

Anticonvulsant Medications: Use in Pediatric Patients



The Centers for Medicare & Medicaid Services (CMS), Medicaid Integrity Group (MIG) has identified issues with the utilization of medications in the anticonvulsant drug therapy class. The U.S. Food and Drug Administration (FDA) approves product labeling for prescription drugs. The MIG has identified that some providers may have prescribed anticonvulsant medications outside of FDA-approved product labeling for indication, age, dosage, or duration of therapy. Therefore, CMS's goal is to improve quality of care and enhance patient safety by educating providers on the proper use of anticonvulsant medications in pediatric patients.

This fact sheet summarizes the current FDA-approved product labeling for the use of anticonvulsant medications in pediatric patients. After reading this fact sheet, providers should be able to accurately:

- Identify the FDA-approved indications for the use of anticonvulsant medications in pediatric patients;
- Identify the available treatment guidelines for the management of seizures in pediatric patients; and
- Summarize the adverse reactions and risks of anticonvulsant medications.

FDA-Approved Indications for Anticonvulsant Medications in Pediatric Patients

Anticonvulsant medications are used for the prevention and treatment of seizures that may or may not be a result of epilepsy. Epilepsy is a neurological disorder that affects approximately 2.3 million people in the United States.[1] Patients diagnosed with epilepsy experience recurrent seizures; however, not all seizures are the result of epilepsy. A seizure may last from a few seconds to several minutes, and can also be caused by low blood sugar, alcohol or drug withdrawal, high fever, or head trauma.[2]

Defining Pediatric Patients

For the purpose of this document, the term "pediatric patients" collectively includes infants, children, and adolescents younger than 18 years old. Infants are further defined to be any patient younger than one year old.

The literature on anticonvulsant medications does not have well-defined age ranges for pediatric patients. Some studies define children as patients 1 to 12 years old and adolescents as patients 13 to 17 years old. Other studies define children as patients 1 to 17 years old. The ages of the patients were also inconsistent in the clinical trials conducted for medication approval. This inconsistency is reflected in the age ranges in Figure 1 and in the "Anticonvulsant Medications: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Pediatric Patients" document.



ACRONYMS

AHRQ	Agency for Healthcare Research and Quality
CDER	Center for Drug Evaluation and Research
CMS	Centers for Medicare & Medicaid Services
FDA	U.S. Food and Drug Administration
LFT	liver function test
LGS	Lennox-Gastaut syndrome
MIG	Medicaid Integrity Group
OTC	over the counter
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
WBC	white blood cell

For children, anticonvulsant medications are only FDA approved for seizure disorders; however, not all anticonvulsant medications are FDA approved for every type of seizure disorder. The FDA-approved indications for the use of anticonvulsant medications in pediatric patients are:

- Epilepsy;
- Prevention and treatment of seizures occurring during and following neurosurgery;
- Seizures (absence, myoclonic, partial-onset, and tonic-clonic); and
- Seizures associated with Lennox-Gastaut syndrome (LGS).

Even though they are used as anticonvulsant medications, the benzodiazepines and barbiturates are not discussed in this fact sheet. The indications and dosages for the anticonvulsant medications discussed in this fact sheet are provided in the “Anticonvulsant Medications: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Pediatric Patients” document. A summary of the pediatric age ranges, indications, and the anticonvulsants approved to treat each indication are provided in Figure 1.

Figure 1. Age Ranges for Anticonvulsant Medications by Seizure Type or Indication

	Age Range (Years)																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Absence (petit mal)																	
divalproex ER[3]																	
ethosuximide*[4]																	
methsuximide*†[5]																	
valproic acid‡[6, 7, 8]																	
Complex partial																	
divalproex ER																	
ethotoin[9]																	
phenytoin†[10]																	
valproic acid‡																	
Epilepsy																	
carbamazepine§[11]																	
carbamazepine XR[12]																	
lamotrigine[13]																	
topiramate[14]																	
LGS																	
felbamate[15]																	
rufinamide[16]																	
Myoclonic																	
levetiracetam[17]																	

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Figure 1. Age Ranges for Anticonvulsant Medications by Seizure Type or Indication (Cont.)

Partial	Age Range (Years)																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
gabapentin[18]																	
lacosamide[19]																	
lamotrigine XR[20]																	
levetiracetam																	
levetiracetam XR[21]																	
oxcarbazepine[22]																	
perampanel[23]																	
tiagabine[24]																	
zonisamide[25]																	
Tonic-clonic (grand mal)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
ethotoin																	
lamotrigine XR																	
levetiracetam																	
phenytoin†																	

■ Monotherapy ■ Adjunct ■ Adjunct or monotherapy ■ Adjunct or monotherapy not specified

ER and XR = extended release

*May be administered in combination with other anticonvulsant medications when other forms of epilepsy coexist with absence (petit mal) seizures.

† No age specified.

‡ Includes Depakene®, Depakote® (divalproex), and Stavzor®.

§ As young as “children under 6 years of age.”

|| Beginning at one month old.



Monitoring Parameters for Selected Anticonvulsant Medications

Some of the anticonvulsant medications require monitoring of drug levels to ensure their safe use. The therapeutic drug levels of the anticonvulsant medications that require drug level monitoring are provided in Table 1.

Table 1. Therapeutic Drug Levels for Anticonvulsant Medications

Medication	Therapeutic Level
carbamazepine[26]	4 mcg per ml to 12 mcg per ml
ethosuximide[27]	40 mcg per ml to 100 mcg per ml
phenytoin[28]	10 mcg per ml to 20 mcg per ml
valproic acid[29]	50 mcg per ml to 100 mcg per ml

Treatment Guidelines for the Management of Seizures in Pediatric Patients

The Agency for Healthcare Research and Quality (AHRQ) hosts a database of treatment guidelines. The AHRQ is a branch of the U.S. Department of Health and Human Services. Please visit <http://www.guideline.gov> for the AHRQ's National Guideline Clearinghouse. Links to some of the treatment guidelines for the management of seizures and the use of anticonvulsant medications in pediatric patients are provided in Table 2.

Table 2. Treatment Guidelines for Anticonvulsant Medications

Sponsoring Organization	Title of Guideline	Link to Guideline
American Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Febrile Seizures	Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures.	http://www.guideline.gov/content.aspx?id=24597
National Institute for Health and Clinical Excellence (NICE)	The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care.	http://www.guideline.gov/content.aspx?id=36082

Adverse Reactions and Risks of Anticonvulsant Medications

The prescribing information for each anticonvulsant medication provides details on the adverse reactions and risks of that medication. The adverse reactions and risks vary with each medication. Prescribing information can

be found by searching the medication name at either <http://www.accessdata.fda.gov/scripts/cder/drugsatfda> on the FDA website or <http://dailymed.nlm.nih.gov> on the DailyMed website.



Several of the anticonvulsant medications have boxed warnings that draw attention to serious and potentially life-threatening adverse reactions of the medications. The anticonvulsant medications with boxed warnings are lamotrigine, carbamazepine, valproic acid, felbamate, and perampanel.

Lamotrigine

Serious skin rashes have been associated with lamotrigine. The risk of occurrence may be related to concomitant valproate therapy, exceeding the recommended initial dose, or rapidly increasing the dose. Children also have an increased risk of developing a rash from lamotrigine. The medication should be discontinued if a patient presents with a drug-induced rash.[30]

The boxed warning for lamotrigine states:[31]

WARNING: SERIOUS SKIN RASHES

LAMICTAL® can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (2 to 16 years of age) receiving LAMICTAL as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy. In clinical trials of bipolar and other mood disorders, the rate of serious rash was 0.08% (0.8 per 1,000) in adult patients receiving LAMICTAL as initial monotherapy and 0.13% (1.3 per 1,000) in adult patients receiving LAMICTAL as adjunctive therapy. In a prospectively followed cohort of 1,983 pediatric patients (2 to 16 years of age) with epilepsy taking adjunctive LAMICTAL, there was 1 rash-related death. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate.

Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash caused by LAMICTAL. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of LAMICTAL with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose of LAMICTAL, or (3) exceeding the recommended dose escalation for LAMICTAL. However, cases have occurred in the absence of these factors.

Nearly all cases of life-threatening rashes caused by LAMICTAL have occurred within 2 to 8 weeks of treatment initiation. However, isolated cases have occurred after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as means to predict the potential risk heralded by the first appearance of a rash.

Although benign rashes are also caused by LAMICTAL, it is not possible to predict reliably which rashes will prove to be serious or life-threatening. Accordingly, LAMICTAL should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life threatening or permanently disabling or disfiguring [see *Warnings and Precautions (5.1)*].

Carbamazepine

Carbamazepine may cause dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS). These reactions can be fatal. The medication should be discontinued if a patient presents with a drug-induced rash.[32] If anticonvulsant therapy is required, the patient should be treated with a different anticonvulsant medication.

Aplastic anemia and agranulocytosis have also been associated with carbamazepine therapy. Baseline white blood cell (WBC) and platelet counts should be obtained before starting carbamazepine and should be monitored periodically based on clinical judgment.[33] Boxed warnings have been added to alert patients and providers to these risks.

The boxed warnings for carbamazepine state:[34]

WARNINGS

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH TEGRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE **WARNINGS AND PRECAUTIONS, LABORATORY TESTS**).

APLASTIC ANEMIA AND AGRANULOCYTOSIS

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

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BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Valproic Acid and Divalproex

Valproic acid and its derivatives, including divalproex, have been associated with hepatotoxicity, teratogenicity, and pancreatitis. Patients requiring valproic acid therapy should be made aware of these risks prior to the initiation of therapy. Hepatotoxicity usually occurs in children younger than two years old and within the first six months of therapy, although it may occur at any time and may occur in patients older than two years old. Liver function tests (LFTs) should be monitored prior to initiation of therapy and periodically throughout the course of treatment.[35]

The risks of treatment should be discussed with the patient and weighed against the potential benefits. Valproic acid is a known teratogen. Female patients in their childbearing years, including sexually active teenage girls, should also be provided with the medication guide (included in the prescribing information) that describes the teratogenic potential of valproic acid.[36] In addition, studies indicate that exposure to valproic acid in utero causes adverse effects on cognitive function in children; they “have lower cognitive test scores than children exposed in utero to either another antiepileptic drug or to no antiepileptic drugs.”[37] Female patients who become pregnant while taking valproic acid should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry. Information on the registry can be found at <http://www.massgeneral.org/aed> on the Massachusetts General Hospital website.[38] Pancreatitis may occur in children and adults. Patients should be educated about and evaluated for the warning signs of pancreatitis and encouraged to seek treatment if they occur.[39] The boxed warnings for valproic acid and its derivatives are provided in Appendix A.

Felbamate

Aplastic anemia and hepatotoxicity have been associated with the use of felbamate. The risks of felbamate therapy should be weighed against the potential benefits. Boxed warnings have been added to alert patients and providers to these risks.[40] The boxed warnings for felbamate are provided in Appendix B.

Perampanel

Perampanel has been associated with serious psychiatric and behavioral reactions. Patients should be monitored for signs and symptoms of psychiatric and behavioral adverse reactions including aggression, anger, irritability, hostility, and homicidal ideation and threats. Patients and caregivers should be instructed to contact a healthcare provider if any of these reactions or changes in behavior are observed.[41]

Risk of Suicidality

Anticonvulsant medications have shown an increased risk of suicidality. In pooled analyses that included eleven anticonvulsant medications, results showed that patients taking an anticonvulsant were almost twice as likely to experience suicidal behavior or ideation than those patients taking a placebo.[43] The FDA requires the manufacturers of anticonvulsant medications to include a warning in the prescribing information.

A Medication Guide has also been developed to alert patients and caregivers to the risk of suicidality. The Medication Guide is dispensed with every new and refilled prescription. Links to the required Medication Guides can be found at <http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm> on the FDA website.

Resources

Please visit <http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-State/By-State.html> for links to State Medicaid program websites.

The Center for Drug Evaluation and Research (CDER) hosts a website providing health professionals with current information on over-the-counter (OTC) and prescription drugs. Visit <http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals> to access drug-related databases, information on drug recalls and alerts, current information on new and generic drug approvals, and information on drug safety and availability.

Section 1927(g)(1)(B) of the Social Security Act identifies the predetermined standards that the State's drug use review program must use to assess data on drug use. Visit http://www.ssa.gov/OP_Home/ssact/title19/1927.htm for information on the compendia.

The boxed warning for perampanel states:[42]

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

- **Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA (5.1)**
- **These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression (5.1)**
- **Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA (5.1)**
- **Closely monitor patients particularly during the titration period and at higher doses (5.1)**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening (5.1)**

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- 43 U.S. Department of Health and Human Services. U.S. Food and Drug Administration. (2008, December 16). Information for Healthcare Professionals: Suicidal Behavior and Ideation and Antiepileptic Drugs. Retrieved September 26, 2011, from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm100192.htm>

Appendix A

The boxed warnings for valproic acid and its derivatives are provided in the prescribing information for all of the products. The boxed warnings printed in the Depakote® (divalproex) prescribing information (June 2013) can be found at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018723s049lbl.pdf on the FDA website.

The boxed warnings for valproic acid and its derivatives state:

WARNING: LIFE THREATENING ADVERSE REACTIONS

Hepatotoxicity

Hepatic failure resulting in fatalities has occurred in patients receiving valproate and its derivatives. Children under the age of two 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. When Depakote 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. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

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

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Appendix A (Cont.)

Fetal Risk

Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores following *in utero* exposure.

Valproate is therefore contraindicated in pregnant women treated for prophylaxis of migraine [*see Contraindications (4)*]. Valproate should only be used to treat pregnant women with epilepsy or bipolar disorder if other medications have failed to control their symptoms or are otherwise unacceptable.

Valproate should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine). Women should use effective contraception while using valproate [*see Warnings and Precautions (5.2, 5.3, 5.4)*].

A Medication Guide describing the risks of valproate is available for patients [*see Patient Counseling Information (17)*].

Pancreatitis

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated [*see Warnings and Precautions (5.5)*].

Appendix B

The boxed warnings for felbamate are provided in the prescribing information for all of the products. The boxed warnings printed in the Felbatol® (felbamate) prescribing information (July 2011) can be found at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020189s023lbl.pdf on the FDA website.

The boxed warnings for felbamate state:

WARNING

1. APLASTIC ANEMIA

THE USE OF FELBATOL® (felbamate) IS ASSOCIATED WITH A MARKED INCREASE IN THE INCIDENCE OF APLASTIC ANEMIA. ACCORDINGLY, FELBATOL® SHOULD ONLY BE USED IN PATIENTS WHOSE EPILEPSY IS SO SEVERE THAT THE RISK OF APLASTIC ANEMIA IS DEEMED ACCEPTABLE IN LIGHT OF THE BENEFITS CONFERRED BY ITS USE (SEE INDICATIONS). ORDINARILY, A PATIENT SHOULD NOT BE PLACED ON AND/OR CONTINUED ON FELBATOL® WITHOUT CONSIDERATION OF APPROPRIATE EXPERT HEMATOLOGIC CONSULTATION.

(Continued on next page)

Appendix B (Cont.)

AMONG FELBATOL® TREATED PATIENTS, APLASTIC ANEMIA (PANCYTOPENIA IN THE PRESENCE OF A BONE MARROW LARGELY DEPLETED OF HEMATOPOIETIC PRECURSORS) OCCURS AT AN INCIDENCE THAT MAY BE MORE THAN A 100 FOLD GREATER THAN THAT SEEN IN THE UNTREATED POPULATION (I.E., 2 TO 5 PER MILLION PERSONS PER YEAR). THE RISK OF DEATH IN PATIENTS WITH APLASTIC ANEMIA GENERALLY VARIES AS A FUNCTION OF ITS SEVERITY AND ETIOLOGY; CURRENT ESTIMATES OF THE OVERALL CASE FATALITY RATE ARE IN THE RANGE OF 20 TO 30%, BUT RATES AS HIGH AS 70% HAVE BEEN REPORTED IN THE PAST.

THERE ARE TOO FEW FELBATOL® ASSOCIATED CASES, AND TOO LITTLE KNOWN ABOUT THEM TO PROVIDE A RELIABLE ESTIMATE OF THE SYNDROME'S INCIDENCE OR ITS CASE FATALITY RATE OR TO IDENTIFY THE FACTORS, IF ANY, THAT MIGHT CONCEIVABLY BE USED TO PREDICT WHO IS AT GREATER OR LESSER RISK.

IN MANAGING PATIENTS ON FELBATOL®, IT SHOULD BE BORNE IN MIND THAT THE CLINICAL MANIFESTATION OF APLASTIC ANEMIA MAY NOT BE SEEN UNTIL AFTER A PATIENT HAS BEEN ON FELBATOL® FOR SEVERAL MONTHS (E.G., ONSET OF APLASTIC ANEMIA AMONG FELBATOL® EXPOSED PATIENTS FOR WHOM DATA ARE AVAILABLE HAS RANGED FROM 5 TO 30 WEEKS). HOWEVER, THE INJURY TO BONE MARROW STEM CELLS THAT IS HELD TO BE ULTIMATELY RESPONSIBLE FOR THE ANEMIA MAY OCCUR WEEKS TO MONTHS EARLIER. ACCORDINGLY, PATIENTS WHO ARE DISCONTINUED FROM FELBATOL® REMAIN AT RISK FOR DEVELOPING ANEMIA FOR A VARIABLE, AND UNKNOWN, PERIOD AFTERWARDS.

IT IS NOT KNOWN WHETHER OR NOT THE RISK OF DEVELOPING APLASTIC ANEMIA CHANGES WITH DURATION OF EXPOSURE. CONSEQUENTLY, IT IS NOT SAFE TO ASSUME THAT A PATIENT WHO HAS BEEN ON FELBATOL® WITHOUT SIGNS OF HEMATOLOGIC ABNORMALITY FOR LONG PERIODS OF TIME IS WITHOUT RISK.

IT IS NOT KNOWN WHETHER OR NOT THE DOSE OF FELBATOL® AFFECTS THE INCIDENCE OF APLASTIC ANEMIA.

IT IS NOT KNOWN WHETHER OR NOT CONCOMITANT USE OF ANTIEPILEPTIC DRUGS AND/OR OTHER DRUGS AFFECTS THE INCIDENCE OF APLASTIC ANEMIA.

APLASTIC ANEMIA TYPICALLY DEVELOPS WITHOUT PREMONITORY CLINICAL OR LABORATORY SIGNS, THE FULL BLOWN SYNDROME PRESENTING WITH SIGNS OF INFECTION, BLEEDING, OR ANEMIA. ACCORDINGLY, ROUTINE BLOOD TESTING CANNOT BE RELIABLY USED TO REDUCE THE INCIDENCE OF APLASTIC ANEMIA, BUT, IT WILL, IN SOME CASES, ALLOW THE DETECTION OF THE HEMATOLOGIC CHANGES BEFORE THE SYNDROME DECLARES ITSELF CLINICALLY. FELBATOL® SHOULD BE DISCONTINUED IF ANY EVIDENCE OF BONE MARROW DEPRESSION OCCURS.

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Appendix B (Cont.)

2. HEPATIC FAILURE

EVALUATION OF POSTMARKETING EXPERIENCE SUGGESTS THAT ACUTE LIVER FAILURE IS ASSOCIATED WITH THE USE OF FELBATOL®. THE REPORTED RATE IN THE U.S. HAS BEEN ABOUT 6 CASES OF LIVER FAILURE LEADING TO DEATH OR TRANSPLANT PER 75,000 PATIENT YEARS OF USE. THIS RATE IS AN UNDERESTIMATE BECAUSE OF UNDER REPORTING, AND THE TRUE RATE COULD BE CONSIDERABLY GREATER THAN THIS. FOR EXAMPLE, IF THE REPORTING RATE IS 10%, THE TRUE RATE WOULD BE ONE CASE PER 1,250 PATIENT YEARS OF USE.

OF THE CASES REPORTED, ABOUT 67% RESULTED IN DEATH OR LIVER TRANSPLANTATION, USUALLY WITHIN 5 WEEKS OF THE ONSET OF SIGNS AND SYMPTOMS OF LIVER FAILURE. THE EARLIEST ONSET OF SEVERE HEPATIC DYSFUNCTION FOLLOWED SUBSEQUENTLY BY LIVER FAILURE WAS 3 WEEKS AFTER INITIATION OF FELBATOL®. ALTHOUGH SOME REPORTS DESCRIBED DARK URINE AND NONSPECIFIC PRODROMAL SYMPTOMS (E.G., ANOREXIA, MALAISE, AND GASTROINTESTINAL SYMPTOMS), IN OTHER REPORTS IT WAS NOT CLEAR IF ANY PRODROMAL SYMPTOMS PRECEDED THE ONSET OF JAUNDICE.

IT IS NOT KNOWN WHETHER OR NOT THE RISK OF DEVELOPING HEPATIC FAILURE CHANGES WITH DURATION OF EXPOSURE.

IT IS NOT KNOWN WHETHER OR NOT THE DOSAGE OF FELBATOL® AFFECTS THE INCIDENCE OF HEPATIC FAILURE.

IT IS NOT KNOWN WHETHER CONCOMITANT USE OF OTHER ANTIEPILEPTIC DRUGS AND/OR OTHER DRUGS AFFECT THE INCIDENCE OF HEPATIC FAILURE.

FELBATOL® SHOULD NOT BE PRESCRIBED FOR ANYONE WITH A HISTORY OF HEPATIC DYSFUNCTION.

TREATMENT WITH FELBATOL® SHOULD BE INITIATED ONLY IN INDIVIDUALS WITHOUT ACTIVE LIVER DISEASE AND WITH NORMAL BASELINE SERUM TRANSAMINASES. IT HAS NOT BEEN PROVED THAT PERIODIC SERUM TRANSAMINASE TESTING WILL PREVENT SERIOUS INJURY BUT IT IS GENERALLY BELIEVED THAT EARLY DETECTION OF DRUG-INDUCED HEPATIC INJURY ALONG WITH IMMEDIATE WITHDRAWAL OF THE SUSPECT DRUG ENHANCES THE LIKELIHOOD FOR RECOVERY. THERE IS NO INFORMATION AVAILABLE THAT DOCUMENTS HOW RAPIDLY PATIENTS CAN PROGRESS FROM NORMAL LIVER FUNCTION TO LIVER FAILURE, BUT OTHER DRUGS KNOWN TO BE HEPATOTOXINS CAN CAUSE LIVER FAILURE RAPIDLY (E.G., FROM NORMAL ENZYMES TO LIVER FAILURE IN 2-4 WEEKS). ACCORDINGLY, MONITORING OF SERUM TRANSAMINASE LEVELS (AST AND ALT) IS RECOMMENDED AT BASELINE AND PERIODICALLY THEREAFTER. WHILE THE MORE FREQUENT THE MONITORING THE GREATER THE CHANCES OF EARLY DETECTION, THE PRECISE SCHEDULE FOR MONITORING IS A MATTER OF CLINICAL JUDGEMENT.

FELBATOL® SHOULD BE DISCONTINUED IF EITHER SERUM AST OR SERUM ALT LEVELS BECOME INCREASED ≥ 2 TIMES THE UPPER LIMIT OF NORMAL, OR IF CLINICAL SIGNS AND SYMPTOMS SUGGEST LIVER FAILURE (SEE PRECAUTIONS). PATIENTS WHO DEVELOP EVIDENCE OF HEPATOCELLULAR INJURY WHILE ON FELBATOL® AND ARE WITHDRAWN FROM THE DRUG FOR ANY REASON SHOULD BE PRESUMED TO BE AT INCREASED RISK FOR LIVER INJURY IF FELBATOL® IS REINTRODUCED. ACCORDINGLY, SUCH PATIENTS SHOULD NOT BE CONSIDERED FOR RE-TREATMENT.

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