5.8, 5.10, 5.12, 5.13, 5.14, 5.15) 3/2008
Pediatric Use (8.4) 3/2008

INDICATIONS AND USAGE

Divalproex sodium extended-release tablets are indicated for:

- Monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures (1.2)
- Prophylaxis of migraine headaches (1.3)

DOSAGE AND ADMINISTRATION

- Divalproex sodium extended-release tablets are intended for once-a-day oral administration. Divalproex sodium extended-release tablets should be swallowed whole and should not be crushed or chewed.
- Complex Partial Seizures: Start at 10 to 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day to achieve optimal clinical response; if response is not satisfactory, check valproate plasma level; see full prescribing information for conversion to monotherapy (2.2). The maximum recommended dosage is 60 mg/kg/day (2.2).
- Absence Seizures: Start at 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizure control or limiting side effects (2.2). The maximum recommended dosage is 60 mg/kg/day (2.2).
- Migraine: The recommended starting dose is 500 mg/day for one week, thereafter increasing to 1000 mg/day (2.3).

DOSAGE FORMS AND STRENGTHS

Tablets: 250 mg and 500 mg (3)

CONTRAINDICATIONS

- Hepatic disease or significant hepatic dysfunction (4, 5.1)
- Known hypersensitivity to the drug (4, 5.9)
- Urea cycle disorders (4, 5.4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: monitor liver function tests (5.1)
- Teratogenic effects: weigh divalproex sodium extended-release tablets benefits of use during pregnancy against risk to the fetus (5.2)
- Pancreatitis: divalproex sodium extended-release tablets should ordinarily be discontinued (5.3)

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ADVERSE REACTIONS

- Epilepsy
- Migraine

FULL PRESCRIBING INFORMATION**WARNING: LIFE-THREATENING ADVERSE REACTIONS**

Hepatotoxicity: Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Children under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When divalproex sodium extended-release tablets are used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

These incidents usually have occurred during the first 6 months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months (See *Warnings and Precautions* (5.1)).

Teratogenicity: Valproate can produce teratogenic effects such as neural tube defects (e.g., spina bifida). Accordingly, the use of divalproex sodium extended-release tablets in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g., migraine) is contemplated. (See *Warnings and Precautions* (5.2)).

An information sheet describing the teratogenic potential of valproate is available for patients (See Patient Counseling Information (17.1)).

Pancreatitis: Cases of life threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative therapy for the underlying medical condition should be initiated as clinically indicated (See *Warnings and Precautions* (5.3)).

1 INDICATIONS AND USAGE**1.2 Epilepsy**

Divalproex sodium extended-release tablets are indicated as monotherapy and adjunctive therapy in the treatment of adult patients and pediatric patients down to the age of 10 years with complex partial seizures that occur either in isolation or in association with other types of seizures. Divalproex sodium extended-release tablets are also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures in adults and children 10 years of age or older, and adjunctively in adults and children 10 years of age or older with multiple seizure types that include absence seizures. Simple absence is defined as very brief clauding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

1.3 Migraine

Divalproex sodium extended-release tablets are indicated for prophylaxis of migraine headaches in adults.

- Thrombocytopenia; monitor platelet counts and coagulation tests (5.5)
- Hyperammonemia and Hyperammonemic encephalopathy: measure ammonia level if unexplained lethargy and vomiting or changes in mental status, and also with concomitant topiramate use; consider discontinuation of valproate therapy (5.4, 5.6, 5.7)
- Hypothermia: Hypothermia has been reported during valproate therapy with or without associated hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate (5.8)

- Multi-organ hypersensitivity reaction; discontinue divalproex sodium extended-release tablets (5.9)
- Somnolence in the elderly can occur. Divalproex sodium extended-release tablets dosage should be increased slowly and with regular monitoring for fluid and nutritional intake (5.11)

ADVERSE REACTIONS

- Most common adverse reactions (reported $\geq 5\%$) reported in adult studies are nausea, somnolence, dizziness, vomiting, asthenia, abdominal pain, dyspepsia, rash, diarrhea, increased appetite, tremor, weight gain, back pain, alopecia, headache, fever, anorexia, constipation, diplopia, amblyopia/blurred vision, ataxia, nystagmus, emotional lability, thinking abnormal, anorexia, flu syndrome, infection, bronchitis, rhinitis, ecchymosis, peripheral edema, insomnia, nervousness, depression, pharyngitis, dyspnea, tinnitus (6.2, 6.3, 6.4).

- Most common, drug-related adverse reactions (reported in $> 5\%$ and twice the rate of placebo) reported in a controlled pediatric mania study are nausea, upper abdominal pain, somnolence, increased ammonia, gastritis and rash.

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. toll free at 1-877-448-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088, or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Hepatic enzyme-inducing drugs (e.g., phenytoin, carbamazepine, primidone, phenobarbital, rifampin) can increase valproate clearance, while enzyme inhibitors (e.g., felbamate) can decrease valproate clearance. Therefore increased monitoring of valproate and concomitant drug concentrations and dose adjustment is indicated whenever enzyme-inducing or inhibiting drugs are introduced or withdrawn (7.1)
- Aspirin, carbapenem antibiotics: Monitoring of valproate concentrations are recommended (7.1)
- Coadministration of valproate can affect the pharmacokinetics of other drugs (e.g., diazepam, ethosuximide, lamotrigine, phenytoin) by inhibiting their metabolism or protein binding displacement (7.2)
- Dosage adjustment of amitriptyline/nortriptyline, warfarin, and zidovudine may be necessary if used concomitantly with divalproex sodium extended-release tablets (7.2)
- Topiramate: Hyperammonemia and encephalopathy (5.7, 7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Divalproex sodium extended-release tablets can cause congenital malformations including neural tube defects (5.2, 8.1)
- Pediatric: Children under the age of 2 years are at a considerably higher risk of fatal hepatotoxicity (5.1, 8.4)
- Geriatric: reduce starting dose; increase dosage more slowly; monitor fluid and nutritional intake, and somnolence (5.11, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

DIVER-R:4ppb/PL-DIVER-R3
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*Sections or subsections omitted from the full prescribing information are not listed.

headaches. There is no evidence that divalproex sodium extended-release tablets are useful in the acute treatment of migraine headaches. Because it may be a hazard to the fetus, divalproex sodium extended-release tablets should be considered for women of childbearing potential only after this risk has been thoroughly discussed with the patient and weighed against the potential benefits of treatment. (See *Warnings and Precautions* (5.2), *Patient Counseling Information* (17.3)).

2 DOSAGE AND ADMINISTRATION

Divalproex sodium extended-release tablets are an extended-release product intended for once-a-day oral administration. Divalproex sodium extended-release tablets should be swallowed whole and should not be crushed or chewed.

2.2 Epilepsy

Divalproex sodium extended-release tablets are administered orally, and must be swallowed whole. As divalproex sodium extended-release tablets dosage is titrated upward, concentrations of clozapepam, diazepam, ethosuximide, lamotrigine, tolbutamide, phenobarbital, carbamazepine, and/or phenytoin may be affected (See *Drug Interactions* (7.2)).

Complex Partial Seizures

For adults and children 10 years of age or older.

Monotherapy (Initial Therapy)

Divalproex sodium extended-release tablets have not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendations regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 mcg/mL in females and 135 mcg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy

Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendations regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of divalproex sodium extended-release tablets therapy, or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy

Divalproex sodium extended-release tablets may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

In a study of adjunctive therapy for complex partial seizures in which patients were

This label may be updated by FDA.

For current labeling information, please visit <https://www.fda.gov/drugsatfda>

receiving either carbamazepine or phenytoin in addition to valproate, no adjustment of carbamazepine or phenytoin dosage was needed (See *Clinical Studies* (14.3)). However, since valproate may interact with other concurrently administered AEDs as well as other drugs, periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (See *Drug Interactions* (7)).

Simple and Complex Absence Seizures

The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentration for most patients with absence seizures is considered to range from 50 to 100 mcg/mL. Some patients may be controlled with lower or higher serum concentrations (See *Clinical Pharmacology* (12.3)). As divalproex sodium extended-release tablets dosage is titrated upward, blood concentrations of carbamazepine or phenytoin may be affected (See *Drug Interactions* (7.2)). Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

2.3 Migraine

Divalproex sodium extended-release tablets are indicated for prophylaxis of migraine headaches in adults.

The recommended starting dose is 500 mg once daily for one week, thereafter increasing to 1000 mg once daily. Although doses other than 1000 mg once daily of divalproex sodium extended-release tablets have not been evaluated in patients with migraine, the effective dose range of divalproex sodium delayed-release tablets in these patients is 500 to 1000 mg/day. As with other valproate products, doses of divalproex sodium extended-release tablets should be individualized and dose adjustment may be necessary, if a patient requires smaller dose adjustments than that available with divalproex sodium extended-release tablets, divalproex sodium delayed-release tablets should be used instead.

2.4 Conversion from Divalproex Sodium Delayed-Release Tablets to Divalproex Sodium Extended-Release Tablets

In adult patients and pediatric patients 10 years of age or older with epilepsy previously receiving divalproex sodium delayed-release tablets, divalproex sodium extended-release tablets should be administered once daily using a dose 8% to 20% higher than the total daily dose of divalproex sodium delayed-release tablets (Table 1). For patients receiving divalproex sodium delayed-release tablets total daily dose cannot be directly converted to divalproex sodium extended-release tablets, consideration may be given at the clinician's discretion to increase the patient's divalproex sodium delayed-release tablets total daily dose to the next higher dose before converting to the appropriate total daily dose of divalproex sodium extended-release tablets.

Table 1

Dose Conversion	Divalproex Sodium Delayed-Release Tablets Total Daily Dose (mg)	Divalproex Sodium Extended-Release Tablets (mg)
	500* to 625	750
	750* to 875	1000
	1000* to 1125	1250
	1250 to 1375	1500
	1500 to 1625	1750
	1750 to 2000	2000
	2000 to 2125	2500
	2125 to 2250	2750
	2250 to 2375	3000
	2375 to 2500	3250
	2500 to 2625	3500
	3000 to 3125	3000

* These total daily doses of divalproex sodium delayed-release tablets cannot be directly converted to an 8% to 20% higher total daily dose of divalproex sodium extended-release tablets because the required dosing strengths of divalproex sodium extended-release tablets are not available. Consideration may be given at the clinician's discretion to increase the patient's divalproex sodium extended-release tablets total daily dose to the next higher dose before converting to the appropriate total daily dose of divalproex sodium extended-release tablets.

There is insufficient data to allow a conversion factor recommendation for patients with divalproex sodium delayed-release tablets doses above 3125 mg/day.

Plasma valproate C_{max} concentrations for divalproex sodium extended-release tablets on average are equivalent to divalproex sodium delayed-release tablets, but may vary across patients after chronic use. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL) (See *Clinical Pharmacology* (12.2)).

2.5 General Dosing Advice

Dosing in Elderly Patients

Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Starting doses in the elderly lower than 250 mg can only be achieved by the use of divalproex sodium delayed-release tablets. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse reactions. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (See *Warnings and Precautions* (5.11)).

Dose Related Adverse Reactions

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males) (See *Warnings and Precautions* (5.5)). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

6.1 Irritation

Patients who experience GI irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

Compliance

Patients should be informed to take divalproex sodium extended-release tablets every day as prescribed. If a dose is missed it should be taken as soon as possible, unless it is almost time for the next dose. If a dose is skipped, the patient should not double the next dose.

3 DOSAGE FORMS AND STRENGTHS

The 250 mg tablets are white, film-coated, round, biconvex, unscored tablets debossed with "M 473" on one side of the tablet and blank on the other side. Each tablet contains divalproex sodium equivalent to 250 mg of valproic acid.

The 500 mg tablets are white, film-coated, oval, biconvex, unscored tablets debossed with "M 473" on one side of the tablet and blank on the other side. Each tablet contains divalproex sodium equivalent to 500 mg of valproic acid.

4 CONTRAINDICATIONS

- Divalproex sodium extended-release tablets should not be administered to patients with hepatic disease or significant hepatic dysfunction (See *Warnings and Precautions* (5.1)).
- Divalproex sodium extended-release tablets should not be administered to patients with known hypersensitivity to the drug (See *Warnings and Precautions* (5.9)).
- Divalproex sodium extended-release tablets are contraindicated in patients with known urea cycle disorders (See *Warnings and Precautions* (5.4)).

5 WARNINGS AND PRECAUTIONS**5.1 Hepatotoxicity**

Hepatic failure resulting in fatalities has occurred in patients receiving valproate. These incidents usually have occurred during the first 6 months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months (See *Warnings and Precautions* (5.1)).

Regarding the safety of valproate for use at doses above 60 mg/kg/day, no recommendations regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 mcg/mL in females and 135 mcg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy

Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendations regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of divalproex sodium extended-release tablets therapy, or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy

Divalproex sodium extended-release tablets may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

In a study of adjunctive therapy for complex partial seizures in which patients were

receiving either carbamazepine or phenytoin in addition to valproate, no adjustment of carbamazepine or phenytoin dosage was needed (See *Clinical Studies* (14.3)). However, since valproate may interact with other concurrently administered AEDs as well as other drugs, periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (See *Drug Interactions* (7)).

The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentration for most patients with absence seizures is considered to range from 50 to 100 mcg/mL. Some patients may be controlled with lower or higher serum concentrations (See *Clinical Pharmacology* (12.3)). As divalproex sodium extended-release tablets dosage is titrated upward, blood concentrations of carbamazepine or phenytoin may be affected (See *Drug Interactions* (7.2)). Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. (See *Boaed Warning and Use in Specific Populations* (8.1)).

5.3 Pancreatitis

Cases of life threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. In clinical trials, there were two cases of pancreatitis without alternative etiology in 2,416 patients, representing 1/344 patient-years experience. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, divalproex sodium extended-release tablets should ordinarily be discontinued. Alternative therapy for the underlying medical condition should be initiated as clinically indicated (See *Boaed Warning*).

5.4 Urea Cycle Disorders

Divalproex sodium extended-release tablets are contraindicated in patients with known urea cycle disorders (UCD). Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of divalproex sodium extended-release tablets therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pre- or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders (See *Contraindications* (4) and *Warnings and Precautions* (5.6)).

5.5 Thrombocytopenia

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose related. In a clinical trial of valproate as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets $\leq 75 \times 10^9/L$. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

5.6 Hyperammonemia

Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients

reflect potentially serious hepatotoxicity (See **Warnings and Precautions (5.1)**).

Endocrine
Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. **Abnormal thyroid function tests** (See **Warnings and Precautions (5.13)**). There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic
Acute pancreatitis including fatalities (See **Warnings and Precautions (5.3)**).

Metabolic
Hypernatremia (See **Warnings and Precautions (5.6)**), hyponatremia, and inappropriate ADH secretion).

There have been rare reports of Fanconi's syndrome occurring chiefly in children. Decreased cationic concentrations have been reported although the clinical relevance is undetermined. Hyperglycemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hypoglycemia.

Enteroantral
Erosions and antral tract infection.

Special Senses
Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

Other
Allergic reaction, anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, fever, and hyperthermia.

7 DRUG INTERACTIONS

7.1 Effects of Coadministered Drugs on Valproate Clearance

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving carbamazepine and antiepilepsy drugs. In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for Which a Potentially Important Interaction Has Been Observed

Aspirin
A study involving the coadministration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n = 6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The β -oxidation pathway consisting of 2-*E*-valproic acid, 3-*OH*-valproic acid, and 3-keto valproic acid was decreased from 23% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Whether or not the interaction observed in this study applies to adults is unknown, but caution should be observed if valproate and aspirin are to be coadministered.

Carbamazepine
A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbamazepine antiepileptics (carbamazepine, imipramine, meperidine) and may result in loss of seizure control. The mechanism of this interaction is not well understood. Serum valproic acid concentrations should be monitored frequently after initiating carbamazepine therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates (See **Warnings and Precautions (5.10)**).

Felbamate

A study involving the coadministration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n = 10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 mcg/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 mcg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Rifampin

A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is coadministered with rifampin.

Drugs for Which Either no Interaction or a Likely Clinically Unimportant Interaction Has Been Observed

Anticids

A study involving the coadministration of valproate 500 mg with commonly administered anticids (Zantac, Trisolvac, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine

A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg BID) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol

A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg BID) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine

Cimetidine and ranitidine do not affect the clearance of valproate.

7.2 Effects of Valproate on Other Drugs

Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrolase, and glucuronosyltransferases.

The following list provides information about the potential for an influence of valproate coadministration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs for Which a Potentially Important Valproate Interaction Has Been Observed

Amphetamine/Nortriptyline

Administration of a single oral 50 mg dose of amphetamine to 15 normal volunteers (ten males and five females) who received valproate (500 mg BID) resulted in a 21% decrease in plasma clearance of amphetamine and a 34% decrease in the net clearance of nortriptyline. Rare post-marketing reports of concurrent use of valproate and amphetamine resulting in an increased amphetamine level have been received. Concurrent use of valproate and amphetamine has rarely been associated with toxicity. Monitoring of amphetamine levels should be considered for patients taking valproate concomitantly with amphetamine. Consideration should be given to lowering the dose of amphetamine/nortriptyline in the presence of valproate.

Carbamazepine/Carbamazepine-10,11-Epoide

Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon coadministration of valproate and CBZ to epileptic patients.

Clozapem

The concomitant use of valproic acid and clozapem may induce absence status in patients with a history of absence type seizures.

Diazepam

Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Coadministration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n = 6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide

Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg/day) to healthy volunteers (n = 6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone.

Fentanyl

Valproate displaces fentanyl from its plasma albumin binding sites and inhibits its metabolism. Coadministration of valproate (1500 mg daily) increased the free fraction of fentanyl (10 mg) by 90% in healthy volunteers (n = 6). Plasma clearance and volume of distribution for free fentanyl were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Lamotrigine

In a steady-state study involving ten healthy volunteers, the elimination half-life of lamotrigine increased from 19 to 70 hours with valproate coadministration to 165% increase). The dose of lamotrigine should be reduced when coadministered with valproate. Skin reactions (such as Stevens-Johnson Syndrome and toxic epidermal necrolysis) has been reported with concomitant lamotrigine and valproate administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant valproate administration.

Phenobarbital

Valproate was found to inhibit the metabolism of phenobarbital. Coadministration of valproate (250 mg BID for 14 days) with phenobarbital to normal subjects (n = 6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single dose). The fraction of phenobarbital dose excreted unchanged in or excreted by 50% in presence of valproate. There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations, in all patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone

Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.

Phenytoin

Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its

hepatic metabolism. Coadministration of valproate (400 mg TID) with phenytoin (250 mg) in normal volunteers (n = 7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were increased by 25%.

In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Tolbutamide

From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20% to 32% which added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Warfarin

In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if valproic acid therapy is instituted in patients taking anticoagulants.

Zidovudine

In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 mg or 500 mg q8h); the half-life of zidovudine was unaffected.

Drugs for Which Either no Interaction or a Likely Clinically Unimportant Interaction Has Been Observed

Acetaminophen

Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.

Clozapem

In psychotic patients (n = 11), no interaction was observed when valproate was coadministered with clozapem.

Lithium

Coadministration of valproate (500 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers (n = 16) had no effect on the steady-state kinetics of lithium.

Lorazepam

Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers (n = 9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Oral Contraceptives

Administration of a single dose of ethinylestradiol (50 mcg)/levonorgestrel (250 mcg) to six women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

7.3 Topiramate

Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy (See **Contraindications and Warnings and Precautions (4, 5, 6, 5.7)**). Concomitant administration of topiramate with valproic acid has also been associated with hyperthermia in patients who have tolerated either drug alone. It has been reported to examine blood ammonia levels in patients in whom the onset of hyperthermia has been reported (See **Warnings and Precautions (5.6, 5.8)**).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category D.

Use of divalproex sodium extended-release tablets during pregnancy can cause congenital malformations including neural tube defects. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Divalproex sodium extended-release tablets should be considered for women of childbearing potential only after the risks have been thoroughly discussed with the patient and weighed against the potential benefits of treatment.

8.2 Lactation

Use of divalproex sodium extended-release tablets during pregnancy can cause congenital malformations including neural tube defects. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Divalproex sodium extended-release tablets should be considered for women of childbearing potential only after the risks have been thoroughly discussed with the patient and weighed against the potential benefits of treatment.

8.3 Nursing Mothers

Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy (See **Contraindications and Warnings and Precautions (4, 5, 6, 5.7)**). Concomitant administration of topiramate with valproic acid has also been associated with hyperthermia in patients who have tolerated either drug alone. It has been reported to examine blood ammonia levels in patients in whom the onset of hyperthermia has been reported (See **Warnings and Precautions (5.6, 5.8)**).

8.4 Pediatric Use

Divalproex sodium delayed-release tablets were studied in seven pediatric clinical trials. Two of the pediatric studies were placebo-controlled to evaluate the efficacy of divalproex sodium extended-release tablets for the indications of mania (150 patients aged 10 to 17 years, 76 of whom were on divalproex sodium extended-release tablets) and migraine (304 patients aged 12 to 17 years, 231 of whom were on divalproex sodium extended-release tablets).

A single 4-week outpatient, double-blind, placebo-controlled study of 150 patients aged 10 to 17 years of age with pediatric bipolar disorder was conducted to evaluate the efficacy of divalproex sodium extended-release tablets in the treatment of pediatric bipolar disorder. Initial daily doses of 15 mg/kg (max. 750 mg/day) and flexible dosing was used to achieve a clinical response or/and a target serum valproate level of 80 to 125 mcg/mL.

Patients with maximum allowable daily doses of 15 mg/kg tablets on stimulant medications at screening were allowed to continue and maintain current stimulant doses during the trial provided that doses were clinically stable. The trial efficacy endpoint was change from baseline on the YRS scale at final visit.

Results from the trial revealed that the mean maximum daily dose of 1457 mg (27.1

mg/kg) with a mean final serum valproate concentration of 80 mcg/mL was attained in this clinical trial. Efficacy was not established in this study.

Migraine Prophylaxis

A 26-week, randomized, placebo-controlled, parallel-group, four equal armed (placebo, 250 mg, 500 mg and 1000 mg) trial was performed to evaluate the efficacy of valproate sodium extended-release tablets in adolescent patients with migraine (304 patients, ages 12 to 17 years old). The study consisted of a 4 week baseline period followed by a 12 week experimental period (including an initial 2 week titration phase).

The primary endpoint was the reduction from baseline in the 4 week migraine headache rate. Placebo was compared to each dose.

Efficacy was not established in this migraine study.

Epilepsy

Divalproex sodium extended-release tablets have not been proven to be safe and effective for epilepsy in children less than 10 years of age.

Pediatric Safety

Two 6-month pediatric studies were conducted to evaluate the long-term safety of divalproex sodium extended-release tablets in the indication of mania (292 patients aged 10 to 17 years). Two 12-month pediatric studies were conducted to evaluate the long-term safety of divalproex sodium extended-release tablets in the indication of migraine (353 patients aged 12 to 17 years). One 12-month study was conducted to evaluate the safety of divalproex sodium capsules (sprinkle) in the indication of partial seizures (169 patients aged 3 to 10 years).

Safety Studies-Mania

Safety Study-Controlled Mania Trial

The incidence of treatment-emergent events for the pediatric population was based on the data from the single placebo-controlled clinical trial of divalproex sodium extended-release tablets in the treatment of manic or mixed episodes associated with bipolar disorder. Table 6 includes those adverse reactions reported for pediatric patients in the placebo-controlled mania trial where the incidence rate in the valproate-treated group was > 5% and was at least twice the rate than that for placebo patients.

Table 6

Common, Drug-Related Adverse Reactions Reported by > 5% of Divalproex Sodium Extended-Release Tablets-Treated Patients During Placebo Controlled Trials for Pediatric Acute Mania

Adverse Reaction—Preferred Term	Divalproex Sodium Extended-Release Tablets (N = 76)	Placebo (N = 74)
Nausea	9%	1%
Upper Abdominal Pain	8%	1%
Somnolence	7%	1%
Increased Ammonia	5%	0
Gastritis	5%	0
Rash	5%	1%

In addition, patients taking divalproex sodium extended-release tablets had a statistically significant 1.5 lbs mean increase in weight and 0.4 unit BMI mean increase from baseline values over placebo-treated patients.

Safety Study-Open-Label Mania Safety Data

In the two long-term (6-month) safety studies in pediatric patients (n = 292) between the ages of 10 and 17 years old, no clinically meaningful differences in the adverse reaction profile were observed when compared to adults.

The safety and tolerability of divalproex sodium extended-release tablets in pediatric patients were shown to be comparable to those in adults (See **Adverse Reactions (6.2, 6.3)**).

Safety Studies-Epilepsy (Open-Label)

Epilepsy and tolerability in this study was found comparable to that observed in adult patients.

Safety Studies-Migraine (Controlled and Open-Label)

Safety and tolerability in this study was found comparable to that observed in adult migraine studies.

Prior Safety Experience

Experience has indicated that pediatric patients under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the hepatogenous group of other antiepileptic drug monotherapies combined. The increased teratogenic risk from valproic acid in women with epilepsy is expected to be reflected in an increased risk in other indications (e.g., migraine or bipolar disorder).

Human Data

Congenital Malformations

The North American Antiepileptic Drug Pregnancy Registry reported 16 cases of congenital malformations among the offspring of 143 women with epilepsy who were exposed to valproic acid monotherapy during the first trimester of pregnancy at doses of approximately 1000 mg per day, for a prevalence rate of 10.7% (95% CI 6.3% to 16.9%). Three of the 149 offspring (2%) had neural tube defects and 6 of the 149 (4%) had less severe malformations. Among epileptic women who were exposed to other antiepileptic drug monotherapies during pregnancy (1,048 patients) the malformation rate was 2.9% (95% CI 2% to 4.1%). There was a 4-fold increase in congenital malformations among infants with valproic acid-exposed mothers compared with those treated with other antiepileptic monotherapies as a group (Odds Ratio 4.95% CI 2.1 to 7.4). This increased risk does not reflect a comparison versus any specific antiepileptic drug, but the risk versus the heterogeneous group of all other antiepileptic drug monotherapies combined.

The increased teratogenic risk from valproic acid in women with epilepsy is expected to be reflected in an increased risk in other indications (e.g., migraine or bipolar disorder).

Neural Tube Defects

The incidence of neural tube defects in the fetus is increased in mothers receiving valproate during the first trimester of pregnancy. The Centers for Disease Control (CDC) has estimated the risk of valproic acid exposed women having children with spina bifida to be approximately 1% to 2%. The American College of Obstetricians and Gynecologists (ACOG) estimates the general population risk for congenital neural tube defects as 0.14% to 0.2%.

Tests to detect neural tube and other defects using currently accepted procedures should be considered a part of routine prenatal care in pregnant women receiving valproate. Evidence suggests that pregnant women who receive folic acid supplementation may be at decreased risk for congenital neural tube defects in their offspring compared to pregnant women not receiving folic acid. Whether the risk of neural tube defects in the offspring of women receiving valproate specifically is reduced by folic acid supplementation is unknown. Dietary folic acid supplementation both prior to and during pregnancy should be routinely recommended to patients contemplating pregnancy.

Other Adverse Pregnancy Effects

Patients taking valproate may develop clotting abnormalities (See **Warnings and Precautions (5.5)**). A patient who had low fibrinogen when taking multiple anticonvulsants including valproate gave birth to an infant with fibrinogenemia who subsequently died of hemorrhage. If valproate is used in pregnancy, the clotting parameters should be monitored carefully.

Patients taking valproate may develop hepatic failure (See **Warnings and Precautions (5.1)**). Fatal hepatic failures, in a newborn and in an infant, have been reported following the maternal use of valproate during pregnancy.

Animal Data

Reproductive studies have demonstrated valproate-induced teratogenicity. Less severe malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals; however, neural tube closure defects were observed in mice exposed during organogenesis to maternal plasma valproate concentrations 2.3 times the upper limit of the human therapeutic range.

In pregnant rats, oral administration during organogenesis of a dose \geq 0.5 times the maximum recommended daily human dose on a mg/m² basis (MRHD) produced malformations (e.g., skeletal, cardiac, and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of \approx 3.4 times the upper limit of the human therapeutic range. Behavioral deficits have been reported in the offspring of rats given 0.5 times the MRHD on a mg/m² basis throughout most of pregnancy.

Valproate produced skeletal and visceral malformations in the offspring of pregnant rats given an oral dose approximately 2 times the MRHD on a mg/m² basis during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following an oral dose equal to the MRHD on a mg/m² basis during organogenesis. This dose resulted in peak maternal plasma valproate levels 2.8 times the upper limit of the human therapeutic range.

Registry

Women who become pregnant while using valproic acid should be encouraged to enroll in the AED (antiepileptic drug) Pregnancy Registry at 1-888-233-2334.

8.5 Geriatric Use

In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor.

Concomitant use of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from pre-existing medical illness and concomitant medication use among these patients.

A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence (See **Warnings and Precautions (5.1)**). The starting dose of valproate in elderly patients should be reduced to 50% of the starting dose. Discontinuation of valproate was associated with the maximum recommended daily human dose (MRHD). They were not used at a dose 0.4 times the MRHD.

8.6 Effect of Disease

Liver Disease

(See **Boed Warning, Contraindications (4)**, and **Warnings and Precautions (5)** and **Clinical Pharmacology (12.3)**). Liver disease impairs the capacity to eliminate valproate.

10 OVER DOSAGE

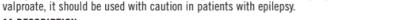
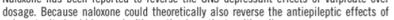
Over dosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from valproate levels as high as 2120 mcg/mL.

In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate over dosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

11 DESCRIPTION

Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis(2-propylenanato)divalproex sodium has the following structure:



Divalproex sodium occurs as a white crystalline powder with a characteristic odor.

Divalproex sodium extended-release 250 mg and 500 mg tablets are for oral administration. Divalproex sodium extended-release tablets contain divalproex sodium in a once-a-day extended-release formulation equivalent to 250 mg or 500 mg of valproic acid.

Inactive ingredients: amoxicillin hydroxide, colloidal anhydrous silica, colloidal silicon dioxide, dibutyl sebacate, ethylcellulose, hydroxyethyl cellulose, hydroxylose, oleic acid