

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}**Mylan-Divalproex**

divalproex sodium

Delayed-Release Tablets, 125 mg, 250 mg, 500 mg divalproex sodium, Oral

Manufacturer's Standard

Antiepileptic

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	10/2021
7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential	04/2021
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	03/2020

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Mylan-Divalproex (divalproex sodium) delayed-release tablets is indicated for:

Epilepsy

- use as sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal, and is useful in primary generalized seizures with tonic-clonic manifestations.
- use adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

In accordance with the International Classification of Seizures, simple absence is defined as a very brief clouding of the sensorium or loss of consciousness (lasting usually 2 to 15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

Acute Mania

- the treatment of the manic episodes associated with bipolar disorder (DSM-III-R).

The safety and efficacy of Mylan-Divalproex for long-term use in mania, that is for more than 3 weeks, has not been evaluated in controlled trials.

Mylan-Divalproex is not indicated for use as a mood stabilizer in patients under 18 years of age.

See 2 CONTRAINDICATIONS, and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity for statement regarding serious or fatal hepatic dysfunction.

1.1 Pediatrics

Pediatrics (< 18 years of age): When Mylan-Divalproex is used in children under the age of 2 years, it should be used with extreme caution and as a sole agent. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups. For a brief discussion, see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics. The safety and efficacy of Mylan-Divalproex for the treatment of acute mania has not been studied in individuals below the age of 18 years.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): The safety and efficacy of Mylan-Divalproex in elderly patients with epilepsy or mania has not been evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic and renal dysfunctions, and limited experience with Mylan-Divalproex in this population. For a brief discussion, see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics, 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations, Dosing in Elderly Patients and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics.

2 CONTRAINDICATIONS

Mylan-Divalproex (divalproex sodium) is contraindicated in:

- Patients with known hypersensitivity to the drug, any ingredient in the formulation or component of the container. For a complete listing of ingredients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- The treatment of epilepsy
 - in pregnancy unless there is no suitable alternative treatment (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program, and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).
 - in women of childbearing potential, unless the conditions of the Pregnancy Prevention Program are fulfilled (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program, and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).
- The treatment of bipolar disorder
 - in pregnancy (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program, and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).
 - in women of childbearing potential, unless the conditions of the Pregnancy Prevention Program are fulfilled (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program, and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).
- Patients with hepatic disease or significant hepatic dysfunction (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Hepatotoxicity and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity).
- Patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG; e.g., Alpers-Huttenlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- Patients with known urea cycle disorders (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Urea Cycle Disorders).
- Patients with known porphyria.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Hepatotoxicity:** Hepatic failure resulting in fatalities has occurred in patients receiving Mylan-Divalproex (divalproex sodium). These incidences usually occurred during the first 6 months of treatment with Mylan-Divalproex. Caution should be observed when administering Mylan-Divalproex to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of 2 years are at a considerably increased risk

of developing fatal hepatotoxicity, especially those on multiple anticonvulsants (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity and 8 ADVERSE REACTIONS, 8.1 Adverse Reaction Overview, Pediatric Population).

- **Female children/Women of childbearing potential/Pregnancy (Teratogenicity):** Mylan-Divalproex (divalproex sodium) can cause fetal harm. Because of its high teratogenic potential and risk of developmental disorders in infants exposed *in utero*, Mylan-Divalproex (divalproex sodium) should not be used in female children, in women of childbearing potential, and pregnant women unless alternative treatments are ineffective or not tolerated. In women planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Female children/Women of childbearing potential/Pregnancy and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Pregnancy Exposure Risk Related to Valproate and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Risk in the neonate).
- **Patients with Mitochondrial Disease:** There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase γ (POLG) gene (e.g. Alpers Huttenlocher Syndrome). Divalproex sodium is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder (see 2 CONTRAINDICATIONS). In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Mylan-Divalproex should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Mylan-Divalproex for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Patients with Mitochondrial Disease).
- **Pancreatitis:** Cases of life-threatening pancreatitis have been reported in both children and adults receiving divalproex sodium. Patients and guardians should be warned that abdominal pain, nausea, vomiting and/or anorexia can be symptoms of pancreatitis that require prompt medical attention. If pancreatitis is diagnosed, divalproex sodium should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Pancreatitis).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Epilepsy

Patients receiving combined antiepileptic therapy require careful monitoring when another agent is started, stopped or when the dose is altered (see 9 DRUG INTERACTIONS).

As the dosage of divalproex sodium is titrated upward, blood concentrations of phenobarbital, carbamazepine and/or phenytoin may be affected (see 9 DRUG INTERACTIONS).

Anti-epileptic drugs (AEDs) 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.

Any changes in dosage and administration, or the addition or discontinuance of concomitant drugs, should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

When changing therapy involving drugs known to induce hepatic microsomal enzymes (e.g., carbamazepine) or other drugs with valproate interactions, (see 9 DRUG INTERACTIONS), it is advisable to monitor serum valproate concentrations.

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. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, urinary tract infection, and other adverse events. Dose reductions or discontinuation of Mylan-Divalproex 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 clinical response (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics).

Dose-Related Adverse Events

The frequency of adverse events (particularly elevated liver enzymes and thrombocytopenia) may be dose related. The probability of thrombocytopenia appears to increase significantly at total valproate concentration of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males) (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Dose-related Adverse Events: Thrombocytopenia). Therefore, the benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse effects.

4.2 Recommended Dose and Dosage Adjustment

Epilepsy

Mylan-Divalproex (divalproex sodium) delayed-release tablets are administered orally. The recommended initial dosage 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 maximal recommended dosage is 60 mg/kg/day. When the total daily dose is 250 mg and over, it should be given in a divided regimen (Table 1).

Table 1. Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total Daily Dose (mg)	Dosage (mg) equivalent to valproic acid		
kg	lb		Dose 1	Dose 2	Dose 3
10 to 24.9	22 to 54.9	250	125	0	125
25 to 39.9	55 to 87.9	500	250	0	250
40 to 59.9	88 to 131.9	750	250	250	250
60 to 74.9	132 to 164.9	1,000	250	250	500
75 to 89.9	165 to 197.9	1,250	500	250	500

- **Therapeutic Blood Levels**

A good correlation has not been established between daily dose, total serum valproate concentration and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with epilepsy will range from 50 to 100 mcg/mL (350 to 700 micromole/L). Some patients may be controlled with lower or higher serum concentrations (see 7 WARNINGS AND PRECAUTIONS).

- **Conversion from DEPAKENE® to Mylan-Divalproex**

Mylan-Divalproex (divalproex sodium) delayed-release tablets dissociate to the valproate ion in the gastrointestinal tract. Divalproex sodium tablets are uniformly and reliably absorbed, however, because of the enteric coating, absorption is delayed by an hour when compared to DEPAKENE® (valproic acid).

The bioavailability of both types of divalproex sodium tablets (divalproex sodium and divalproex sodium ER) is equivalent to that of DEPAKENE® capsules.

In patients previously receiving DEPAKENE® therapy, Mylan-Divalproex should be initiated at the same daily dosing schedule. After the patient is stabilized on Mylan-Divalproex, a dosing schedule of two or three times a day may be elected in selected patients. Changes in dosage administration of divalproex sodium or concomitant medications should be accompanied by increased monitoring of plasma concentrations of valproate and other medications, as well as the patient's clinical status.

- **Female children, women of childbearing potential and pregnant women**

Divalproex sodium treatment must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program, and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Program (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program).

In the exceptional circumstance when valproate is the only treatment option during pregnancy in epileptic women, divalproex sodium should preferably be prescribed as monotherapy and at the lowest effective dose, if possible, as a prolonged release formulation to avoid high peak plasma concentrations. During pregnancy, the daily dose immediate release formulations should be divided into at least two single doses.

Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy. Therefore monotherapy should be

avored when possible.

Acute Mania:

Mylan-Divalproex is not indicated for the treatment of the symptoms of mania in patients under 18 years of age.

The recommended initial dose is 250 mg three times a day. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect or the desired range of plasma concentrations. However the safety and efficacy of Mylan-Divalproex for long-term use in mania, that is for more than 3 weeks, has not been evaluated in controlled trials (see 1 INDICATIONS).

In placebo-controlled trials, 84% of patients received and tolerated maximum daily doses of between 1,000 to 2,500 mg/day. The maximum recommended dosage is 60 mg/kg/day.

The relationship of plasma concentration to clinical response has not been established for divalproex sodium. In controlled clinical studies in acute mania, 79% of patients achieved and tolerated serum valproate concentrations between 50 and 125 mcg/mL.

- **Female children, women of childbearing potential and pregnant women**

Divalproex sodium treatment must be initiated and supervised by a specialist experienced in the management of mania. Mylan-Divalproex should not be used in pregnancy (see 2 CONTRAINDICATIONS). Mylan-Divalproex should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated and all conditions of the Pregnancy Prevention Program are fulfilled (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program, and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Program (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program).

In the exceptional circumstance when valproate is the only option for the treatment of epilepsy during pregnancy it should preferably be prescribed as monotherapy and at the lowest effective dose, and if possible, as a prolonged-release formulation to avoid high peak plasma concentrations. During pregnancy, the daily dose of immediate release formulations should be divided into at least two single doses.

Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy. Therefore monotherapy should be favored when possible.

4.4 Administration

Mylan-Divalproex may be taken with or without food.

Patients who experience gastrointestinal irritation may benefit from administration of the drug with food or by a progressive increase of the dose from the initial low level. The tablets should be swallowed without chewing. Co-administration of Mylan-Divalproex with food should cause no clinical problems in the management of patients with epilepsy.

4.5 Missed Dose

The patient should not abruptly stop taking their medication because of the risk of increasing their seizures.

If the patient misses a dose, they should not try to make up for it by doubling up on their next dose. They should take their next regularly scheduled dose and try not to miss any more doses.

5 OVERDOSAGE

Overdosage with divalproex sodium may result in somnolence, muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, hypotension, metabolic acidosis, heart block, deep coma and circulatory collapse/shock. Cases of intracranial hypertension related to cerebral oedema have been reported. Fatalities have been reported; however, patients have recovered from valproate levels as high as 2,120 mcg/mL.

The presence of sodium content in the valproate formulations may lead to hyponatremia when taken in overdose.

In a reported case of overdosage with divalproex sodium after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An electroencephalogram (EEG) recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

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 prevention of hypovolemia and the maintenance of adequate urinary output.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
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oral	delayed-release tablets / 125 mg	diacetylated monoglycerides, FD&C Red No. 40, hydroxypropylmethyl cellulose phthalate, povidone, pregelatinized starch (contains corn starch), silicon dioxide, talc, titanium dioxide, and vanillin.
	250 mg	diacetylated monoglycerides, FD&C Yellow No. 6, hydroxypropylmethyl cellulose phthalate, povidone, pregelatinized starch (contains corn starch), silicon dioxide, talc, titanium dioxide and vanillin.
	500 mg	diacetylated monoglycerides, FD&C Blue No. 2, D&C Red No. 30, hydroxypropylmethyl cellulose phthalate, povidone, pregelatinized starch (contains corn starch), silicon dioxide, talc, titanium dioxide and vanillin.

Mylan-Divalproex delayed-release tablets are formulated for oral administration containing divalproex sodium in three strengths: 125 mg, 250 mg and 500 mg.

Mylan-Divalproex 125 mg delayed-release tablets are supplied as salmon-pink, ovaloid, film-coated tablets, with the Mylan “M” logo printed on one side, and are available in bottles of 100 tablets.

Mylan-Divalproex 250 mg delayed-release tablets are supplied as peach, ovaloid, film-coated tablets, with the Mylan “M” logo printed on one side, and are available in bottles of 100 and 500 tablets.

Mylan-Divalproex 500 mg delayed-release tablets are supplied as pink, ovaloid, film-coated tablets, with the Mylan “M” logo printed on one side, and are available in bottles of 100 and 500 tablets.

7 WARNINGS AND PRECAUTIONS

Pregnancy Prevention Program:

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for major congenital malformations and neurodevelopmental disorders (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

Mylan-Divalproex is contraindicated in the treatment of epilepsy during pregnancy unless no other suitable alternative can be found, and in the treatment of bipolar disorder in pregnancy (see 2 CONTRAINDICATIONS).

- **Conditions of Pregnancy Prevention Program**

The prescriber must ensure that

- individual circumstances are evaluated in each case and discussed with the patient. This is to guarantee the patient’s engagement and understanding of the therapeutic options together with the risks and the measures needed to mitigate the risks.

- the potential for pregnancy is assessed for all female patients.
- the patient understands and acknowledges the risks of major congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment with valproate as deemed necessary by the patient or treating physician. It is recommended that testing be done following a missed period, the failure of the selected method of contraception or as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective and reliable contraception (see subsection contraception of this warning), without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy, or bipolar disorder.
- the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her physician if she becomes pregnant.
- the patient has received the patient guide.
- the patient has acknowledged that she has understood the risks associated with valproate use and necessary precautions to be taken during treatment (Annual Risk Acknowledgement Form).

These conditions also apply to women who are not currently sexually active unless the prescriber considers that there are compelling and convincing reasons to indicate that there is no risk of pregnancy.

- **Pharmacist or other health care professional must ensure that**
 - the patient card is provided with every valproate dispensing and that the patients understand its content.
 - the patients are advised not to stop valproate treatment and to immediately contact a specialist in case of planned or suspected pregnancy.
- **Female Children**
 - The prescriber must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child receiving valproate treatment experiences menarche.
 - The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of major congenital malformations and neurodevelopmental disorders including the

magnitude of these risks for children exposed to valproate *in utero*.

- In patients who have experienced menarche, the prescribing specialist must reassess the need for continuing valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the patient must use at least one effective and reliable method of contraception (preferably a user-independent form) or two complementary forms of contraception. Patient must also meet all other conditions of the Pregnancy Prevention Program. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

- **Pregnancy Test**

Pregnancy must be excluded **before** the start of treatment with valproate. Treatment **must not** be initiated in women of child bearing potential **without a negative plasma** pregnancy test result, confirmed by a health care provider, to rule out unintended use in pregnancy.

- **Contraception**

Women of childbearing potential who are prescribed valproate must use at least one form of effective and reliable contraception (preferably a user-independent form) or two complementary forms of contraception without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective and reliable contraception. At least 1 of these forms of contraception must be a primary form, which include tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and topical/injectable/insertable hormonal birth control products. Secondary or barrier forms of contraception include diaphragms, latex condoms, and cervical caps. A diaphragm and cervical cap must each be used with a spermicide.

Estrogen-containing hormonal contraceptives may result in decreased serum valproate levels and potentially lower valproate efficacy. Patients taking Mylan-Divalproex should be advised not to start or stop such products without consulting their physician. Prescribers should monitor valproate serum levels and clinical response when initiating or discontinuing estrogen-containing products (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant women and 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4).

- **Annual Treatment Reviews by a Specialist**

The specialist should, at least annually, review whether valproate is the most suitable treatment option for the patient. The specialist should discuss the Annual Risk Acknowledgement Form, at initiation of treatment and during each annual review and ensure that the patient has understood its content.

- **Pregnancy Planning**

For the epilepsy indication, if a woman is planning to become pregnant, a specialist, experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women). If switching is not possible, the woman should receive further counselling

regarding valproate risks for the unborn child to support her informed decision making regarding family planning.

For the bipolar disorder indication, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder, must be consulted. If needed, alternative treatment options should be considered. Treatment with valproate should be discontinued prior to conception, and before contraception is discontinued.

- **In Case of Pregnancy**

If a woman receiving valproate treatment becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative options. Patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in pre-natal medicine for evaluation and counselling regarding the exposed pregnancy (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

Where available, prenatal diagnostic testing to detect neural tube and other defects, should be offered to pregnant women receiving Mylan-Divalproex treatment.

- **Educational Materials**

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorization Holder has provided educational materials to reinforce related warnings and provide guidance regarding use of valproate in women of childbearing potential and details of the Pregnancy Prevention Program. A patient guide and patient card should be provided to all women of childbearing potential receiving valproate treatment.

A Risk Acknowledgement Form must be used at the time of treatment initiation and during each annual review of valproate treatment by the specialist, and when a woman is planning a pregnancy or has become pregnant. Specialist should reassess benefits and risks of valproate treatment and determine if the patient should continue to receive valproate therapy.

General:

Antiepileptic drugs (AEDs), including Mylan-Divalproex (divalproex sodium), should be withdrawn gradually to minimize the potential for seizures or increased seizure frequency (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

- **Interaction with Carbapenem Antibiotics**

Carbapenem antibiotics (ertapenem, imipenem, meropenem, doripenem) can reduce serum valproic acid concentrations to sub-therapeutic levels. This can result in loss of seizure control in epileptic patients or loss of efficacy in non-epileptics. In some cases of co-administration in epileptic patients, breakthrough seizures have occurred. Increasing valproic acid dose may not be sufficient to overcome this interaction. If co-administration is essential, serum valproic acid concentrations should be monitored daily after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4).

- **Effects of Valproate on HIV and CMV Viruses Replication**

There are *in vitro* studies that suggest valproate stimulates the replication of the Human

Immunodeficiency Virus and Cytomegalovirus (HIV and CMV) viruses under certain experimental conditions. The clinical relevance of these *in vitro* data is unknown. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

Carcinogenesis and Mutagenesis:

Long-term animal toxicity studies indicate that valproic acid is a weak carcinogen or promoter in rats and mice. The significance of these findings for humans is unknown at present (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and 16 NON-CLINICAL TOXICOLOGY, Genotoxicity).

Driving and Operating Machinery:

Mylan-Divalproex may produce central nervous system (CNS) depression, especially when combined with another CNS depressant, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Endocrine and Metabolism:

• Urea Cycle Disorders

Mylan-Divalproex (divalproex sodium) delayed-release tablet is contraindicated in patients with known urea cycle disorders. Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of Mylan-Divalproex in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to initiation of Mylan-Divalproex, evaluation for urea cycle disorders (UCD) should be considered in the following patients:

- those with a history of unexplained encephalopathy or coma, encephalopathy associated with protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine;
- those with signs and symptoms of UCD, for example, cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low blood urea nitrogen (BUN), protein avoidance;
- those with a family history of UCD or a family history of unexplained infant deaths (particularly males);
- those with other signs or symptoms of UCD. Patients receiving Mylan-Divalproex who develop symptoms of unexplained hyperammonemic encephalopathy should receive prompt treatment (including discontinuation of Mylan-Divalproex) and be evaluated for underlying urea cycle disorders (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia and Encephalopathy Associated with Concomitant use of Topiramate, Acetazolamide, Phenobarbital or Phenytoin).

• Hyperammonemia

Hyperammonemia has been reported in association with Mylan-Divalproex and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in

mental status, hyperammonemic encephalopathy should be considered as a possible cause and serum ammonia level should be measured. Hyperammonemia should also be considered in patients who present with hypothermia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypothermia). If serum ammonia is increased, Mylan-Divalproex should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Urea Cycle Disorders and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia and Encephalopathy Associated with Concomitant use of Topiramate, Acetazolamide, Phenobarbital or Phenytoin).

Asymptomatic elevations of serum ammonia are more common and, when present, require close monitoring of serum ammonia levels. If the elevation persists, discontinuation of Mylan-Divalproex should be considered.

- **Hyperammonemia and Encephalopathy Associated with Concomitant use of Topiramate, Acetazolamide, Phenobarbital or Phenytoin**

Concomitant administration of topiramate, acetazolamide, phenobarbital or phenytoin and divalproex sodium has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Hypothermia can also be a manifestation of hyperammonemia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypothermia). In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction.

It is not known if topiramate, acetazolamide, phenobarbital or phenytoin monotherapy is associated with hyperammonemia.

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, an interaction of topiramate, acetazolamide, phenobarbital or phenytoin and Mylan-Divalproex may exacerbate existing defects or unmask deficiencies in susceptible persons (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Urea Cycle Disorders and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia).

- **Hypothermia**

Hypothermia, defined as an unintentional drop in core body temperature to < 35°C (95°F), has been reported in association with divalproex sodium therapy both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with divalproex sodium after starting topiramate treatment or after increasing the daily dose of topiramate (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia, 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia and Encephalopathy Associated with Concomitant use of Topiramate, Acetazolamide, Phenobarbital or Phenytoin and 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4). Hypothermia may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels. Consideration should be given to stopping Mylan-Divalproex in patients who develop hypothermia (see 7 WARNINGS AND

PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia and Encephalopathy Associated with Concomitant use of Topiramate, Acetazolamide, Phenobarbital or Phenytoin).

Hematologic:

- **Thrombocytopenia**

Because of reports of thrombocytopenia, inhibition of the second phase of platelet aggregation, and abnormal coagulation parameters (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving Mylan-Divalproex be monitored for platelet count and coagulation parameters prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy (see also 7 WARNINGS AND PRECAUTIONS, Hematologic, Dose-related Adverse Events: Thrombocytopenia).

- **Dose-related Adverse Events: Thrombocytopenia**

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. In a clinical trial of divalproex sodium 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).

In addition, the findings from a crossover clinical trial conducted with divalproex sodium extended-release tablets, in 44 epilepsy patients, indicate that the frequency of treatment-emergent mild thrombocytopenia (platelet count between 100 to $150 \times 10^9/L$) was significantly higher after 12 weeks of treatment with divalproex sodium extended-release tablets than after 12 weeks of treatment with divalproex sodium (7 versus 3 low counts, respectively).

The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse events.

Hepatic/Biliary/Pancreatic:

- **Serious or Fatal Hepatotoxicity**

Hepatic failure resulting in fatalities has occurred in patients receiving divalproex sodium and its derivatives. These incidences usually occurred during the first 6 months of treatment with divalproex sodium. Caution should be observed when administering Mylan-Divalproex to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

Experience has indicated that children under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. The risk in this age group decreased considerably in patients receiving divalproex sodium as monotherapy. Similarly, patients aged 3 to 10 years were at somewhat greater risk if they received multiple anticonvulsants than those who received only divalproex sodium. Above

the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patients. No deaths have been reported in patients over 10 years of age who received divalproex sodium alone.

If Mylan-Divalproex is to be used for the control of seizures in children 2 years old or younger, it should be used with extreme caution and as a sole agent. In this patient population, concomitant use of salicylates and Mylan-Divalproex should be avoided due to the risk of liver toxicity. The benefits of therapy should be weighed against the risks (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics).

Serious or fatal hepatotoxicity may be preceded by nonspecific 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. Patients and parents should be instructed to report such symptoms. Because of the nonspecific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking Mylan-Divalproex.

Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 months of therapy, especially in patients at risk as described above (see also 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4). However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

In high-risk patients, it might also be useful to monitor serum fibrinogen and albumin for decreases in concentration and serum ammonia for increases in concentration. If changes occur, Mylan-Divalproex should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug. The frequency of adverse hepatic effects (particularly elevated liver enzymes) may increase with increasing dose. The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects (see 2 CONTRAINDICATIONS).

- **Patients with Mitochondrial Disease**

Valproate induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) (e.g., Alpers-Huttenlocher Syndrome) at a higher rate than those without these syndromes (see 2 CONTRAINDICATIONS).

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders.

In patients over two years of age who are clinically suspected of having a hereditary mitochondrial

disease, Mylan-Divalproex should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Mylan-Divalproex for the development of acute liver injury with regular clinical assessments and liver function test monitoring.

In the presence of significant hepatic dysfunction, suspected or apparent, Mylan-Divalproex should be discontinued and alternative therapy initiated. In some cases, hepatic dysfunction has progressed in spite of discontinuation of the drug (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

- **Pancreatitis**

Cases of life-threatening pancreatitis have been reported in both children and adults receiving Mylan-Divalproex. Some of the cases have been described as hemorrhagic with a 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 divalproex sodium. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2,416 patients, representing 1,044 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, Mylan-Divalproex should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Monitoring and Laboratory Tests:

Since Mylan-Divalproex may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy and whenever enzyme-inducing drugs are introduced or withdrawn (see 9 DRUG INTERACTIONS).

- **Monitoring Valproate Concentrations**

Protein binding of valproate is reduced in the elderly, in patients with renal impairment, and in the presence of other drugs (e.g., acetylsalicylic acid). Accordingly, measurements of plasma levels of valproate may be misleading in these patients, as actual drug exposure may be higher than measured values (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics, 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia, 7 WARNINGS AND PRECAUTIONS, Hematologic, Thrombocytopenia and 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4).

- **Medication Residue**

There have been rare reports of medication residue in the stool, some of which have occurred in the context of transient diarrhea or those with anatomic or functional gastrointestinal disorders with shortened transit time (e.g., ileostomy, colostomy, etc). It is recommended that patients with shortened gastrointestinal transit time be only given the immediate release formulation of valproate. Plasma valproate levels should be checked if a patient is experiencing uncontrolled and/or unexpected seizures. If clinically indicated, valproate should be gradually discontinued and alternative treatment considered.

Musculoskeletal/Rhabdomyolysis:

Rare cases of rhabdomyolysis, independent of neuroleptic malignant syndrome, have been reported to occur in patients treated with divalproex sodium. Cases have included renal failure and fatalities.

Patients should be carefully monitored for muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever or tea-coloured urine. Blood creatine phosphokinase (CPK) levels should be assessed in patients experiencing these symptoms and divalproex sodium therapy should be discontinued if markedly elevated CPK levels are measured or if the patient develops signs and symptoms indicative of rhabdomyolysis.

Caution should be exercised in prescribing Mylan-Divalproex to patients with predisposing/risk factors, including: prior history of muscular disorders such as CPT II deficiency (carnitine palmitoyltransferase type II); uncontrolled hypothyroidism; hepatic or renal impairment; concomitant medications that are known to be associated with rhabdomyolysis (eg statins, antipsychotics, diuretics, some antidepressants).

Neurologic:

- **Brain Atrophy**

There have been postmarketing reports of reversible and irreversible cerebral and cerebellar atrophy with neurological symptoms, in children, adults, and the elderly, receiving valproate therapy. A temporal relationship between valproate therapy and the development of cerebral atrophy and associated signs and symptoms was also demonstrated. In some cases, symptoms disappeared after valproate discontinuation but patients recovered with permanent sequelae (see 8 ADVERSE REACTIONS). The motor and cognitive functions of patients on valproate should be routinely monitored and drug should be discontinued in the presence of suspected or apparent signs of brain atrophy.

- **Neurological Problems in Children after *in utero* Exposure to Valproate**

Reports of cerebral atrophy with various forms of neurological problems including cognitive developmental delays psychomotor impairment and decreased IQ scores have been reported in children who were exposed *in utero* to valproate products (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Female children/Women of childbearing potential/Pregnancy and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Pregnancy Exposure Risk Related to Valproate and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Risk in the neonate).

- **Aggravated convulsions**

As with other antiepileptic drugs, some patients may experience a worsening of convulsion frequency and severity, or the onset of new types of convulsions with valproate. Postmarketing cases of serious aggravated seizures have been reported for valproic acid including status epilepticus and death. In case of aggravated convulsions, patients should be advised to consult their physician immediately.

Psychiatric:

- **Suicidal Behaviour and Ideation**

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs (AEDs), irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which AEDs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indication the treatment (AED or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (AED or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more AED). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on AEDs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (AED or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking AEDs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct AED treatment in both arms.

- **Behavioural Disorders**

There have been postmarketing reports of behavioural disorders, including aggression, agitation, abnormal behaviour, psychomotor hyperactivity, disturbance in attention, and learning disorders. Although patients of all ages were affected, including the elderly, a large number of cases were reported in children (see 8 ADVERSE REACTIONS, 8.1 Adverse Reaction Overview, Pediatric Population). There was no clear trend with respect to valproate dose. In some cases, patients improved or recovered following valproate discontinuation. Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorders and developmental delay have been reported from *in utero* exposure (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

Renal:

- **Renal Impairment**

Renal impairment is associated with an increase in the unbound fraction of valproate. In several studies, the unbound fraction of valproate in plasma from renally impaired patients was approximately double that for subjects with normal renal function. Accordingly, monitoring of total concentrations in patients with renal impairment may be misleading since free concentrations may be substantially elevated whereas total concentrations may appear to be normal. Hemodialysis in renally impaired patients may remove up to 20% of the circulating valproate.

Reproductive Health: Female and Male Potential:

- **Fertility**

Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women using valproate.

The effect of Mylan-Divalproex on testicular development in humans is unknown. See 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology, Fertility for results in animal studies.

Valproate administration has been associated with reduced semen quality in humans and thus may

impair fertility in men (see 8 ADVERSE REACTIONS). Discontinuation or dose reduction of valproate may be associated with the improvement of impaired male fertility markers and could be linked with successful conception, as observed in some case reports.

Sensitivity/Resistance:

- **Multi-organ Hypersensitivity Reaction**

Multi-organ hypersensitivity reactions have been rarely reported in close temporal association to the initiation of divalproex sodium therapy in adult and pediatric patients (median time to detection 21 days; range 1 to 40). Although there have been a limited number of reports, many of these cases resulted in hospitalization and at least one death has been reported. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations may include lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritus, nephritis, oliguria, hepato-renal syndrome, arthralgia, and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here may occur. If this reaction is suspected, Mylan-Divalproex should be discontinued and an alternative treatment started. Although the existence of cross sensitivity with other drugs that produce this syndrome is unclear, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

Skin:

- **Serious Skin Reactions**

The dose of lamotrigine should be reduced when co-administered with Mylan-Divalproex. Serious skin reactions (such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported with concomitant lamotrigine and divalproex sodium administration (see Lamotrigine Product Monograph for details on lamotrigine dosing with concomitant divalproex sodium administration).

7.1 Special Populations:

7.1.1 Pregnant Women

Female children/Women of childbearing potential/Pregnancy:

Mylan-Divalproex can cause fetal harm when administered to pregnant women. Divalproex sodium use during pregnancy is associated with an increased risk of severe birth defects such as neural tube defects (e.g., spina bifida), craniofacial defects, cleft palate, cardiovascular malformations (e.g., atrial septal defect), hypospadias, etc. In some cases, fatal outcomes have been reported (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Birth Defects).

Mylan-Divalproex should not be used to treat female children, women of childbearing potential, and pregnant women unless alternative treatments are ineffective or not tolerated. The benefit and risk should be carefully re-assessed, at least annually, at puberty, and urgently when a woman of childbearing potential plans a pregnancy or becomes pregnant. Since some of the congenital malformations occur in the first trimester of pregnancy before many women know that they are pregnant, all women of childbearing potential should be informed of the potential hazard to the fetus from exposure to Mylan-Divalproex. Women of childbearing potential must use at least one effective

and reliable method of contraception (preferably a user-independent form) or two complementary forms of contraception during treatment with Mylan-Divalproex (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program).

Valproate does not reduce the efficacy of hormonal contraceptives. However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Patients taking Mylan-Divalproex should be advised not to start or stop estrogen-containing products (including oral contraceptives) without consulting their physician. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4).

Pregnancy Exposure Risk Related to Valproate:

Both valproate adjunctive and monotherapy are frequently associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate may also be associated with a greater risk of congenital malformations than valproate monotherapy.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in pregnant women receiving Mylan-Divalproex.

- **Pregnancy Registry**

Pregnant patients taking Mylan-Divalproex should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the following website: <http://www.aedpregnancyregistry.org/>.

- **Pregnancy Prevention Program**

Information on the Pregnancy Prevention Program including educational resources, as well as to report suspected embryo-fetal exposure to valproate, can be found at the following website: <https://www.mylan.ca/en-ca/businesses/brand-specialty>.

If a woman is planning a pregnancy:

- For the **epilepsy indication**, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family.
- For the **bipolar disorder indication**, a specialist experienced in the management of bipolar disorder, must be consulted. Treatment with valproate should be discontinued prior to conception, and before contraception is discontinued. If needed, alternative treatment options should be considered planning (see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Pregnancy Exposure Risk Related to Valproate and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Risk in the neonate).

- **Pregnant Women**

Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy. Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Pregnancy Prevention Program).

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.

During pregnancy, maternal tonic-clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child. If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances, a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment);
- Consider the use of a prolonged release formulation of divalproex sodium, which may be preferable to immediate-release formulations in order to avoid high peak plasma concentrations.

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in pre-natal medicine for evaluation and counselling. Specialized prenatal monitoring should take place to detect possible occurrence of neural tube defects or other malformations. Folate supplementation (5 mg daily) before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However, available evidence does not suggest that folate can prevent birth defects or malformations due to valproate exposure.

- **Risk in the neonate**

Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors.

Afibrinogenemia has also been reported and can be fatal. However, this syndrome must be distinguished from the decrease of vitamin-K factors induced by phenobarbital and other enzymes. Therefore, in neonates, platelet count, plasma level of fibrinogen, coagulation tests and coagulation factors should be investigated.

Cases of hypoglycemia have been reported in neonates whose mothers have taken valproate during the third trimester of pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

Withdrawal syndrome (symptoms include: agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, tonic disorders, tremor, convulsions and feeding disorders) may occur, in the days following birth, in neonates whose mothers have taken valproate during the last trimester of pregnancy.

- **Birth Defects**

Summary

- Valproate can cause fetal harm when administered to pregnant women;
- Maternal valproate use can cause neural tube defects (e.g., spina bifida) and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations such as atrial septal defect, hypospadias, limb malformations such as club foot and polydactyly);
- The rate of congenital malformations among babies born to mothers using valproate monotherapy is about four times higher than the rate among babies born to epileptic mothers using other anti-epileptic monotherapies. This risk is dose-dependent but a threshold dose below which no risk exists cannot be established.

Data

Data described below were gained almost exclusively from women who received valproate to treat epilepsy. Data from Pregnancy Registries indicate an increased risk of congenital anomalies in infants exposed to divalproex sodium monotherapy during the first trimester of pregnancy as compared to other antiepileptic drugs. Based on Pregnancy Registry data and the United States Centers for Disease Control (CDC), the estimated risk of valproate-exposed women having children with spina bifida, oral clefts, neural tube defects, and hypospadias is approximately 1 to 2% as compared to the risk of spina bifida in the general population which is about 0.06 to 0.07%.

In a study using NAAED Pregnancy Registry data, 16 cases of major malformations following prenatal valproate exposure were reported among offspring of 149 enrolled women who used valproate during pregnancy. Three of the 16 cases were neural tube defects; the remaining cases included craniofacial defects, cardiovascular malformations and malformations of varying severity involving other body systems. The NAAED Pregnancy Registry has reported a major malformation rate of 10.7% in the offspring of women exposed to valproate monotherapy during pregnancy (average daily dose: 1000 mg; range: 500 – 2000 mg/day) as compared to major malformation rate of 2.9% among 1,048 epileptic women who received any other antiepileptic drug monotherapy during pregnancy. These data show a four-fold increased risk for any major malformation following valproate exposure *in utero* compared to the risk following exposure *in utero* to any other antiepileptic drug monotherapy.

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16-13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose-dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

In utero exposure to valproate may result in eye malformations that have been observed in conjunction with other congenital malformations. In most cases, valproate was taken as monotherapy during the whole pregnancy and not a specific trimester.

In utero exposure to various therapeutic doses of valproate, during any trimester of pregnancy, can also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect)

and/or to direct toxicity on the hearing function. All cases to date were reported as serious and included both unilateral and bilateral deafness or hearing impairment. When outcomes were reported, the majority of the cases remained unresolved. In 58% of the cases, the age of diagnosis of hearing impairment or deafness was within the first 4 weeks following birth. Monitoring of signs and symptoms of ototoxicity is recommended.

- **Risk of Neurological Problems from *in utero* Exposure**

- **Cerebral Atrophy**

Exposure *in utero* to valproate products has been associated with cerebral atrophy with varying degrees/manifestations of neurological compromise, including developmental delays and psychomotor impairment (see 8 ADVERSE REACTIONS and 7 WARNINGS AND PRECAUTIONS, Neurologic, Brain Atrophy).

- **Developmental Delays**

Available data to date show that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established. The exact gestational period for risk of these effects is uncertain and it is possible that the risk exists throughout the entire pregnancy.

Studies in preschool children exposed to valproate *in utero* show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

- **Decreased IQ**

Valproate can cause decreased Intelligence Quotient (IQ) scores in children following *in utero* exposure. Although it is not known exactly when during pregnancy cognitive effects in valproate-exposed children occur, there is a risk that it may occur early in pregnancy.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other antiepileptics. There is evidence in children exposed to valproate that the risk of intellectual impairment may be independent of maternal IQ.

- **Autism and/or Autism Spectrum Disorders**

There are limited data on long term outcomes. A population-based study was conducted in Denmark based on various national patient registries including the Danish Medical Birth Register. This study showed that children exposed to valproate *in utero* are at increased risk of autism spectrum disorders (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the children of unexposed epileptic women in the same study.

- **Attention Deficit Hyperactivity Disorder (ADHD)**

Another population-based study in Denmark was also conducted based on various national patient registries including the Danish Medical Birth Register. This study showed that children exposed to valproate *in utero* are at increased risk of developing ADHD compared to the children of unexposed

epileptic women in the same study. Data show that 8.4% of the children exposed to valproate *in utero* were diagnosed with ADHD compared to 3.2% of unexposed children in the same study.

Although available studies have some limitations, the weight of the evidence supports a causal association between valproate exposure *in utero* and subsequent adverse effects on neurodevelopment, including increases in the occurrence of autism spectrum disorders.

- **Coagulation Abnormalities**

There have been reported postmarketing cases of coagulation abnormalities in patients of all ages receiving valproate therapy. These include thrombocytopenia, hypofibrinogenemia, and/or decrease in other coagulation factors, which can lead to bleeding and other complications, especially in the cases of decrease in factors VII, VIII and XIII. These abnormalities may not necessarily be dose-dependent. Some of the hemorrhage manifestations may include mucosal bleeding (e.g., menorrhagia, epistaxis, hematuria, melena), easy-bruising, soft-tissue hematoma, hemarthrosis, and intracranial hemorrhage. Caution should be taken in patients taking valproate and anticoagulants and in cases of injury or surgery to avoid life-threatening or fatal bleeding (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Thrombocytopenia).

Pregnant women taking Mylan-Divalproex may also develop coagulation abnormalities, which may result in hemorrhagic complications in the neonate including death (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Thrombocytopenia). If Mylan-Divalproex is used in pregnancy, the coagulation parameters should be monitored carefully.

- **Hepatic Failure**

Hepatic failure, resulting in the death of a newborn and of an infant has been reported following the use of valproate during pregnancy.

- **Hypoglycemia**

Serious postmarketing reports of hypoglycemia have been received for neonates whose mothers received divalproex sodium treatment during pregnancy. In most cases, divalproex sodium was the only reported antiepileptic drug (AED). Most of these neonates also displayed other congenital anomalies including hypospadias, complex facial dysmorphism, limb anomalies, severe cardiac anomalies, etc. Therefore, if a decision has been made to use Mylan-Divalproex during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

- **Thyroid Gland Abnormalities**

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy. There have also been reported cases of increased serum thyroid stimulating hormone or decreased serum thyroxine levels in children receiving valproate therapy. In addition, there have been reported cases of hypothyroidism and hyperthyroidism in adults and children receiving valproate monotherapy.

- **Teratogenicity in Animals**

Animal studies have demonstrated valproic acid induced teratogenicity (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology), and studies in human females have demonstrated placental transfer of the drug. Increased frequencies of 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, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding 230 mcg/mL (2.3 times the upper limit of the human therapeutic range for epilepsy) during susceptible periods of embryonic development.

Administration of an oral dose of 200 mg/kg/day or greater (50% of the maximum human daily dose or greater on a mg/m² basis) to pregnant rats during organogenesis produced malformations (skeletal, cardiac and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of approximately 340 mcg/mL or greater (3.4 times the upper limit of the human therapeutic range for epilepsy or greater). Behavioural deficits have been reported in the offspring of rats given a dose of 200 mg/kg/day throughout most of pregnancy.

An oral dose of 350 mg/kg/day (approximately 2 times the maximum human daily dose on a mg/m² basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following administration of an oral dose of 200 mg/kg/day (equal to the maximum human daily dose on a mg/m² basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 mcg/mL (2.8 times the upper limit of the human therapeutic range for epilepsy).

7.1.2 Breast-feeding

Divalproex sodium is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of maternal serum concentrations. Women should not breastfeed during Mylan-Divalproex treatment and for one month after discontinuation of the drug. Based on literature and clinical experience, hematological disorders have been shown in breastfed newborns/infants of treated women.

7.1.3 Pediatrics

Experience has indicated that children under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity). When Mylan-Divalproex is 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 (see 2 CONTRAINDICATIONS).

Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Mylan-Divalproex should only be used after other anticonvulsants have failed. (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Patients with Mitochondrial Disease).

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproate concentrations. The variability in free fraction limits the clinical usefulness of monitoring total serum valproate concentrations. Interpretation of valproate concentrations in children should include consideration of factors that affect hepatic

metabolism and protein binding.

The safety and efficacy of Mylan-Divalproex for the treatment of acute mania has not been studied in individuals below the age of 18 years.

7.1.4 Geriatrics

Alterations in the kinetics of unbound valproate in the elderly indicate that the initial dosage should be reduced in this population (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

The safety and efficacy of Mylan-Divalproex in elderly patients with epilepsy and mania has not been evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic and renal dysfunctions, and limited experience with Mylan-Divalproex in this population.

A study of elderly patients revealed valproate-related somnolence and discontinuation of Mylan-Divalproex for this adverse event (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics, Somnolence in the Elderly). The starting dose should be reduced in elderly patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (see 4 DOSAGE AND ADMINISTRATION).

- **Somnolence in the elderly**

In a group of elderly patients (mean age 83 years old, n = 172), divalproex sodium doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. Compared to placebo a significantly higher number of valproate-treated patients had somnolence, and although not statistically significant, a higher number of valproate-treated patients experienced dehydration. Discontinuations for somnolence were also significantly higher in valproate-treated patients compared to placebo. In approximately one-half of the patients with somnolence, there was also associated reduced nutritional intake and weight loss. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid intake, dehydration, somnolence, urinary tract infection and other adverse events. Dose reductions or discontinuation of Mylan-Divalproex should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (see 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Epilepsy

The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since divalproex sodium delayed-release tablets has usually been used with other antiepileptics, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to divalproex sodium alone or to the combination of drugs.

Adverse events that have been reported with divalproex sodium from epilepsy trials, spontaneous reports, and other sources are listed below by system organ class.

Blood and Lymphatic System Disorders:	Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and hemorrhage (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Thrombocytopenia). Relative lymphocytosis, macrocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia, including macrocytic with or without folate deficiency, aplastic anemia, pancytopenia, bone marrow suppression, agranulocytosis and acute intermittent porphyria have been reported.
Cardiac Disorders:	Bradycardia
Ear and Labyrinth Disorders:	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.
Gastrointestinal Disorders:	<p>Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, constipation, gingival disorder (mainly gingival hyperplasia) and parotid gland swelling have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients. In some patients, many of whom have functional or anatomic (including ileostomy or colostomy) gastrointestinal disorders with shortened gastrointestinal transit times, there have been postmarketing reports of divalproex sodium extended-release tablets in the stool.</p> <p>There have been reports of acute pancreatitis, including rare fatal cases, occurring in patients receiving divalproex sodium (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Pancreatitis).</p>
General Disorders and Administration Site Conditions:	Edema of extremities, fever and hypothermia
Hepatobiliary Disorders:	Minor elevations of transaminases [e.g., serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT)] and lactate dehydrogenase (LDH) are frequent and appear to be dose-related. Occasionally, laboratory tests also show increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity).
Immune System Disorders:	Allergic reaction, anaphylaxis
Infections and Infestations:	Pneumonia and otitis media
Investigations:	Abnormal thyroid function tests (including both hyperthyroidism and hypothyroidism) (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Thyroid Gland Abnormalities and 9 DRUG

INTERACTIONS, 9.7 Drug-Laboratory Test Interactions).

Metabolism and Nutrition Disorders:

Hyperammonemia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperammonemia), hyponatremia, biotin deficiency/biotinidase deficiency and inappropriate antidiuretic hormone (ADH) secretion. There have been rare reports of Fanconi syndrome (proximal renal tubular dysfunction) occurring primarily in children. Decreased carnitine concentrations have been reported although the clinical relevance is undetermined. Hyperglycinemia (elevated plasma glycine concentration) has been reported and associated with a fatal outcome in a patient with pre-existing non-ketotic hyperglycinemia.

Anorexia with some weight loss and increased appetite with some weight gain have also been reported.

Obesity has been reported in post-marketing experience.

Musculoskeletal and Connective Tissue Disorders:

Weakness, rhabdomyolysis, and bone pain have been reported (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal/Rhabdomyolysis).

Reports have been received of decreased bone mass, potentially leading to osteoporosis and osteopenia, during long-term therapy with some anticonvulsant medications, including divalproex sodium. Some studies have indicated that supplemental calcium and vitamin D may be of benefit to patients who are on chronic divalproex sodium therapy.

A lupus erythematosus-like syndrome has been reported rarely.

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps):

Myelodysplastic syndrome in both adults and children (all children were on valproate monotherapy). In some cases in adults and/or children, myelodysplastic syndrome was reversible upon valproate discontinuation.

Nervous System Disorders:

Sedative effects have been noted in patients receiving divalproex sodium alone but occur most often in patients on combination therapy. Sedation usually disappears upon reduction of other antiepileptic medication.

Hallucination, ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes", tremor (may be dose-related), confusion, dysarthria, dizziness, hypesthesia, vertigo, incoordination, memory impairment, cognitive disorder, and extrapyramidal disorders including parkinsonism have been reported with the use of valproate. Rare cases of coma have been reported in patients receiving divalproex sodium alone or in conjunction with phenobarbital.

Encephalopathy, with or without fever or hyperammonemia, has been reported without evidence of hepatic dysfunction or inappropriate valproate plasma levels. Most patients recovered, with noted improvement of symptoms, upon discontinuation of the drug.

There have been postmarketing reports of reversible and irreversible cerebral and cerebellar atrophy associated with the use of valproate products. In some cases the patients recovered with permanent sequelae (see 7 WARNINGS AND

PRECAUTIONS, Neurologic, Brain Atrophy). Cerebral atrophy seen in children exposed to valproate *in utero* led to various forms of neurological events, including developmental delays and psychomotor impairment. Congenital malformations and developmental disorders have also been reported (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Female children/Women of childbearing potential/Pregnancy and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Pregnancy Exposure Risk Related to Valproate and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Risk in the neonate).

Aggravated convulsions (increase in number of seizures or appearance of new seizure type or worsening of seizures) have been reported in patients with epilepsy treated with valproate monotherapy.

Psychiatric Disorders: Emotional upset, depression, psychosis, aggression, psychomotor hyperactivity, hostility, agitation, disturbance in attention, abnormal behaviour, learning disorder and behavioural deterioration.

See 7 WARNINGS AND PRECAUTIONS, Psychiatric.

Renal and Urinary Disorders: Enuresis, urinary incontinence, acute renal failure, tubulointerstitial nephritis and urinary tract infection.

Reproductive System and Breast Disorders: There have been reports of irregular menses, secondary amenorrhea, breast enlargement and galactorrhea in patients receiving divalproex sodium. Hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased).

There have been post-marketing reports of aspermia, azoospermia, decreased sperm count, decreased spermatozoa motility, abnormal spermatozoa morphology and ultimately, infertility in male patients who received sodium valproate products (effects may be improved by dose reduction or discontinuation).

There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Respiratory, Thoracic and Mediastinal Disorders: Increased cough, pleural effusion

Skin and Subcutaneous Tissue Disorders: Transient and/or dose related alopecia (hair loss) and hair disorders (such as hair texture abnormal, hair colour changes, hair growth abnormal), have been observed. Skin rash, photosensitivity, generalized pruritus, erythema multiforme, Stevens-Johnson syndrome (SJS), and petechiae have rarely been noted.

Rare cases of Toxic Epidermal Necrolysis (TEN) have been reported including a fatal case of a 6 month old infant taking divalproex sodium and several other concomitant medications. An additional case of Toxic Epidermal Necrolysis resulting in death was reported in a 35 year old patient with AIDS taking several

concomitant medications and with a history of multiple cutaneous drug reactions.

Serious skin reactions have been reported with concomitant administration of lamotrigine and divalproex sodium (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4).

Cutaneous vasculitis has also been reported.

Nail and nail bed disorders have also been reported in post-marketing experience.

Divalproex Sodium Tablets versus Divalproex Sodium Extended Release Tablets

A 24 week cross-over study compared the safety and efficacy of divalproex sodium extended-release tablets administered once daily to that of equal doses of divalproex sodium tablets (administered twice daily or three times daily) in the treatment of adolescent and adult epileptic patients with generalized seizures (n=44). Two adverse events occurred in significantly more patients on divalproex sodium extended-release tablets than on divalproex sodium tablets: asthenia (15.9% versus 6.8% respectively) and treatment-emergent mild thrombocytopenia (16.2% versus 6.8%, respectively).

Bipolar Disorder

The incidence of adverse events has been ascertained based on data from two short-term (21 day) placebo-controlled clinical trials of divalproex sodium in the treatment of acute mania, and from 2 long-term (up to 3 years) retrospective open trials.

Most Commonly Observed

During the short-term placebo-controlled trials, the six most commonly reported adverse events in patients (n = 89) exposed to divalproex sodium were nausea (22%), headache (21%), somnolence (19%), pain (15%), vomiting (12%), and dizziness (12%).

In the long-term retrospective trials (634 patients exposed to divalproex sodium), the six most commonly reported adverse events were somnolence (31%), tremor (29%), headache (24%), asthenia (23%), diarrhea (22%), and nausea (20%).

Associated With Discontinuation of Treatment

In the placebo-controlled trials, adverse events which resulted in divalproex sodium discontinuation in at least one percent of patients were nausea (4%), abdominal pain (3%), somnolence (2%), and rash (2%).

In the long-term retrospective trials, adverse events which resulted in divalproex sodium discontinuation in at least one percent of patients were alopecia (2.4%), somnolence (1.9%), nausea (1.7%), and tremor (1.4%). The time to onset of these events was generally within the first two months of initial exposure to divalproex sodium. A notable exception was alopecia, which was first experienced after 3 to 6 months of exposure by 8 of the 15 patients who discontinued divalproex sodium in response to the event.

Pediatric Population

The safety profile of valproate in the pediatric population is comparable to adults, but some adverse reactions are more severe or principally observed in the pediatric population. For example, there is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. These risks appear to decrease with increasing age; young children are also at a higher risk of severe pancreatitis, which may result in fatalities (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Hepatotoxicity, 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity, and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Pancreatitis). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behavior, psychomotor hyperactivity and learning disorder are principally observed in the pediatric population (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Behavioural Disorders).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 3 summarizes those treatment-emergent adverse events reported for patients in the placebo-controlled trials when the incidence rate in the divalproex sodium group was at least 5%. (Maximum treatment duration was 21 days; maximum dose in 83% of patients was between 1,000 to 2,500 mg per day).

Table 3. Treatment-Emergent Adverse Event Incidence (≥5%) in Short-Term Placebo-Controlled Trials (Oral Administration)

System Organ Class/Event	Divalproex sodium N = 89 (%)	placebo N = 97 (%)
Gastrointestinal Disorders		
Nausea	22.5	15.5
Vomiting	12.4*	3.1
Diarrhea	10.1	13.4
Abdominal Pain	9	8.2
Dyspepsia	9	8.2
Constipation	7.9	8.2
General Disorders and Administration Site Conditions		
Pain	14.6	15.5
Asthenia	10.1	7.2
Injury, Poisoning and Procedural Complications		
Accidental Injury	11.2	5.2
Musculoskeletal and Connective Tissue Disorders		

System Organ Class/Event	Divalproex sodium N = 89 (%)	placebo N = 97 (%)
Back Pain	5.6	6.2
Nervous System Disorders		
Headache	21.3	30.9
Somnolence	19.1	12.4
Dizziness	12.4	4.1
Tremor	5.6	6.2
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngitis	6.7	9.3
Skin and Subcutaneous Tissue Disorders		
Rash	5.6	3.1
* Statistically significant at P < 0.05 level.		

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse events not listed above were reported by at least 1%, but less than 5%, of the 89 patients from the two placebo-controlled clinical trials of divalproex sodium tablets.

Cardiovascular:	Palpitations, tachycardia.
Congenital, Familial and Genetic Disorders:	Vascular anomaly.
Ear and Labyrinth Disorders:	Deafness, ear disorder, ear pain, tinnitus, vertigo.
Eye Disorders:	Abnormal vision, amblyopia, conjunctivitis, diplopia, dry eyes, eye pain.
Gastrointestinal Disorders:	Fecal incontinence, flatulence, gastroenteritis, glossitis.
General Disorders and Administration Site Conditions:	Abnormal gait, chest pain, chills, chills and fever, cyst, edema, fever, furunculosis, periodontal abscess, peripheral edema.
Infections and Infestations:	Infection, rhinitis.
Metabolism and Nutrition Disorders:	Anorexia.
Musculoskeletal and Connective Tissue Disorders:	Arthralgia, arthrosis, leg cramps, neck pain, neck rigidity twitching.
Nervous System Disorders:	Ataxia, dysarthria, hypertonia, hypokinesia, paresthesia, reflexes increased, tardive dyskinesia.

Psychiatric Disorders:	Abnormal dreams, agitation, catatonic reaction, confusion, depression, hallucinations, insomnia, thinking abnormalities.
Renal and Urinary Disorders:	Dysurea, urinary incontinence.
Reproductive System and Breast Disorders:	Dysmenorrhea.
Respiratory, Thoracic and Mediastinal Disorders:	Dyspnea.
Skin and Subcutaneous Tissue Disorders:	Alopecia, discoid lupus erythematosus, dry skin, maculopapular rash, seborrhea.
Vascular Disorders:	Ecchymosis, hypertension, hypotension, postural hypotension, vasodilation.

8.5 Post-Market Adverse Reactions

Adverse Events in Elderly Patients

In elderly patients (above 65 years of age), there were more frequent reports of accidental injury, infection, pain, and to a lesser degree, somnolence and tremor, when compared to patients 18 to 65 years of age. Somnolence and tremor tended to be associated with the discontinuation of divalproex sodium tablets.

Reproductive Findings

There have been very rare reports of testicular atrophy, decreased semen volume, male hypogonadism, decreased blood testosterone and/or increased blood prolactin levels in patients treated with valproate products. There are insufficient data to determine the exact effect of valproate therapy on testicular development in humans (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology, Fertility).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Rare cases of coma have been reported in patients receiving Mylan-Divalproex alone or in conjunction with phenobarbital (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4).
- Serious skin reactions (such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported with concomitant lamotrigine and divalproex sodium administration (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Table 4).

9.2 Drug Interactions Overview

Divalproex sodium has been found to be a weak inhibitor of some P₄₅₀ isozymes, epoxide hydrazase, and glucuronyl transferases.

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronyl transferases (such as ritonavir; see **Table 4** below), may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on divalproex sodium monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepileptic drugs.

In contrast, drugs that are inhibitors of cytochrome P₄₅₀ isozymes, such as antidepressants, may be expected to have little effect on divalproex sodium clearance because cytochrome P₄₅₀ microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

The concomitant administration of divalproex sodium with drugs that exhibit extensive protein binding (e.g., acetylsalicylic acid, carbamazepine, dicumarol, warfarin, tolbutamide, and phenytoin) may result in alteration of serum drug levels.

Since divalproex sodium may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy and whenever enzyme-inducing drugs are introduced or withdrawn.

9.3 Drug-Behavioural Interactions

Refer to 7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery for details.

9.4 Drug-Drug Interactions

Table 4 provides information about the potential influence of several commonly prescribed medications on valproate pharmacokinetics as well as the potential influence of valproate on the pharmacokinetics and pharmacodynamics of several commonly prescribed medications. The list is not exhaustive nor could it be, since new interactions are continuously being reported. The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated). Please note that drugs may be listed under specific name, family or pharmacologic class. Reading the entire section is recommended.

- **Risk of liver damage**

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Hepatotoxicity, 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity, and 8 ADVERSE REACTIONS, 8.1 Adverse Reaction Overview, Pediatric Population).

Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Hepatotoxicity, 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity, and 8 ADVERSE REACTIONS, 8.1 Adverse Reaction Overview, Pediatric Population).

Table 4. - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Acetaminophen	CT	↔ acetaminophen	Divalproex sodium had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.
Acetazolamide	C	Effect on drug concentrations unknown	Concomitant administration of valproate and acetazolamide has been associated with encephalopathy and/or hyperammonemia. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism)
Acetylsalicylic Acid	CT	↑ valproate	A study involving the co-administration of acetylsalicylic acid at antipyretic doses (11 to 16 mg/kg) with divalproex sodium 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 acetylsalicylic acid compared to divalproex sodium alone. The beta-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on divalproex sodium alone to 8.3% in the presence of acetylsalicylic acid. Caution should be observed when divalproex sodium is administered with drugs affecting coagulation, [e.g., acetylsalicylic acid and warfarin] (see 8 ADVERSE REACTIONS).
Alcohol	T	No pharmacokinetic (PK) interaction	Divalproex sodium may potentiate the CNS depressant action of alcohol. Alcohol intake is not recommended during treatment with Mylan-Divalproex (see 7 WARNINGS AND PRECAUTIONS).
Amitriptyline / Nortriptyline	CT	In general: ↓ amitriptyline ↓ nortriptyline	Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females)

Proper/Common name	Source of Evidence	Effect	Clinical comment
		Rarely: ↑ amitriptyline ↑ nortriptyline	who received divalproex sodium (500 mg twice daily) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare post-marketing reports of concurrent use of divalproex sodium and amitriptyline resulting in an increased amitriptyline and nortriptyline levels have been received. Concurrent use of divalproex sodium and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking divalproex sodium concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of divalproex sodium.
Antacids	CT	↔ valproate	A study involving the co-administration of divalproex sodium 500 mg with commonly administered antacids (Maalox®, Trisogel, and Titralac™ - 160 milliequivalent doses) did not reveal any effect on the extent of absorption of valproate.
Other - Antipsychotics, Monoamine Oxidase Inhibitors (MAOIs) and Tricyclic Antidepressants	T	Effect on drug concentrations unknown	In addition to enhancing CNS depression when used concurrently with divalproex sodium, antipsychotics, tricyclic antidepressants and MAOIs may lower the seizure threshold. Dosage adjustments for Mylan-Divalproex may be necessary to control seizures.
Antiretroviral agents - Ritonavir - Lopinavir - Zidovudine - Lamivudine	C CT	↓ valproate ↑ zidovudine	Protease inhibitors such as lopinavir and ritonavir decrease valproate plasma level when co-administered with valproate. Reduction of therapeutic effect of valproate was observed in a patient with bipolar disorder with the initiation of HIV treatment with lopinavir/ritonavir, zidovudine, and lamivudine. In 6 patients who were seropositive

Proper/Common name	Source of Evidence	Effect	Clinical comment
			for HIV, the clearance of zidovudine (100 mg every 8 hours) was decreased by 38% after administration of valproate (250 or 500 mg every 8 hours); the half-life of zidovudine was unaffected.
Benzodiazepines	CT	↑ lorazepam ↑ diazepam	Divalproex sodium may decrease oxidative liver metabolism of some benzodiazepines, resulting in increased serum concentrations. See Table 4. Diazepam and Lorazepam.
Cannabidiol (CBD)	CT	↑ Alanine Transaminase (ALT)	Cannabidiol at doses 10 to 25 mg/kg and valproate led to ALT increases greater than 3 times the upper limit of normal in 19% of the patients. Exercise appropriate liver monitoring and consider dose reduction or discontinuation in case of significant anomalies of liver parameters (see 7 WARNINGS AND PRECAUTIONS).
Carbamazepine / carbamazepine-10,11-epoxide	CT	↓ CBZ ↑ CBZ-E ↓ valproate	Concomitant use of carbamazepine (CBZ) with divalproex sodium may result in decreased serum concentrations and half-life of valproate due to increased metabolism induced by hepatic microsomal enzyme activity. Monitoring of serum concentrations is recommended when either medication is added to or withdrawn from an existing regimen. Changes in the serum concentration of the 10,11-epoxide (CBZ-E) metabolite of carbamazepine, however, will not be detected by routine serum carbamazepine assay. Serum levels of carbamazepine decreased 17% while that of carbamazepine-10,11-epoxide increased by 45% upon co-administration of divalproex sodium and CBZ to epileptic patients.
Carbapenem Antibiotics	C	↓ valproate	Carbapenem antibiotics (ertapenem, imipenem, meropenem, doripenem) can reduce serum valproic acid concentrations to sub-therapeutic

Proper/Common name	Source of Evidence	Effect	Clinical comment
			levels. This can result in loss of seizure control in epileptic patients or loss of efficacy in non-epileptics. In some cases of co-administration in epileptic patients breakthrough seizures have occurred. Increasing valproic acid dose may not be sufficient to overcome this interaction. If co-administration is essential, serum valproic acid concentrations should be monitored daily. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates (see 7 WARNINGS AND PRECAUTIONS, General, Interaction with Carbapenem Antibiotics).
Chlorpromazine	CT	↑ valproate	A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving divalproex sodium (200 mg twice daily) revealed a 15% increase in trough plasma levels of valproate. This increase is not considered clinically important.
Cholestyramine	C, CT	↓ valproate	Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.
Cimetidine or Erythromycin	T	↑ valproate	Cimetidine and/or erythromycin may decrease the clearance and increase the half-life of divalproex sodium by altering its metabolism. In patients receiving divalproex sodium, serum valproic acid levels should be monitored when treatment with cimetidine is instituted, increased, decreased, or discontinued. The divalproex sodium dose should be adjusted accordingly.
Clonazepam	T	No PK interaction	The concomitant use of divalproex sodium and clonazepam may induce absence status in patients with a history of absence type seizures.
Clozapine	CT	No interaction	In psychotic patients (n = 11), no interaction was observed when

Proper/Common name	Source of Evidence	Effect	Clinical comment
			divalproex sodium was co-administered with clozapine.
Diazepam	CT	↑ diazepam	Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of divalproex sodium (1,500 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	CT	↑ ethosuximide	Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with divalproex sodium (800 to 1,600 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. Patients receiving divalproex sodium and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.
Estrogen-containing products	C CTT	↓ valproate	Estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control), when adding, or discontinuing estrogen-containing products. Consider monitoring of valproate plasma levels. Valproate usually has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of

Proper/Common name	Source of Evidence	Effect	Clinical comment
			<p>oestroprogestative agents in women receiving hormonal contraception. Based on limited data from literature, an approximate 20% increase in valproate clearance has been reported in some patients that were concomitantly treated with valproate and estrogen-containing products, which may result in a decrease in valproate serum levels. Inter-individual variability has been noted. There are insufficient data to establish a robust PK-PD relationship resulting from this PK interaction.</p>
Felbamate	CT	↑ valproate	<p>A study involving the co-administration of 1,200 mg/day of felbamate with divalproex sodium to patients with epilepsy (n = 10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 mcg/mL) compared to divalproex sodium alone. Increasing the felbamate dose to 2,400 mg/day increased the mean valproate peak concentration to 133 mcg/mL (another 16% increase). A decrease in divalproex sodium dosage may be necessary when felbamate therapy is initiated. Lower doses of divalproex sodium may be necessary when used concomitantly with felbamate.</p>
Haloperidol	CT	↔ valproate	<p>A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving divalproex sodium (200 mg twice daily) revealed no significant changes in valproate trough plasma levels.</p>
Lamotrigine	CT	↑ lamotrigine ↓ valproate	<p>The effects of divalproex sodium on lamotrigine were investigated in 6 healthy male subjects. Each subject received a single oral dose of lamotrigine alone and with divalproex sodium 200 mg every 8 hours for 6 doses starting 1 hour before the lamotrigine dose was given. Divalproex sodium administration</p>

Proper/Common name	Source of Evidence	Effect	Clinical comment
			<p>reduced the total clearance of lamotrigine by 21% and increased the plasma elimination half-life from 37.4 hours to 48.3 hours ($p < 0.005$). Renal clearance of lamotrigine was unchanged. In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with divalproex sodium co-administration (a 165% increase).</p> <p>In a study involving 16 epileptic patients, divalproex sodium doubled the elimination half-life of lamotrigine. In an open-labelled study, patients receiving enzyme inducing AEDs (e.g., carbamazepine, phenytoin, phenobarbital, or primidone) demonstrated a mean lamotrigine plasma elimination half-life of 14 hours while the elimination half-life was 30 hours in patients taking divalproex sodium plus an enzyme inducing antiepileptic agent. The latter value is similar to the lamotrigine half-life during monotherapy indicating that valproic acid may counteract the effect of the enzyme inducer. If divalproex sodium is discontinued in a patient receiving lamotrigine and an enzyme inducing antiepileptic serum lamotrigine concentrations may decrease. Patients receiving combined antiepileptic therapy require careful monitoring when another agent is started, stopped or when the dose is altered.</p> <p>Serious skin reactions (such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported with concomitant lamotrigine and divalproex sodium administration.</p>
Lithium	CT	↔ lithium	In a double-blind placebo-controlled multiple dose crossover study in 16 healthy male volunteers, pharmacokinetic parameters of

Proper/Common name	Source of Evidence	Effect	Clinical comment
			lithium were not altered by the presence or absence of valproate. The presence of lithium, however, resulted in an 11 to 12% increase in the AUC and C_{max} of valproate. T_{max} was also reduced. Although these changes were statistically significant, they are not likely to have clinical importance. Co-administration of divalproex sodium (500 mg twice daily) and lithium carbonate (300 mg three times daily) to normal male volunteers (n = 16) had no effect on the steady-state kinetics of lithium.
Lorazepam	CT	↑ lorazepam	Concomitant administration of divalproex sodium (500 mg twice daily) and lorazepam (1 mg twice daily) in normal male volunteers (n = 9) was accompanied by a 17% decrease in the plasma clearance of lorazepam. This decrease is not considered clinically important.
Mefloquine	C	↓ valproate	Concomitant administration of mefloquine and divalproex sodium can decrease plasma valproate concentrations. This may lead to increased frequency of seizure attacks. Therefore, Mylan-Divalproex dose may need to be adjusted.
Metamizole Not currently marketed in Canada for human use	C, T	↓ valproate	Metamizole may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels and dose adjustment, as appropriate.
Nimodipine	CT	↑ nimodipine	Concomitant treatment of nimodipine with valproic acid may increase nimodipine plasma concentration by 50%.
Olanzapine	CT	↓ olanzapine	Valproate may decrease the olanzapine plasma concentration. Administration of a single 5 mg dose of olanzapine to 10 healthy, non-

Proper/Common name	Source of Evidence	Effect	Clinical comment
			epileptic volunteers with divalproex sodium extended-release tablets 1000 mg QD did not affect olanzapine C _{max} and elimination half-life. However, olanzapine AUC was 35% lower in the presence of divalproex sodium extended-release tablets. The clinical significance of these observations is unknown.
Oral contraceptive Steroids	CT	No PK interaction	Evidence suggests that there is an association between the use of certain AEDs capable of enzyme induction and failure of oral contraceptives. One explanation for this interaction is that enzyme-inducing drugs effectively lower plasma concentrations of the relevant steroid hormones, resulting in unimpaired ovulation. However, other mechanisms, not related to enzyme induction, may contribute to the failure of oral contraceptives. Divalproex sodium is not a significant enzyme inducer and would not be expected to decrease concentrations of steroid hormones. However, clinical data about the interaction of divalproex sodium with oral contraceptives are minimal. Administration of a single-dose of ethinylestradiol (50 mcg)/levonorgestrel (250 mcg) to 6 women on divalproex sodium (200 mg twice daily) therapy for 2 months did not reveal any pharmacokinetic interaction.
Phenobarbital	CT	↑ phenobarbital ↓ valproate	Phenobarbital increases the metabolism of valproic acid and hence, increases valproic acid metabolite levels. Therefore patients treated with this drug should be carefully monitored for signs and symptoms of hyperammonemia. Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of divalproex sodium (250 mg twice daily for 14 days) with phenobarbital to normal

Proper/Common name	Source of Evidence	Effect	Clinical comment
			<p>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 increased by 50% in the presence of valproate.</p> <p>There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. 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.</p>
Phenytoin	CT	↑ phenytoin	<p>Phenytoin increases the metabolism of valproic acid and hence, increases valproic acid metabolite levels. Therefore patients treated with this drug should be carefully monitored for signs and symptoms of hyperammonemia.</p> <p>Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of divalproex sodium (400 mg three times daily) 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 reduced by 25%.</p> <p>In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of divalproex sodium and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.</p>

Proper/Common name	Source of Evidence	Effect	Clinical comment
Primidone	T	↑ phenobarbital	Primidone is metabolized into a barbiturate (phenobarbital), and therefore, may also be involved in a similar or identical interaction with divalproex sodium as phenobarbital.
Propofol	C, CT	↑ propofol	Valproate may inhibit the metabolism of propofol, thus increasing propofol exposure. Reductions in propofol dose of 26 – 35% have been observed when co-administered with valproate. The normal dose of propofol may be excessive for patients receiving oral valproate treatment and may induce complications or delay recovery from anesthesia in electroconvulsive therapy (ECT).
Quetiapine	C, T	Effect on drug concentrations unknown	Co-administration of valproate and quetiapine may increase the risk of neutropenia/leucopenia.
Rifampin	CT	↓ valproate	A study involving the administration of a single dose of divalproex sodium (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. Divalproex sodium dosage adjustment may be necessary when it is co-administered with rifampin.
Rufinamide	C, CT	↑ rufinamide	Valproate may lead to an increase in plasma level of rufinamide in a dose-dependent manner. This increase is dependent on concentration of valproate. Caution should be exercised, particularly in children, as this effect is larger in pediatric population.
Selective Serotonin Re-Uptake Inhibitors (SSRIs)	C	↑ valproate	Some evidence suggests that SSRIs inhibit the metabolism of divalproex sodium, resulting in higher than expected levels of valproate.
Tolbutamide	T	↑ tolbutamide	From <i>in vitro</i> experiments, the unbound fraction of tolbutamide was increased from 20 to 50% when added to plasma samples taken from

Proper/Common name	Source of Evidence	Effect	Clinical comment
			patients treated with divalproex sodium. The clinical relevance of this displacement is unknown.
Topiramate	CT	Effect unknown	<p><u>Hyperammonemia</u> Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonemia. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy (see 2 CONTRAINDICATIONS, patients with known urea cycle disorders and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).</p> <p><u>Hypothermia</u> Concomitant administration of topiramate with divalproex sodium has also been associated with hypothermia in patients who have tolerated either drug alone. Blood ammonia levels should be measured in patients with reported onset of hypothermia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypothermia).</p>
Warfarin	T	Effect unknown	<p>In an <i>in vitro</i> 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 divalproex sodium is instituted in patients taking anticoagulants.</p> <p>Caution is recommended when divalproex sodium is administered with drugs affecting coagulation (see 8 ADVERSE REACTIONS).</p>

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Co-administration of Mylan-Divalproex with food should cause no clinical problems in the management of patients with epilepsy (see 4 DOSAGE AND ADMINISTRATION, 4.4 Administration).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Divalproex sodium is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with divalproex sodium; the clinical significance of these is unknown (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Thyroid Gland Abnormalities).

10 CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Anticonvulsant and mood-stabilizing drug; ATC-Code: N03AG01.

10.1 Mechanism of Action

Divalproex sodium has anticonvulsant properties, and is chemically related to valproic acid. Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. Although its mechanism of action has not yet been established, it has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma aminobutyric acid (GABA). The effect on the neuronal membrane is unknown.

10.2 Pharmacodynamics

A good correlation has not been established between daily dose, serum level and therapeutic effect. In epilepsy, the therapeutic plasma concentration range is believed to be from 50 to 100 mcg/mL (350 to 700 micromole/L) of total valproate. Occasional patients may be controlled with serum levels lower or higher than this range (see 4 DOSAGE AND ADMINISTRATION). In placebo-controlled clinical studies in acute mania, 79% of patients were dosed to a plasma concentration between 50 and 125 mcg/mL. Protein binding of valproate is saturable ranging from 90% at 50 mcg/mL to 82% at 125 mcg/mL.

10.3 Pharmacokinetics

Table 5. - Summary of the Pharmacokinetic Parameters of Divalproex sodium in Healthy, Fasting Subjects

			Mean (SD) Pharmacokinetic Parameters					
Single Dose	Dosage	N	C _{max} (mg/L)	T _{max} (h)	t _½ (h)	AUC ₄ (mg•h/L)	CL (1/h)	V _d (L)
Divalproex sodium	2 x 500 mg once daily	28	93.9 (11.7)	4.0 (1.2)	15.2 (15.3)	1818 (345)	--	--

Absorption:

Peak serum levels of valproic acid occur in 3 to 4 hours. A slight delay in absorption occurs when the

drug is administered with meals but this does not affect the total absorption.

Distribution:

Valproic acid is rapidly distributed throughout the body and the drug is strongly bound (90%) to human plasma proteins. Increases in doses may result in decreases in the extent of protein binding and variable changes in valproic acid clearance and elimination.

- **Protein Binding**

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 mcg/mL to 18.5% at 130 mcg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, in hyperlipidemic patients, and in the presence of other drugs (e.g., acetylsalicylic acid). Conversely, valproate may displace certain protein-bound drugs [e.g., phenytoin, carbamazepine, warfarin, and tolbutamide] (see 9 DRUG INTERACTIONS for more detailed information on the pharmacokinetic interactions of valproate with other drugs).

- **CNS Distribution**

Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (ranging from 7 to 25% of total concentration).

Metabolism:

Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30 to 50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial (beta)-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15 to 20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

Due to the saturable plasma protein binding, the relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather increases to a lesser extent. The kinetics of unbound drug are linear.

Elimination:

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m² and 11 L/1.73 m², respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m² and 92 L/1.73 m², respectively. These estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing AEDs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproic acid clearance, monitoring of valproate and concomitant drug concentrations should be intensified whenever enzyme-inducing drugs are introduced or withdrawn.

Elimination of valproic acid and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine.

The serum half-life (t_{1/2}) of valproic acid is typically in the range of 6 to 16 hours. Half-lives in the lower part of the above range are usually found in patients taking other drugs capable of hepatic enzyme induction.

Special Populations and Conditions:

- **Neonates/Infants:** Within the first 2 months of life, infants have a markedly decreased ability to eliminate valproate compared to children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding). For example, in one study, the half-life in neonates under 10 days ranged from 10 to 67 hours, compared to a range of 7 to 13 hours in children greater than 2 months.
- **Pediatrics:** Patients between 3 months and 10 years have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults.
- **Geriatrics:** The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26 years). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44% (see 4 DOSAGE AND ADMINISTRATION).
- **Sex:** There are no differences in unbound clearance (adjusted for body surface area) between males and females (4.8 ± 0.17 and 4.7 ± 0.07 L/hr per 1.73 m^2 , respectively).
- **Genetic Polymorphism:** No data available on genetic polymorphism.
- **Ethnic Origin:** The effects of race on the kinetics of valproate have not been studied.
- **Hepatic Insufficiency:** See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Serious or Fatal Hepatotoxicity for statements regarding hepatic dysfunction and associated fatalities.
- **Renal Insufficiency:** See 7 WARNINGS AND PRECAUTIONS, Renal, Renal Impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store Mylan-Divalproex (divalproex sodium) delayed-release tablets between 15 and 25°C. Tablets should be protected from light.

12 SPECIAL HANDLING INSTRUCTIONS

No Special Handling Instructions are required for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: divalproex sodium

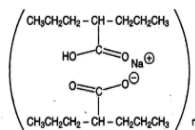
USAN names: INN: valproate semisodium

BAN: semisodium valproate

Chemical name: sodium hydrogen bis (2-propylpentanoate) or sodium hydrogen bis (2-propylvalerate)

Molecular formula and molecular mass: $(C_{16}H_{31}NaO_4)_n$ (310.14)_n

Structural formula:



Physicochemical properties: 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. It is a white powder with a characteristic odor, freely soluble in many organic solvents and in aqueous alkali solutions.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

A 24 week cross-over study compared the safety and efficacy of a controlled-release formulation of divalproex sodium ER administered once daily, to equal doses of a delayed-release formulation of divalproex sodium administered twice daily or three times daily, in the treatment of adolescent and adult epileptic patients with generalized seizures. The seizure control rate did not differ significantly between the two treatments. On divalproex sodium, 41/43 patients, or 95.3%, were seizure-free while the seizure control rate on divalproex sodium ER was 40/43 or 93.0%. This does not appear to be clinically different from the estimated general seizure control rate during the year before the start of the study when 40/44 (90.9%) patients reported being seizure-free on divalproex sodium.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Safety Pharmacology

Valproic acid has been shown to be effective against several types of chemically and electrically induced convulsions in a variety of animal species. These included maximal electroshock, low frequency electroshock, CO₂ withdrawal, pentylene tetrazole, cobalt, bemegride, bicuculline and 1-glutamate. Many forms of photic and auditory induced seizures are also effectively blocked by valproic acid.

In animal studies, valproic acid at doses of 175 mg/kg or less had no effect on locomotor activity and conditioned responses to positive reinforcement.

Doses greater than 175 mg/kg inhibited spontaneous and conditioned behaviour in mice and rats and interfered with coordination of hind limbs in rats. Suppression of spontaneous and evoked brain potentials was also demonstrated at these higher dose levels.

Valproic acid at doses of 175 mg/kg or less had little or no effect on the autonomic nervous system, cardiovascular system, respiration, body temperature, inflammatory responses, smooth muscle contraction or renal activity. Intravenous doses of 22, 43 and 86 mg/kg in animals caused very transient decreases followed by compensatory increases in blood pressure.

Sodium valproate injectable caused decreased activity, ataxia, dyspnea, prostration and death in rats and mice acutely exposed to dosages exceeding 200 mg/kg.

Divalproex sodium produced plasma valproic acid concentrations comparable to those of valproic acid when the two compounds were administered orally at equimolar doses to mice, rats and a beagle dog.

General Toxicology:

The initial animal testing was done with sodium valproate, whereas most of the recent research has been with valproic acid. The conversion factor is such that 100 mg of the sodium salt is equivalent to 87 mg of the acid. References to dosage are in terms of valproic acid activity.

- **Acute Toxicity**

Acute toxicity has been determined in several animal species using oral, intravenous, intraperitoneal and subcutaneous routes. The oral median lethal dose in adult rats and dogs was about 1 to 2 g/kg. Toxicity was similar for both sexes; however, it tended to be greater in newborn and 14-day old rats and in young adult rats. The signs of toxicity were those of central nervous system depression. Specific organ damage was limited to cellular debris in reticuloendothelial tissue and slight fatty degeneration of the liver.

Large oral doses (more than 500 mg/kg) produced irritation of the gastrointestinal tract of rats.

In adult male mice, the oral medial lethal dose of divalproex sodium was 1.66 g/kg (equal to approximately 1.54 g/kg valproic acid).

Pulverized divalproex sodium delayed-release tablets (equivalent to 250 mg valproic acid), suspended in 0.2% methylcellulose, were administered orally to mice and rats of both sexes (10/sex/species/group) in dosages ranging from 1.74 to 4.07 g/kg. The oral median lethal dose (LD₅₀) ranged from 2.06 to 2.71 g/kg. No consistent sex-related or species-related differences were observed.

Signs of central nervous system depression, such as decreased activity, ataxia, and sleep, were observed. At necropsy, discolouration and/or thickening of the glandular mucosa were observed in only 2 female rats treated with 2.71 g/kg that died acutely.

When mature rats and dogs were administered up to 240 mg/kg/day or 120 mg/kg/day, respectively, for at least four consecutive weeks, no significant toxicologic effects were reported. However, significant reductions in testicular weights and total white cell counts in rats given 240 mg/kg/day were considered as evidence of subtle toxicity from sodium valproate injectable. Therefore, 90 mg/kg/day in rats and 120 mg/kg/day in dogs were considered the highest non-toxic doses.

The acute intravenous toxicity of sodium valproate injectable formulation containing the equivalent of 100 mg valproic acid/mL was evaluated in both sexes of mice and rats. Groups of mice and rats

(five/sex/species/group) were treated at dosages ranging from 0.5 to 9.0 mL/kg (50 to 900 mg valproate/kg). No overt signs of toxicity were present in rats and mice given 0.5 mL/kg (50 mg valproate/kg). LD₅₀ values for the test solution in mice and rats (data combined for both sexes) were 7.3 and 7.0 mL/mg (730 and 700 mg valproate/kg), respectively.

- **Subacute and Chronic Toxicity**

Subacute and chronic toxicity studies consisted of 1, 3, 6 and 18 months studies in rats and 3, 6 and 12 months studies in dogs. Pathologic changes included suppression of the hematopoietic system, depletion of lymphocytes from lymphoid tissues and the loss of germinal epithelial cells from seminiferous tubules. Reduced spermatogenesis and testicular atrophy occurred in dogs at doses greater than 90 mg/kg/day and in rats at doses greater than 350 mg/kg/day. In rats, the first indication of toxicity at 350 mg/kg/day was decreased food consumption and growth.

Carcinogenicity:

Two hundred rats were given valproic acid in the diet for 107 weeks. Mean doses consumed in the treatment period were: 81 mg/kg/day (males) and 85 mg/kg/day (females), in the low dose group; 161 mg/kg/day (males) and 172 mg/kg/day (females) in the high dose group (approximately 10 to 50% of the maximum human daily dose on a mg/m² basis). Control animals received corn oil in the diet. The chief finding in the study was an increased incidence of skin fibrosarcomas in treated males of the high-dose group. There were 2 such neoplasms in the low dose group, 5 in the high dose group and none in control males. Fibrosarcomas in rats are relatively infrequent, usually occurring in less than 3% of animals.

Valproic acid was also administered in the diet to female mice for nearly 19 months at doses of 81 and 163 mg/kg/day and to male mice for nearly 23 months at doses of 80 and 159 mg/kg/day. A significant dose related trend occurred in male mice in the incidence of bronchoalveolar adenomas, and when the data were adjusted for the times of death, the incidence in the high dose group was significantly increased.

Depending on the method of statistical analysis, the incidence of hepatocellular carcinomas and/or adenomas also showed significant or almost significant increases for the corresponding observations. The results of these two studies indicate that valproic acid is a weak carcinogen or promoter in rats and mice. The significance of these findings for humans is unknown at present.

Subcutaneous fibrosarcomas were observed in male rats and hepatocellular carcinomas and bronchiolo-alveolar adenomas were observed in male mice at incidences slightly higher than concurrent study controls but comparable to those in registries of historical controls.

Genotoxicity:

- **Mutagenicity**

Valproate was not mutagenic in bacteria (Ames test), or mouse lymphoma L5178Y cells at thymidine kinase locus (mouse lymphoma assay), and did not induce DNA repair activity in primary culture of rat hepatocytes. After oral administration, valproate did not induce either chromosome aberrations in rat bone marrow, or dominant lethal effects in mice.

In literature, after intraperitoneal exposure to valproate, increased incidences of DNA and chromosome damage (DNA strand-breaks, chromosomal aberrations or micronuclei) have been reported in rodents.

However, the clinical significance of the results obtained with the intraperitoneal route of administration is unknown.

Statistically significant higher incidences of sister-chromatid exchange (SCE) have been observed in epileptic children exposed to valproate as compared to healthy children or epileptic children not exposed to valproate. However, contradictory results were reported in another study conducted in a mixed population of adults and children who showed similar SCE frequencies in treated or untreated epileptic patients. The clinical significance of an increase in SCE frequency is not known.

Reproductive and Developmental Toxicology:

- **Development**

Studies in rats have shown placental transfer of the drug. Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats, and rabbits. Doses greater than 65 mg/kg/day given to rats, mice and rabbits produced an increased incidence of skeletal abnormalities of the ribs, vertebrae and palate. Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.

Doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring.

In rats, there was a dose related delay in onset of parturition. Post-natal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period. Embryo lethality or major developmental abnormalities occurred in rats and rabbits at doses of 350 mg/kg/day.

Survival among pups born to the high dose females was very poor but was improved when pups were transferred to control dams shortly after birth.

In published literature, behavioral abnormalities have been reported in first generation offspring of mice and rats after *in utero* exposure to clinically relevant doses/exposures of valproate. In mice, behavioral changes have also been observed in the 2nd and 3rd generations, albeit less pronounced in the 3rd generation, following an acute *in utero* exposure of the first generation from dams dosed with valproate at 300 mg/kg (i.p.) or 500 mg/kg (s.c.) valproate on GD 10 or 10.5, respectively. The relevance of these findings for humans is unknown.

- **Fertility**

Chronic toxicity studies in adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of valproic acid of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m² basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m² basis). Segment I fertility studies in rats have shown that oral doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m² basis) for 60 days have no effect on fertility.

In juvenile rats, a decrease in testes weight was only observed at doses exceeding the maximum tolerated dose (from 240 mg/kg/day by intraperitoneal or intravenous route) and with no associated histopathological changes. No effects on the male reproductive organs were noted at tolerated doses (up to 90 mg/kg/day). There are insufficient data to determine the effect of valproate on testicular development in humans (see 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions, Reproductive

Findings).

17 SUPPORTING PRODUCT MONOGRAPHS

1. EPIVAL® tablet (delayed-release), 125 mg, 250 mg, 500 mg, submission control 253012, Product Monograph, BGP Pharma ULC. OCT 14, 2021

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^{Pr}**Mylan-Divalproex**

divalproex sodium delayed-release tablets

Read this carefully before you start taking **Mylan-Divalproex** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Mylan-Divalproex**.

Serious Warnings and Precautions

- **Liver Failure:** cases of fatal liver failure have occurred in patients receiving Mylan-Divalproex. If liver failure occurs, it usually happens during the first 6 months of treatment. You are more at risk for liver failure if you:
 - take other drugs used to treat seizures
 - are a child (especially a child under 2 years of age taking multiple drugs to treat seizures)
 - have a history of liver disease
 - were born with a metabolic disorder
 - have seizures with an intellectual disability
 - have brain disease
- **Birth Defects and development disorders:**
 - Mylan-Divalproex can cause birth defects in your child if you take it during pregnancy. These birth defects can seriously affect your child and result in disabilities which can be severe. The most frequently reported birth defects include:
 - *spina-bifida* (a condition where the bones of the spine are not properly developed);
 - problems with the development of the bones of the face and skull;
 - heart, kidney, urinary and sexual organ malformations; limb defects;
 - multiple associated malformations affecting several organs and parts of the body (including eye malformations);
 - hearing problems or deafness;
 - If you take Mylan-Divalproex during pregnancy, it can affect the way in which the child develops as it grows, including the following:
 - problems with early childhood development such as slow to walk and talk, lower IQ or problems with brain development;
 - autism or autism spectrum disorders;

- Attention Deficit Hyperactivity Disorder (ADHD)

These can begin early in the pregnancy, even before you know that you are pregnant. Mylan-Divalproex should not be used in female children, in women of childbearing potential or in pregnant women unless your doctor decides that you should. If you are taking Mylan-Divalproex and are of childbearing potential, you should use an effective method of birth control. If you become pregnant, or think you may be pregnant while taking Mylan-Divalproex, tell your doctor **right away**.

- **Mitochondrial Disorders:** if you or your child have a mitochondrial disorder such as Alpers Huttenlocher Syndrome, do not take Mylan-Divalproex. If your child is under 2 years of age and you think they may have a mitochondrial disorder, they should not be given Mylan-Divalproex unless all other medications have failed.
- **Pancreatitis** (inflammation of the pancreas): cases of life-threatening pancreatitis have occurred in both children and adults taking Mylan-Divalproex. Some instances happen shortly after the first use of Mylan-Divalproex, while others after several years of use. Talk to your healthcare professional right away if you start to have any symptoms of pancreatitis.

(See the **Serious side effects and what to do about them** table below for symptoms of liver failure and pancreatitis).

What is Mylan-Divalproex used for?

Mylan-Divalproex is used to:

- control epilepsy **in adults and children** on its own or with other medicines
- treat symptoms of mania associated with bipolar disorder **in adults**, such as aggressiveness, agitation, impulsive behaviour or excessively elevated mood.

Please follow your doctor's instructions carefully.

How does Mylan-Divalproex work?

Mylan-Divalproex is thought to work by increasing the amount of an amino acid in the brain called "gamma-aminobutyric acid" (GABA). By changing the amount of GABA in the brain, Mylan-Divalproex is able to help control epilepsy and stabilize mood.

What are the ingredients in Mylan-Divalproex?

Medicinal ingredients: divalproex sodium

Non-medicinal ingredients:

diacetylated monoglycerides, FD&C Red No. 40 (125 mg tablet only), FD&C Yellow No. 6 (250 mg tablet only), FD&C Blue No. 2 and D&C Red No. 30 (500 mg tablet only), hydroxypropylmethyl cellulose phthalate, povidone, pregelatinized starch (contains corn starch), silicon dioxide, talc, titanium dioxide, and vanillin.

Mylan-Divalproex comes in the following dosage forms:

Delayed-release tablets; 125 mg, 250 mg, and 500 mg.

Do not use Mylan-Divalproex if:

- you are allergic to divalproex sodium or to any other ingredient in Mylan-Divalproex
- you are pregnant, think you are pregnant or are planning to become pregnant, unless you and your doctor have decided you should
- you are a woman of childbearing potential, unless you meet all conditions of the **Pregnancy Prevention Program**, your doctor will talk to you about this
- you have liver disease or severe liver problems
- you have a mitochondrial disorder such as Alpers-Huttenlocher Syndrome. Children under 2 years of age who may have a mitochondrial disorder should not take Mylan-Divalproex
- you have or have a family history of a urea cycle disorder (a condition that affects how your body removes waste)
- you have porphyria (a condition that affects the nervous system and skin)
- you or any of your close relatives have a history of severe hepatitis, especially when caused by medicines

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Mylan-Divalproex. Talk about any health conditions or problems you may have, including if you:

- have or have a history of liver disease or liver problems;
- are breastfeeding or planning to breastfeed. You must discuss with your doctor whether to breastfeed or take Mylan-Divalproex, you cannot do both. Do not breastfeed for one month after stopping Mylan-Divalproex;
- have kidney disease or kidney problems;
- have Human Immunodeficiency Virus (HIV) or Cytomegalovirus (CMV);
- have a history of muscular disorders (including carnitine palmitoyl transferase type II deficiency);
- have other medical conditions including a history of unexplained coma, intellectual disability or any type of brain dysfunction;
- drink alcohol on a regular basis;
- are elderly (65 years of age or older)

Other warnings you should know about:

Pregnancy: Mylan-Divalproex may harm your unborn baby. Your doctor may require you to do a pregnancy test before you start treatment with Mylan-Divalproex to make sure that you are not pregnant. **You must use effective methods of birth control.** It is recommended that you use a form of birth control that does not depend on you to remember to use or take it, such as an intrauterine device (IUD) or 2 forms of birth control, such as the pill and a condom. You should use birth control:

- for at least one month before starting Mylan-Divalproex;
- while you are taking Mylan-Divalproex;
- for at least one month after stopping Mylan-Divalproex

Talk to your doctor about the best form of birth control for you. Some hormonal birth controls that

contain estrogen may affect how well Mylan-Divalproex works.

Before prescribing Mylan-Divalproex, your doctor should have explained to you what might happen to your baby if you become pregnant while taking Mylan-Divalproex (see the **Serious warnings and precautions** box above). If you are a parent or caring for a female child taking Mylan-Divalproex, tell the doctor as soon as your child has her first period. If you have any questions about what may happen if you become pregnant, talk to a healthcare professional. If you become pregnant, or think you are pregnant while taking Mylan-Divalproex, tell your doctor **right away**.

When you are prescribed Mylan-Divalproex:

- your doctor will give you a patient guide;
- you should receive a patient card every time you get Mylan-Divalproex from the pharmacy.

Make sure you understand these documents.

Pregnancy Registry: If you become pregnant while taking Mylan-Divalproex, talk to your doctor about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicines during pregnancy. Information on the registry can also be found at the following website: <http://www.aedpregnancyregistry.org/>.

Pregnancy Prevention Program: Information on the Pregnancy Prevention Program including educational resources, as well as to report suspected embryo-fetal exposure to valproate, can be found at the following website: <https://www.mylan.ca/en-ca/businesses/brand-specialty>.

Fertility:

Use in Women: If you are female and taking Mylan-Divalproex you may no longer get your period. You may also develop cysts (fluid filled sacs) on the ovaries and your testosterone levels may increase.

Use in Men: Mylan-Divalproex may affect male fertility during treatment. Mylan-Divalproex can make you less fertile or infertile. This **may or may not** be reversible if your dose is decreased or if you stop taking Mylan-Divalproex.

If you have interest in starting a family, talk to your doctor. Do not stop taking Mylan-Divalproex unless your doctor has told you to do so.

Monitoring and Blood Tests: Your doctor should do blood tests before starting treatment with Mylan-Divalproex and while you are taking it. These tests will monitor:

- platelet (a type of blood cell) count and your blood's ability to clot
- liver function
- the amount of valproate (the active ingredient in Mylan-Divalproex) in the body
- the amount of any other medications you are taking in your body

Your doctor will monitor your response to Mylan-Divalproex on a regular basis. If you start to have more seizures or your seizures get worse, tell your doctor immediately.

Suicidal Thoughts and Behaviour Changes: If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital right away. Mylan-Divalproex may also cause behavioural

changes in you or your child such as aggression, agitation, change in attention span and learning disorders.

Driving and Using Machines: Mylan-Divalproex may cause you to become drowsy or light-headed. Avoid driving, using machinery, or doing dangerous activities until you know how Mylan-Divalproex affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Mylan-Divalproex:

- **phenobarbital and lamotrigine, which are anticonvulsants (drugs used to treat seizures). These might cause serious life-threatening effects when mixed with Mylan-Divalproex;**
- other anticonvulsants such as carbamazepine, primidone, topiramate, felbamate, phenytoin, ethosuximide, rufinamide;
- anticoagulants (drugs used to thin blood) such as acetylsalicylic acid, warfarin, dicumarol;
- benzodiazepines such as diazepam, lorazepam, clonazepam;
- some medicines used to treat infections such as rifampin;
- some medicines used to treat diabetes such as tolbutamide;
- some HIV-antiviral medicines such as zidovudine, ritonavir, lopinavir, lamivudine;
- antibiotics in the carbapenem class such as doripenem, ertapenem, imipenem, meropenem;
- some medicines used to treat heartburn and peptic ulcers such as cimetidine;
- medicines used to treat depression such as Selective Serotonin Re-Uptake Inhibitors (SSRIs), Monoamine Oxidase Inhibitors (MAOIs), Tricyclic antidepressants such as amitriptyline, nortriptyline;
- acetazolamide, a drug used to treat glaucoma and epilepsy;
- cholestyramine, a drug used to lower cholesterol;
- propofol, a drug used to relax you before and after surgery;
- nimodipine, a drug used to prevent brain damage;
- metamizole (used to treat pain and fever; not approved in Canada for human use);
- antipsychotics (drugs used to manage psychosis) such as olanzapine, chlorpromazine, quetiapine;
- estrogen-containing products (including contraceptives that contain estrogen);
- alcohol
- cannabidiol (CBD)

How to take Mylan-Divalproex:

- Mylan-Divalproex treatment must only be started and supervised by a doctor specialised in the treatment of epilepsy or mania (bipolar disorders).
- It is important to keep your appointments for medical checkups.
- Take Mylan-Divalproex exactly as your doctor prescribes, do not change your dose unless your doctor tells you to.
- Do not stop taking Mylan-Divalproex suddenly as this can increase the number of seizures you have and their severity.
- Mylan-Divalproex can be taken with or without food.

- Swallow tablets whole, do not chew.

Usual dose:

Your doctor will decide the dose of Mylan-Divalproex for you. The dose is based on your weight, your seizures or manic episodes and the other medicines you or your child take. Your doctor will slowly increase the dosage until your or your child's condition is well controlled, without side effects.

Mylan-Divalproex is not for the treatment of the symptoms of mania in patients under 18 years of age.

Overdose:

If you think you, or a person you are caring for, have taken too much Mylan-Divalproex, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you or your child misses a dose, do not try to make up for it by doubling the next dose. Take or give the next regularly scheduled dose and try not to miss any more doses.

What are possible side effects from using Mylan-Divalproex?

These are not all the possible side effects you or your child may have when taking Mylan-Divalproex. If you or your child experience any side effects not listed here, tell your healthcare professional.

- headache
- nausea or vomiting
- indigestion
- diarrhea
- tremors (involuntary shaking)
- feeling tired
- feeling weak or dizzy
- hair loss or hair growth on the face, chest or back
- increased appetite that may lead to weight gain

Additional side effects in children:

Compared to adults, some side effects of Mylan-Divalproex occur more frequently and/or are more severe in children. These include liver damage, inflammation of the pancreas (pancreatitis), aggression, agitation, disturbance in attention, abnormal behavior, hyperactivity and learning disorder.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
COMMON			
Allergic reaction: difficulty swallowing or breathing, wheezing;			X

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			
Hallucinations (seeing or hearing things that are not there)	X		
Urinary incontinence (involuntary loss of urine)		X	
UNCOMMON			
Aggravated convulsions (an increase in the number of seizures you have or having new types of seizures)			X
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death. If you have a history of depression, your depression may become worse		X	
Hyperammonemia (high ammonia levels in the blood): tiredness, vomiting, abnormal walking, extreme irritability, combative/bizarre behaviour, not wanting to eat meat or high protein products			X
Hypothermia (low body temperature): shivering, slurred speech or mumbling, slow, shallow breathing, weak pulse, very low energy, confusion or memory loss		X	
Kidney problems: nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine,		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, mental status changes (drowsiness, confusion, coma)			
Liver injury: yellowing of the skin or eyes, itchy skin, dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite			X
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			X
Serious skin reactions when taken with lamotrigine: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine			X
Thoughts of suicide or hurting yourself			X
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		X	
RARE			
Brain atrophy (loss of brain cells): memory loss, seizures, loss of motor skills, difficulty speaking, reading or understanding.		X	
Coagulation abnormalities (problems with how your blood clots): abnormal bleeding, bruising easily, won't stop bleeding when you are injured, sudden		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
nosebleeds, fatigue, headache			
Rhabdomyolysis (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine			X

If you or your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Mylan-Divalproex tablets should be stored between 15 and 25°C. Tablets should be protected from light.

Keep out of reach and sight of children.

If you want more information about Mylan-Divalproex:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website www.mylan.ca, or by calling 1-844-596-9526.

This leaflet was prepared by Mylan Pharmaceuticals ULC.

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