REDACTED - Long Term Care Pharmacy Provider "LTCPP"

February 9, 2004

REDACTED - Abbott's Long Term Care - National Account Manager "LTC-NAM"

Abbott Laboratories, Inc.
REDACTED - LTC-NAM
National Account Manager
REDACTED

Dear REDACTED - LTC-NAM

As we continue to partner together for the benefit of our nation's elderly, we find the need to request the support of our stronger partners in order to offer high quality educational programs to our colleagues, patients, and customers.

REDACTED - LTCPP's second quarter focus will be on behavior management in long-term care. Therefore the purpose of this letter is to request funding for a restricted medical education grant in the amount of $16,250. This grant will be used to fund a targeted national educational mailer to the top 4000 prescribers of atypical antipsychotic and the top 1000 prescribers of benzodiazepine medications in long-term care. The value of this mailer will be to educate physicians on the benefits of using alternative methods to control difficult behaviors. The budget of this program includes:

- Data query and manipulation $1562.50
- Sequential addressing and materials sorting $625.00
- Labor; Copying; Material duplication and assembly $5625.00
- US Postage, logo envelopes $6250.00
- Oversight & Planning $2187.50

I'm sure that Abbott Laboratories will find significant value and merit in supporting these efforts.

We thank you for this opportunity to partner with Abbott Laboratories.

Sincerely,

REDACTED - LTCPP's National Director of Clinical Program Development "LTCPP-NDCPD"

National Director of Clinical Program Development
REDACTED - LTCPP
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Attn: REDACTED - LTCPP-NDCPD
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Abbott Grant Req mailer 2-04

REDACTED - LTCPP

EDUCATIONAL GRANT ORIGINATION SHEET

DATE ON CHECK: 3-5-04

PHARMA OR COMPANY SPONSOR: Abbott Labs

TARGETED DISEASE OR TOPIC: Mailing - ~~#~~ Antipsychotic/Benzo

EXPECTED CLOSE DATE:* 3-5-05
*Default will be 12 months from opening

GRANT NUMBER: _____

GL ACCOUNT: REDACTED

ORIGINAL GRANT AMOUNT: $ 16,250

ORIGINATING PHARMACY OR DEPARTMENT: Clinical

CONTACT PERSON/ PHONE #: REDACTED - LTCPP-NDCPD

MANAGING DEPARTMENT: (Circle One)

AMBULATORY (CLINICAL) CONSULTING HOSPITALS IV / HCP

* Authorized Signer below must match with the Department

APPROVAL: REDACTED - LTCPP-NDCPD

Last Updated: 1/10/02 by LPF

ANS'D MAR 19 2004

ABBOTT LABORATORIES 200 Abbott Park Road • P.O. Box 177 • Abbott Park, IL. 60064-6164 • (847) 937-8053 **Remittance Advice**

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January 2004

Dear Health Care Professional:

As you are aware, REDACTED - LTCPP has developed a geriatric-specific drug formulary. We would like to share some important information about our Select Formulary with you. Our preferred pharmaceutical products are selected through a three-tier evaluation process that begins with review by an expert external national Pharmacy and Therapeutics (P&T) Committee. Based on the P&T Committee's evaluation and further analysis of pharmacoeconomic and cost data, REDACTED - LTCPP selects the most appropriate products for elderly residents to include within the Select Formulary.

Depakote and its derivatives have FDA approval for a variety of indications including bipolar disorder, seizure disorders, and migraine headache prophylaxis. In addition to these uses, Depakote and Depakote-ER are being used with increasing frequency to treat/manage agitation, anger, and hostility associated with dementia in the elderly. For elderly residents requiring therapy for a dementia related behavior disorder, **Depakote ER®** has been granted preferred status on the REDACTED - LTCPP's formulary. Depakote ER® is a logical cost-effective choice for treating elderly patients with these challenging behavioral symptoms.

Depakote ER® should be considered for patients with dementia related behaviors including:

- Initial therapy for patients with agitation anger, and hostility symptoms
- Adjunctive therapy for patients partially responsive to an atypical antipsychotic (antipsychotic can be tapered to a lower dose or eliminated after stabilization of behaviors)
- Replacement therapy for patients receiving benzodiazepines

- **Depakote ER®** can be dosed once daily and has improved side effects profiles vs the original Depakote DR (delayed release) with significant decreases in sedation and gastrointestinal complaints.

- **Depakote ER®** 500mg costs less than equivalent doses of the original Depakote DR (delayed release) with additional pharmacoeconomic savings in decreased med-asses and increased quality of life.

- Use of **Depakote ER®** instead of atypical antipsychotics and benzodiazepines can also positively impact the nursing facilities Quality Indicator Report.

Physician prescribing in compliance with the formulary can maintain or improve resident outcomes while containing costs. This also will minimize the number of calls and interventions from nursing and pharmacy to change prescriptions to formulary-preferred drugs. We appreciate your support of these formulary preferences for our long-term care patients.
Enclosed you will find complete prescribing information that will be helpful.

If you have any questions, please contact the REDACTED - LTCPP consultant pharmacist in the facility where you practice.

Sincerely,

REDACTED - LTCPP-NDCPD

National Director of Clinical Program Development
Chair, P&T Liaison Committee

Disclaimer: Information contained in this letter is for general guidelines only. Prescribing and dosing should be based on individual patient conditions. Portions of the accompanying literature have been supported by an unrestricted educational grant from Abbott Laboratories.

REDACTED - LTCPP

Divalproex Sodium Extended-Release (Depakote® ER, Abbott)

Preferred Extended-Release Divalproex

WHY DEPAKOTE® ER IS OUR PREFERRED DIVALPROEX OF CHOICE:

Depakote® ER (extended-release divalproex sodium) is a new formulation of divalproex sodium which is dosed once daily. At therapeutic doses, it has been shown to have significantly less somnolence and fewer adverse G.I. effects than all other valproate formulations while delivering more stable blood levels. Tolerability of Depakote ER is superior to the older products (refer to full prescribing information for specifics – available upon request).

Current indications of Depakote ER are as follows[1]:

Monotherapy and adjunctive therapy in complex partial seizures in adults
Monotherapy and adjunctive therapy in simple and complex absence seizures in adults
Migraine prophylaxis

Non-FDA-approved indications of valproic acid and divalproex sodium include agitation and aggression of dementia[2-5]. Depakote delayed-release carries the indication for mania and bipolar disorder. Current studies to evaluate the effectiveness of Depakote ER for such indications are ongoing.[6]

GERIATRIC USE:

- The most common use for Depakote ER and Depakote in the elderly is to manage agitation and aggression secondary to dementia. Consideration should be given to the effects of reduced protein binding in the elderly. This can result in an increase in the free fraction in plasma.
- Dosing for behaviors in dementia is different from that used for acute manic episodes or seizures. For behaviors, the best approach is to start low and go slow. As with all valproate formulations, Depakote ER dose should be individualized based on patient response.
- Extended release tablets should be swallowed whole and not crushed, cut or split. For nursing home residents who cannot swallow well or who use a PEG tube, consideration can be given to using Depakote Sprinkle caps.

EQUIVALENT ORAL DOSING GUIDELINES: The average bioavailability of Depakote ER given once-daily (fasting or before meals) was 81-89% relative to original Depakote delayed-release tabs given BID on a mg for mg basis. Dosing adjustments may be required when switching patients from original Depakote delayed-release tablets to Depakote ER. Such conversions are handled differently for patients with behaviors of dementia vs. control of seizures, mania, bipolar, or migraine prophylaxis. Dosing for behaviors is generally based on patient response rather than blood level, making a mg for mg conversion less important than providing a dose which improves the resident's functional status.

	DOSE CONVERSION	
INDICATION	**Prescribed Drug: Depakote®**	**Depakote Extended-Release (Depakote ER) given once daily**
Agitation and Aggression 2nd to Dementia	250 mg	**250 mg**
	375	**500**
	500	**500**
	625	**750**
	750	**750**
	875	**1000**

REDACTED - LTCPP

Divalproex Sodium Extended-Release (Depakote® ER, Abbott)

Preferred Extended-Release Divalproex

CONVERSION WHEN USED FOR SEIZURE DISORDERS:
Depakote ER carries an indication for monotherapy and adjunctive therapy in complex partial seizures in adults and monotherapy and adjunctive therapy in simple and complex absence seizures in adults.

In clinical practice, some epilepsy patients will be converted from Depakote DR to Depakote ER. REDACTED - LTCPP supports this conversion provided that stable patients (i.e. those without seizure for 6 months) are evaluated first for stable plasma valproic acid levels. Then with that baseline level, a corresponding dose of Depakote ER can be selected, with a repeat plasma level in one to two weeks and adjusting the Depakote-ER regimen based on the follow-up lab data.

	DOSE CONVERSION	
INDICATION	Prescribed Drug: Depakote®	→ Depakote Extended-Release (Depakote ER) given once daily
Seizure Disorders[1,7] (monotherapy or adjunctive)	1000 mg	**1250 mg**
	1250-1375	**1500**
	1500-1625	**1750**
	1750	**2000**
	1875-2000	**2250**
	2125-2250	**2500**
	2375	**2750**
	2500-2750	**3000**
	2875	**3250**
	3000-3125	**3500**
Migraine Prophylaxis	250mg BID, titrate as needed up to 500mg BID	**250 - 500mg once daily x 1 week minimum, thereafter titrating to 1000mg once daily if needed.**

DOSAGE FORMS
Depakote ER is available in 250mg and 500mg tablets.

Supporting References:
1. Depakote ER P.I. Abbot Laboratories. North Chicago, IL. Rev 06.2002.
2. Clinical Pharmacology 2000 v.2.0.6. Electronic version. Accessed 01.2003
3. Lackner TE. Strategies for Optimizing Antiepileptic Drug Therapy in Elderly People. Pharmacotherapy. 2002;22(3):329-364.
4. Gardner ME, Ditmanson LF, Garrett RW, Slack M. Effectiveness of Divalproex Sodium in Severe Dementia-Related Aggression. *The Consultant Pharmacist.* 2001;16(9):839-843.
5. Alexopoulos GS et al (eds.) The Expert Consensus Guideline Series: Agitation in Older Persons with Dementia. A Postgraduate Medicine Special Report. April 1998. McGraw-Hill.
6. Centorrino F, Kelleher JP, Berry JM, et al. A Pilot Study of Extended Release Divalproex Sodium Switch from Standard Formulation of Divalproex Sodium in Maintenance Treatment of Bipolar Disorder and Schizoaffective Disorder, Bipolar Type. Paper presented at 42nd Annual New Clinical Drug Evaluation Unit (NCDEU) Meeting. Boca Raton, FL: 2002 June 10-13.
7. Uthman BM, Biton V, Dutta S, et al. Comparison of the Bioavailability of a Depakote Extended-Release Formulation Relative to the Depakote Delayed-Release Tablet Formulation in Adult Patients with Epilepsy on the Depakote Delayed-Release Tablet Formulation and an Enzyme-Inducing Antiepileptic Drug. Information on file at Abbott Laboratories.

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Divalproex Sodium Extended-Release (Depakote® ER, Abbott)

Preferred Extended-Release Divalproex

Divalproex Sodium Use in the Elderly: A New Formulation Offers New Opportunities

The use of anticonvulsant medications for a variety of indications is commonplace in nursing facilities. Divalproex sodium is used for migraine headaches, bipolar disease, and behavioral disorders associated with head trauma, mental retardation, and dementia. It also is used for the management of seizures. The new formulation of divalproex (Depakote ER) may offer some new opportunities for use in nursing facility residents.

The average long-term care facility resident (patient) of today is often sicker, receives more medication, and is more prone to manifesting medication side effects and interactions. Comorbidities such as Parkinson's disease, seizure disorders, and variant forms of dementia such as Lewy body dementia are common. These comorbidities affect on drug selection and increase the risk of serious side effects from commonly prescribed medications for behavioral symptoms: Side effects may include worsening of motor function, increased seizure rate, and falls.

Antipsychotics remain the preferred agents for the treatment of the symptoms of psychosis including hallucinations, harmful delusions, and paranoia. However, antipsychotics do not appear to offer significant advantages over divalproex sodium when treating mood disorders, including those associated with abnormal aggression and idiopathic agitation. The case series by Goldberg reported a 54% "much or more improved" Global Rating Scale, with an additional 18% "minimal improved" level of behavior in 22 elderly demented residents who failed to respond to eight weeks of 2 mg to 4 mg of risperidone.[1] The divalproex sodium dose was typical for such studies and ranged between 375 mg to 1,500 mg per day, with a mean serum level of 67.2 g/mL. The author also noted the subsequent reduction of other prescribed psychoactive medications, including trazodone, anticonvulsants, benzodiazepines, and antipsychotics. Although the results are observational, the results may have implications for addressing the issue of polypharmacy and for reducing the time for nurses to administer medication.

Although antipsychotics remain effective medications for the treatment of psychotic and possibly other symptoms of dementia, there are growing concerns over potential adverse effects. Concerns exist over the impact of antipsychotics on movement disorders, sedation, orthostatic hypotension, and control of blood glucose. Recently, preliminary analyses suggest the potential of atypical antipsychotics to increase the incidence of cerebrovascular adverse events (i.e., transient ischemic attacks and strokes). It is important to note that the clinical significance of these observations is hotly debated. These concerns have increased interest in alternative drug therapies with different safety profiles for treating behavioral and psychological symptoms of dementia.

One such class of medications is the mood stabilizers (e.g., carbamazepine, divalproex, gabapentin). Although mood stabilizers such as divalproex sodium have significant side effect profiles, clinicians have had time to develop effective dosing and monitoring strategies to minimize their occurrence and clinical impact. A recent double-blind, randomized, multicenter study reported the experience of divalproex sodium as an adjuvant with risperidone and olanzapine in the treatment of schizophrenic patients.[2] These results suggest a possible additional benefit in the elderly demented resident who does not optimally respond to antipsychotics alone. The improvement in symptom control may also provide an opportunity to reduce antipsychotic dosages.

Valproic acid, as an immediate-release, short-acting compound has seen limited use because its frequent dosage administration schedule and frequently occurring side effects of nausea, somnolence, and weight gain. These troublesome side effects appear to be associated with the more frequent peaks in the serum levels inherent in the shorter-duration valproic acid. Sedation in the elderly may increase the risk of falls and interfere with the normal activities of daily living (ADLs). Gastrointestinal upset, nausea, and vomiting may lead to the use of additional gastrointestional medications for symptomatic relief. Although not life-threatening, these side effects can lead to reduced compliance, diminished efficacy, and/or reduced quality of life for the patient.

Because of wide variation in serum level peaks and valleys with valproic acid, interpretation and timing of serum level samples is more difficult. In this respect, once-a-day Depakote ER, with its steady, flat serum level curve, has an advantage over valproic acid and the 12-hour Depakote or Depakote Sprinkle, with their two peaks per day. Side effects such as som-

nolence, nausea, vomiting, and weight gain are associated with the peaks of the serum levels and is significantly lessened when using Depakote ER.

Valproic acid's frequent dosing also increases the time needed for nurses to administer the drug and the opportunities for medication errors. Divalpoex sodium was developed in part to reduce the number of daily doses, thus improving compliance and reducing side effects and medication administration time. By comparing the package insert data, this sustained-release formulation resulted in about a 50% reduction in GI and central nervous system side effects. The tablet offers twice-a-day or every 12-hour dosing. Depakote also is available as Depakote Sprinkles, a sustained release product for twice-a-day or every 12-hour dosing. The Sprinkle capsule can be opened for use by residents who cannot swallow or have feeding tubes.

Depakote ER 500 mg was originally released with an indication for treatment of migraine headaches. The low incidence of side effects plus once-a-day dosing of 500 mg to 1,000 mg proved effective and well tolerated by migraine headache sufferers.[1] Recent-ly, Depakote ER was released in 250 mg strength, with an additional indication for use in seizure disorders. When only the 500-mg strength was available, the recommended gradual titration used in the elderly with behavioral disorders had to be carried out with Depakote tablets or Sprinkle, followed by a subsequent conversion to Depakote ER. Gradual titration is important in the elderly to limit the incidence of somnolence and other side effects.

The complexity with later conversion, especially in seizure patients, is compounded by the lack of bioequivalence between the two products. The bioequivalence issue results from an 11% to 19% lower serum level of valproic acid associated with Depakote ER than with Depakote. Although this difference is likely to be clinically insignificant when Depakote ER is used to control mood or behavior, it should be taken into account when converting from Depakote tablets to Depakote ER in a seizure patient. A dosing conversion table is shown in Table 1.

The degree of difference in serum levels is related to administration of Depakote ER with food. Depakote ER, under fasting and non-fasting conditions, given once daily produced an average bioavailability of 85% relative to an equal total daily dose of Depakote tablets given bid.[3]

The introduction of a lower strength of Depakote ER (250 mg) permitted the more gradual dosage titration recommended in the elderly with seizures or mood/behavior disturbances. Based on clinical experience, the maintenance dose for control of behaviors in most elderly residents will be between 500 mg and 1500 mg Depakote ER at bedtime. For the frail elderly, Depakote ER 250 mg administered at bedtime is the recommended starting dose, with an increase of 250 mg every five to seven days, based on response and presence of side effects. In less-frail elderly patients, a starting dose of 500 mg at bedtime may be appropriate, increasing the dose every five to seven days by 250 mg at bedtime.

TABLE 1. DOSE CONVERSION FROM DEPAKOTE TO DEPAKOTE ER

Depakote Total Daily Dose (mg)	Depakote ER (mg)
500 – 625	750
750 – 875	1000
1000 – 1125	1250
1250 – 1375	1500
1500 -1625	1750
1750	2000
1875 – 2000	2250
2125 – 2250	2500
2375	2750
2500 – 2750	3000
2875	3250
3000 – 3125	3500

Adapted from reference 3.

There is no information from well-designed clinical trials to suggest a target serum concentration range for divalproex in the treatment of behavioral symptoms in patients with dementia. The valproic acid level associated with control of behavior, however, is thought to be less than that required for seizure management. Seizure therapeutic ranges on laboratory reports may actually be misinterpreted as those required for behavior control by clinicians and state surveyors alike. Serum levels are useful to rule out high levels as a cause of toxicity and to help investigate reasons for

lack of benefit with normal dosage schedules. In the latter case, serum levels may detect noncompliance, drug interactions, and other causes of unexpected outcomes. For patients with dementia, the American Psychiatric Association recommends gradual dose increases based on behavioral response and side effects or until blood levels reach 50 mcg/mL to 60 mcg/ml for valproate[4].

Divalproex sodium and valproic acid carry additional side effect risks including thrombocytopenia. Although the risk for significant thrombocytopenia (<90,000/mm³) is small and often transient, a baseline complete blood count with a repeat count in four weeks to eight weeks is recommended when initiating therapy. Small decreases in platelet counts need to be assessed for the possibility of a dilutional effect. The risk of hepatotoxicity is seen most commonly in children less than two years of age with mental retardation and receiving multiple anticonvulsants. In older adults, the risk of hepatotoxicity is 1 per 118,000.[5] A baseline liver function panel, with a repeat in four weeks, is recommended. Subsequent liver function studies are ordered based on these preliminary findings or at six-month intervals. A suggested approach is to follow alanine aminotransferase (ALT) and intensify monitoring if the ALT rises more than three times the baseline. Ammonia levels are typically not obtained since false positives are common and liver function studies would need to be obtained to verify the clinical importance of an elevated ammonia level.

Divalproex sodium-induced tremors are associated with higher doses than commonly used to treat behavioral disturbances. Tremors, in my experience, if they occur, can usually be controlled with a beta-blocker, such as propranolol. Hemorrhagic pancreatitis was identified as a rare, but potentially serious, side effect at the time of the original submission to the Food and Drug Administration in 1985. Two cases occurred in the study population of 2,416 for an incidence rate of <1%. The side effect can occur up to two years into therapy and can be life threatening. The unpredictability and rarity of the side effect makes random amylase levels cost-ineffective. Amylase levels should be obtained when pancreatitis is suspected or when the gastrointestinal symptoms of pancreatitis, which are quite severe, are observed.

Divalproex sodium also has been widely accepted for treating a broad range of seizure disorders. Although the recommendation to convert seizure residents with newly diagnosed behavioral symptoms from their existing anticonvulsant therapy (i.e., phenytoin, carbamazepine, etc.) to Depakote ER would seem justified, in practice it is often challenging. Resistance is more common if the seizure disorder is under control. The consultant pharmacist may find greater acceptance to a conversion or consolidation of therapy if the seizure control is not adequate or if the treatment of seizures is just being initiated. The consultant pharmacist may need to work with the consultant neurologist, if one is involved in the resident's care. In these situations, the consultant pharmacist needs to carefully plan for gradual conversion and titration of medication as recommended in the package inserts. The pharmacist also should thoroughly screen for drug interactions, anticipating and explaining their significance to the prescriber. Often the interactions will affect the results and interpretation of the anticonvulsant serum levels.

In closing, Depakote ER offers an alternative medication for the control of behaviors commonly associated with dementia in the elderly. Mood-stabilizing agents have been included as alternatives to other psychoactive medications for the management of behavioral and psychological symptoms of dementia in several published guidelines. These include the International Psychogeriatric Associations Educational Pack on behavioral and psychological symptoms of dementia and in the American Family Physicians Guidelines for the management of dementia (see Table 2). Its lack of negative effects on dopamine and seizure threshold provides a unique opportunity for the drug's use in treating behavioral or mood disorders associated with Parkinson's disease, Lewy body dementia, and in behavioral-problem patients with seizure disorders. The once-a-day convenience of the dosage form combined with the improved safety profile makes Depakote ER a useful agent for first-line treatment as well as complimenting existing therapy for non-psychotic symptoms in dementia such as aggression, mania, idiopathic agitation, mood disorders, and bipolar-disease disease. Its value in the co-administration with atypical antipsychotics in schizophrenic patients suggests a benefit in treating

TABLE 2. MOOD-STABILIZING (ANTI-AGITATION) DRUGS IN ALZHEIMER'S DISEASE

Recommended uses: control of problematic delusions, hallucinations, severe psychomotor agitation, and combativeness; useful alternatives to antipsychotic agents for control of severe agitated, repetitive, and combative behaviors

General cautions: See comments about specific agents.

Trazodone (Desyrel)	*Initial dosage*: 25 mg per day; Maximum: 200 mg to 400 mg per day in divided doses	*Comments*: Use with caution in patients with premature ventricular contractions.
Carbamazepine (Tegretol)	*Initial dosage*: 100 mg twice daily; titrate to therapeutic blood level (4 mcg to 8 mcg per mL)	*Comments*: Monitor complete blood cell count and liver enzyme levels regularly; carbamazepine has problematic side effects and drug interactions.
Divalproex sodium (Depakote)	*Initial dosage*: 125 mg twice daily or Depakote ER 250 mg at bedtime; titrate to therapeutic blood level (40 mcg per mL to 90 mcg per mL)	*Comments*: Generally better tolerated than other mood stabilizers; monitor liver enzyme levels; monitor platelets, prothrombin time, and partial thromboplastin time as indicated.

Adapted from Reference 6.

of those only partially responding to antipsychotics or experiencing dose-related side effects. Opportunities to consolidate therapy of co-existing disorders with once-a-day therapy offers occasion to address the issues of polypharmacy and long medication pass times while simplifying the drug regimen with a relatively low cost, well-understood medication.

Thomas C. Snader, PharmD, FASCP
President TCS Pharmacy Consultants
He received a publication grant for this article from Abbott Laboratories.

REFERENCES
1. Goldberg R. The use of adjunctive divalproex for neuroleptic unresponsive behavioral disturbances in nursing home residents with dementia. Annals of Long-Term Care 1999;7:63-6.
2. Casey DE, Daniel DG, Wasser AA et al. Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. Neuropsychopharmacology 2003;28:182-92.
3. Depakote package insert, Abbott Laboratories. North Chicago, IL. January 2003.
4. American Psychiatric Association. Practice guideline for the treatment of patients with Alzheimer's disease and other dementias of late life. May 1997. Washington, DC: American Psychiatric Association. Available at http://www.psych.org/clin_res/prac_guide.cfm.
5. Pellock JM, Willmore LJ. A rational guide to routine blood monitoring in patients receiving antiepileptic drugs. Neurology 1991;41:961-4.
6. Cummings JL, Frank JC. Guidelines for managing Alzheimer's disease: part II. Treatment. Am Fam Physician 2002;65:2525-34.

Package insert

(Nos. 3826 and 7126)
03-5235-R4-Rev. January, 2003

DEPAKOTE® ER
DIVALPROEX SODIUM EXTENDED-RELEASE TABLETS

℞ only

IN PATIENTS RECEIVING
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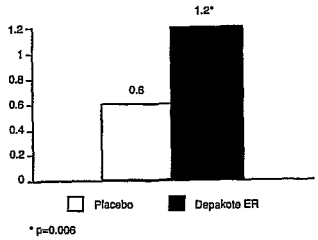
Figure 1
Mean Reduction In 4-Week
Migraine Headache Rates



* p=0.006

Epilepsy

The efficacy of DEPAKOTE in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in two controlled trials using DEPAKOTE (divalproex sodium delayed-release tablets).

In one, multiclinic, placebo controlled study employing an add-on design, (adjunctive therapy) using DEPAKOTE, 144 patients who continued to suffer eight or more CPS per 8 weeks during an 8 week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range" were randomized to receive, in addition to their original antiepilepsy drug (AED), either DEPAKOTE or placebo. Randomized patients were to be followed for a total of 16 weeks. The following table presents the findings.

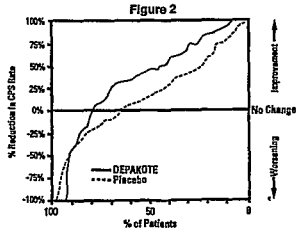
Adjunctive Therapy Study
Median Incidence of CPS per 8 Weeks

Add-on Treatment	Number of Patients	Baseline Incidence	Experimental Incidence
DEPAKOTE	75	16.0	8.9*
Placebo	69	14.5	11.5

* Reduction from baseline statistically significantly greater for DEPAKOTE than placebo at p ≤0.05 level.

Figure 2 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the adjunctive therapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo. This figure shows that the proportion of patients achieving any particular level of improvement was consistently higher for DEPAKOTE than for placebo. For example, 45% of patients treated with DEPAKOTE had a ≥50% reduction in complex partial seizure rate compared to 23% of patients treated with placebo.

Figure 2



The second study assessed the capacity of DEPAKOTE to reduce the incidence of CPS when administered as the sole AED. The study compared the incidence of CPS among patients randomized to either a high or low dose treatment arm. Patients qualified for entry into the randomized comparison phase of this study only if 1) they continued to experience 2 or more CPS per 4 weeks during an 8 to 12 week long period of monotherapy with adequate doses of an AED (i.e., phenytoin, carbamazepine, phenobarbital, or primidone) and 2) they made a successful transition over a two week interval to DEPAKOTE. Patients entering the randomized phase were then brought to their assigned target dose, gradually tapered off their concomitant AED and followed for an interval as long as 22 weeks. Less than 50% of the patients randomized, however, completed the study. In patients converted to DEPAKOTE monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 µg/mL in the low dose and high dose groups, respectively.

The following table presents the findings for all patients randomized who had at least one post-randomization assessment.

Monotherapy Study
Median Incidence of CPS per 8 Weeks

Treatment	Number of Patients	Baseline Incidence	Randomized Phase Incidence
High dose DEPAKOTE	131	13.2	10.7*
Low dose DEPAKOTE	134	14.2	13.8

* Reduction from baseline statistically significantly greater for high dose than low dose at p ≤0.05 level.

Figure 3 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the monotherapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for a more effective treatment is shifted to the left of the curve for a less effective treatment. This figure shows that the proportion of patients achieving any particular level of reduction was consistently higher for high dose DEPAKOTE than for low dose DEPAKOTE. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose DEPAKOTE monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates

THE DATA DESCRIBED BELOW WERE GAINED ALMOST EXCLUSIVELY FROM WOMEN WHO RECEIVED VALPROATE TO TREAT EPILEPSY. THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPSY DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.

OTHER CONGENITAL ANOMALIES (EG, CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPTIC DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TO CONGENITAL ANOMALIES.

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES. A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

Animal studies have demonstrated valproate-induced teratogenicity. 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 approximately 230 µg/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/m^2 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 µg/mL or greater (3.4 times the upper limit of the human therapeutic range for epilepsy or greater). Behavioral 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/m^2 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/m^2 basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 µg/mL (2.8 times the upper limit of the human therapeutic range for epilepsy).

The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

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

PRECAUTIONS

Hepatic Dysfunction

See **BOXED WARNING, CONTRAINDICATIONS** and **WARNINGS.**

Pancreatitis

See **BOXED WARNING** and **WARNINGS.**

Hyperammonemia

Hyperammonemia has been reported in association with valproate therapy 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 and an ammonia level should be measured. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see **CONTRAINDICATIONS** and **WARNINGS – Urea Cycle Disorders**).

Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered.

General

Because of reports of thrombocytopenia (see **WARNINGS**), inhibition of the secondary 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 DEPAKOTE be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of DEPAKOTE 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 ≤ 75 x 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 µg/mL (females) or ≥ 135 µg/mL (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Since DEPAKOTE 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 where clinically appropriate (see **PRECAUTIONS – Drug Interactions**).

Nervous System		
Somnolence	7%	2%
Other		
Infection	15%	14%

[1]The following adverse events occurred in greater than 5% of DEPAKOTE ER-treated patients and at a greater incidence for placebo than for DEPAKOTE ER: asthenia and flu syndrome.

The following additional adverse events were reported by greater than 1% but not more than 5% of DEPAKOTE ER-treated patients and with a greater incidence than placebo in the placebo-controlled clinical trial for migraine prophylaxis:

Body as a Whole: Accidental injury, viral infection.
Digestive System: Increased appetite, tooth disorder.
Metabolic and Nutritional Disorders: Edema, weight gain.
Nervous System: Abnormal gait, dizziness, hypertonia, insomnia, nervousness, tremor, vertigo.
Respiratory System: Pharyngitis, rhinitis.
Skin and Appendages: Rash.
Special Senses: Tinnitus.

Table 2 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in the DEPAKOTE-treated group was greater than 5% and was greater than that for placebo patients.

Table 2
Adverse Events Reported by >5% of DEPAKOTE-Treated Patients During Migraine Placebo-Controlled Trials with a Greater Incidence than Patients Taking Placebo[1]

Body System Event	Depakote (N=202)	Placebo (N=81)
Gastrointestinal System		
Nausea	31%	10%
Dyspepsia	13%	9%
Diarrhea	12%	7%
Vomiting	11%	1%
Abdominal Pain	9%	4%
Increased Appetite	6%	4%
Nervous System		
Asthenia	20%	9%
Somnolence	17%	5%
Dizziness	12%	6%
Tremor	9%	0%
Other		
Weight Gain	8%	2%
Back Pain	8%	6%
Alopecia	7%	1%

[1]The following adverse events occurred in greater than 5% of DEPAKOTE -treated patients and at a greater incidence for placebo than for DEPAKOTE: flu syndrome and pharyngitis.

The following additional adverse events not referred to above were reported by greater than 1% but not more than 5% of DEPAKOTE-treated patients and with a greater incidence than placebo in the placebo-controlled clinical trials:

Body as a Whole: Chest pain.
Cardiovascular System: Vasodilatation.
Digestive System: Constipation, dry mouth, flatulence, stomatitis.
Hemic and Lymphatic System: Ecchymosis.
Metabolic and Nutritional Disorders: Peripheral edema.
Musculoskeletal System: Leg cramps.
Nervous System: Abnormal dreams, confusion, paresthesia, speech disorder, thinking abnormalities.
Respiratory System: Dyspnea, sinusitis.
Skin and Appendages: Pruritus.
Urogenital System: Metrorrhagia.

Epilepsy

Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, DEPAKOTE was generally well tolerated with most adverse events rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the DEPAKOTE-treated patients (6%), compared to 1% of placebo-treated patients.

Table 3 lists treatment-emergent adverse events which were reported by ≥5% of DEPAKOTE-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse events can be ascribed to DEPAKOTE alone, or the combination of DEPAKOTE and other antiepilepsy drugs.

Table 3
Adverse Events Reported by ≥ 5% of Patients Treated with DEPAKOTE During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures

Body System/Event	Depakote (%) (n = 77)	Placebo (%) (n = 70)
Body as a Whole		
Headache	31	21
Asthenia	27	7
Fever	6	4
Gastrointestinal System		
Nausea	48	14
Vomiting	27	7
Abdominal Pain	23	6
Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
Nervous System		
Somnolence	27	11
Tremor	25	6
Dizziness	25	13
Diplopia	16	9
Amblyopia/Blurred Vision	12	9

(including ileostomy or colostomy) gastrointestinal disorders with shortened GI transit times, there have been postmarketing reports of DEPAKOTE ER tablets in the stool.

CNS Effects: Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, and parkinsonism have been reported with the use of valproate. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with hyperammonemic encephalopathy, particularly in patients with underlying urea cycle disorers (see **WARNINGS – Urea Cycle Disorders** and **PRECAUTIONS**).

Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

Dermatologic: Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6 month old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis 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.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

Musculoskeletal: Weakness.

Hematologic: Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage (see **PRECAUTIONS - General and Drug Interactions**). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, and acute intermittent porphyria.

Hepatic: Minor elevations of transaminases (eg, SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see WARNINGS).

Endocrine: Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests (see **PRECAUTIONS**).

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

Pancreatic: Acute pancreatitis including fatalities (see **WARNINGS**).

Metabolic: Hyperammonemia (see **PRECAUTIONS**), hyponatremia, and inappropriate ADH secretion.

There have been rare reports of Fanconi's syndrome occurring chiefly in children.

Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.

Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary: Enuresis and urinary tract infection.

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

Other: Anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, and fever.

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

DEPAKOTE ER is an extended-release product intended for once-a-day oral administration. DEPAKOTE ER tablets should be swallowed whole and should not be crushed or chewed.

Migraine

The recommended starting dose is 500 mg once daily for 1 week, thereafter increasing to 1000 mg once daily. Although doses other than 1000 mg once daily of DEPAKOTE ER have not been evaluated in patients with migraine, the effective dose range of DEPAKOTE (divalproex sodium delayed-release tablets) in these patients is 500-1000 mg/day. As with other valproate products, doses of DEPAKOTE ER should be individualized and dose adjustment may be necessary. If a patient requires smaller dose adjustments than that available with DEPAKOTE ER, DEPAKOTE should be used instead.

Epilepsy

DEPAKOTE ER is indicated as monotherapy and adjunctive therapy in complex partial seizures in adult patients, and in simple and complex absence seizures in adult patients. As the DEPAKOTE ER dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see **PRECAUTIONS -- Drug Interactions**).

Complex Partial Seizures for adult patients:

Monotherapy (Initial Therapy) : DEPAKOTE ER has not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 µg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 µg/mL in females and 135 µg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidenceof adverse reactions.

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

ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
PRINTED IN U.S.

Patient Information Leaflet

Important Information for Women Who Could Become Pregnant About the Use of DEPAKOTE® ER (divalproex sodium) Tablets for Migraine

Please read this leaflet carefully before you take DEPAKOTE® ER (divalproex sodium) tablets. This le provides a summary of important information about taking DEPAKOTE ER for migraine to women who c become pregnant. DEPAKOTE ER may also be prescribed for uses other than those discussed in this leafl you have any questions or concerns, or want more information about DEPAKOTE ER, contact your doct pharmacist.

Information For Women Who Could Become Pregnant

DEPAKOTE ER is used to prevent or reduce the number of migraines you experience. DEPAKOTE ER ca obtained only by prescription from your doctor. The decision to use DEPAKOTE ER for the preventic migraine is one that you and your doctor should make together, taking into account your individual needs medical condition.

Before using DEPAKOTE ER, women who can become pregnant should consider the fact that DEPAK has been associated with birth defects, in particular, with spina bifida and other defects related to fal of the spinal canal to close normally. Although the incidence is unknown in migraine patients treated DEPAKOTE, approximately 1 to 2% of children born to women with epilepsy taking DEPAKOTE in first 12 weeks of pregnancy had these defects (based on data from the Centers for Disease Control, a agency based in Atlanta). The incidence in the general population is 0.1 to 0.2%.

Information For Women Who Are Planning To Get Pregnant

- Women taking DEPAKOTE ER for the prevention of migraine who are planning to get pregnant sh discuss with their doctor temporarily stopping DEPAKOTE ER, before and during their pregnancy.

Information For Women Who Become Pregnant While Taking DEPAKOTE ER

- If you become pregnant while taking DEPAKOTE ER for the prevention of migraine, you should contact doctor immediately.

Other Important Information About DEPAKOTE ER Tablets

- DEPAKOTE ER tablets should be taken exactly as it is prescribed by your doctor to get the most benefits fr DEPAKOTE ER and reduce the risk of side effects.
- If you have taken more than the prescribed dose of DEPAKOTE ER, contact your hospital emergency ro or local poison center immediately.
- This medication was prescribed for your particular condition. Do not use it for another condition or give drug to others.

Facts About Birth Defects

It is important to know that birth defects may occur even in children of individuals not taking any medications without any additional risk factors.

Facts About Migraine

About 23 million Americans suffer from migraine headaches. About 75% of migraine sufferers are women. migraine is described as a throbbing headache that gets worse with activity. Migraine may also include naus and/or vomiting as well as sensitivity to light and sound. Migraine usually happens about once a month, but so people may have them as often as once or twice a week. Often, the symptoms from a migraine can cause peo to miss work or school.

If you have frequent migraines, or if acute treatment is not working for you, your doctor may prescribe preventative therapy. Preventative (prophylactic) treatment is used to prevent attacks and reduce the frequency a severity of headache events.

This summary provides important information about the use of DEPAKOTE ER for migraine to women who cou become pregnant. If you would like more information about the other potential risks and benefits of DEPAKO ER, ask your doctor or pharmacist to let you read the professional labeling and then discuss it with them. If y have any questions or concerns about taking DEPAKOTE ER, you should discuss them with your doctor.

03-5235-R4

Revised: January, 2003

Manufactured by:

ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.

PRINTED IN U.S.

REDACTED - LTCPP-Clinical Project Manager
"LTCPP-CPM"

From: REDACTED - LTCPP-NDCPD
Sent: Wednesday, January 21, 2004 10:41 AM
To: REDACTED - LTCPP-CPM
Subject: FW: Abbott Mailing Content

REDACTED - LTCPP-CPM

Items included in the Depakote-ER mailer:

- Cover Letter
- Depakote-ER Package Insert (Mail Marketing will have to reprint)
- Consultant Pharmacist Journal: Tom Snader article (get permission and/or reprints from ASCP starting at 10,000. Check for a price break at 5000 and over)
- Depakote-ER Monograph (Mail Marketing will have to reprint)

REDACTED should be finalizing the data analysis today, then REDACTED - LTC-NAM and I will determine the total quantity for the mailed pieces.

Thanks,
REDACTED - LTCPP-NDCPD

-----Original Message-----
From: REDACTED - LTC-NAM@abbott.com [mailto REDACTED - LTC-NAM@abbott.com]
Sent: Tuesday, January 20, 2004 9:10 PM
To: REDACTED - LTCPP-NDCPD
Subject: RE: Mailing Content

Hi REDACTED - LTCPP-NDCPD
I bet she knows some good words. Well when REDAC is gone she won't have him to cuss. I have a transition conference call with her and REDACT next Fri.

Will have to work on the PI. Don't know if we have a 2 pg one..what if we don't? I would rather come up with a publication/reprint that was a little more independent and less an Abbott marketing piece. I am still thinking of Snader's Sept Depakote ER article in the Cons Pharmacist...can you get that fairly quickly to make a Feb mailing...I just think whatever we send needs to have some meat. If needed I can talk to REDACTED about it.

Any word on the # Docs for the mailing? That and a budget and I can get things rolling for a check.

Did REDACTED have numbers on the # of letters sent by the CPs for new Depakote patients?..I have to believe REDACTED asked.

Weather better for golf than fishing. A lot of wind. Nice this afternoon. All the conditions were good but fish hard to find. One small Mako shark. Nasty little 3 footer. We are hoping for a nice full day of fishing tomorrow.

Call me if we need to discuss this or other. I have my cell REDACTED

REDACTED - LTC-NAM
LTC National Account Manager
Abbott Laboratories
Phone: REDACTED
Fax: REDACTED
REDACTED - LTC-NAM@abbott.com

'REDACTED - LTCPP-NDCPD@REDACTED - LTCPP.com>

01/20/2004 02:18 PM

To: REDACTED - LTC-NAM@abbott.com'" <REDACTED - LTC-NAM@abbott.com>
cc:
Subject: RE: Mailing Content

REDACTED - LTC-NAM

Well REDACTED was still complaining on the growth contract issue and cussed you once or twice, but other than that all went OK.

- The PI you sent is the 27 page version. I need the 1 or 2 page version.
- "Improving Quality of Life: Use of Mood Stabilizers in Senior Care" is an Abbott publication. I'll send it to you when you return.
- I'll add the Depakote Monograph in place of the sprinkle sheet.
- Med-asses corrected to Med-passes. (that would have been VERY embarrassing!, thanks)

Here's to Good Fishing!
REDACTED - LTCPP-NDCPD

-----Original Message-----
From: REDACTED - LTC-NAM@abbott.com [mailto REDACTED - LTC-NAM@abbott.com]
Sent: Tuesday, January 20, 2004 11:27 AM
To: REDACTED - LTCPP-NDCPD
Subject: Mailing Content

REDACTED - LTCPP-NDCPD

I will be fishing in the warm waters of the FL keys all this week. Call me on my cell anytime you need to REDACTED. Let me know as soon as you have a Doc list and a budget.
See thoughts and questions below in red.

Thanks for all your support. (Please put in a good word for me and Depakote at the vendor meetings this week)

REDACTED - LTC-NAM

REDACTED - LTC-NAM
LTC National Account Manager
Abbott Laboratories
Phone: REDACTED
Fax: REDACTED
REDACTED - LTC-NAM@abbott.com

'REDACTED - LTCPP-NDCPD@REDACTED - LTCPP.com>

01/14/2004 03:39 PM

To: REDACTED - LTC-NAM@abbott.com" <REDACTED - LTC-NAM@abbott.com>
cc:
Subject: RE: LTCPP Depakote data request

Mr Depakote:

If you can interrupt your *ice* (foolish) fishing for a moment,

Here's the letter I will include in the mailer along with the PI and need your thoughts on an appropriate study to include as well.
I have a publication from the CNS/LTC entitled:
Special Report: "Improving Quality of Life: Use of Mood Stabilizers in Senior Care" that I can fax if needed or I'm open to suggestions. I do not have this and would like to read it. (This is not one of those Abbott sponsored publications is it?) Will try and find a fax machine in FL if I need to.

So far Items included in the mailer are:

- Cover Letter Looks excellent! One typo on bullet point w/ med-Passes
- PI Attached
- Clinical Study or review publication (TBD)
- Depakote Sprinkle Administration sheet that has the chart of Depakote benefits listed vs. VPA on the reverse side Good idea...or maybe we send the REDACTED - LTCPP Depakote ER monograph...that might help us more with new RXs. That would also have the conversion table (Docs might well keep the piece in their office as a reference to) OR we can send them both.
  Do you have an e-copy of the 1 page Depakote-ER PI? Attached below

  Thanks for the support!
  REDACTED - LTCPP-NDCPD

-----Original Message-----
From: REDACTED - LTC-NAM@abbott.com [mailto REDACTED - LTC-NAM@abbott.com]
Sent: Tuesday, January 13, 2004 2:27 PM
To: REDACTED; REDACTED; REDACTED; REDACTED
Cc: REDACTED - Abbott s LTC Dir. of Sales; REDACTED - LTCPP-NDCPD; REDACTED; REDACTED
Subject: LTCPP Depakote data request

Hi Everyone,

I had a chance to put the together the analysis and comparisons that were requested during our meeting on December 18th.

- Slide #1 shows the kgs/bed for each of the LTCPPs. 3/4 LTCPPs have virtually identical amounts of Depakote used per serviced bed. One LTCPP falls slightly below the others. This information would suggest that the opportunity for Depakote growth is similar for all major LTCPPs
  - Slide #2 illustrates the average annual growth rates for the LTCPPs. Two LTCPPs had higher rates of growth in 2002 than in 2003 and the other two LTCPPs had higher

growth rates in 2003 vs 2002. REDACTED - LTCPP's growth in 2002 was significantly greater than in 2003, and I believe this was due primarily to the successful conversion of VPA to Depakote to Depakote ER. The average rate of growth through Q3 2003 for the other LTCPPs averaged 9%. I did receive some information for Q4 2003 for LTCPP "C" and the growth rate was 15% for the quarter and this is reflected in Slide #3

- Slide #3 indicates the growth of the LTCPPs by quarter. Slide #4 shows the rate of ER conversion by quarter through Q3 2003

Depakote growth continues to be steady across the LTC channel. Abbott is fully committed to our partnership with REDACTED - LTCPP with regards to Depakote. Significant opportunity remains for Depakote's use in LTC and I believe that if we execute our planned strategy our successes will continue in 2004 and beyond.
I will be working at all levels to help ensure the success of the Depakote Initiatives.

Please feel free to contact me with any questions on the information

Regards,
REDACTED - LTC-NAM

REDACTED - LTC-NAM
LTC National Account Manager
Abbott Laboratories
Phone: REDACTED
Fax: REDACTED
REDACTED - LTC-NAM@abbott.com

REDACTED

REDACTED - LTCPP-CPM

From: REDACTED - LTCPP-NDCPD
Sent: Tuesday, January 06, 2004 2:50 PM
To: REDACTED - LTC-NAM@abbott.com
Cc: REDACTED - LTCPP-CPM
Subject: RE: REDACTED - LTCPP mailing-follow up questions

REDACTED - LTC-NAM

Happy New Year! Are you sober yet?

The mailer can be done as soon as the materials are developed and drop shipped to the printer. That entails:

- Data pull to determine the scope of the project (assume 10,000 joint prescribers of benzos and aytpicals)
- Just a PDF of the Depakote PI will do. The printer will reproduce the qty. we need.
- Getting enough reprints for the project will be the time limiting factor if we need to obtain and pay for publishing rights then print 10,000.
- Assuming all goes smoothly, Feb. 1 is a good date for the release.

REDACTED - LTCPP-CP and I will begin working on the mailer and REDACTED - LTCPP-CP will be our primary point person.

We'll work with REDACTED (our account executive in Texas) on the Daybreak project. His contact numbers are attached below.

Thanks Depakote Man!
PS. What happened to Michigan??

-----Original Message-----
From: REDACTED - LTC-NAM@abbott.com [mailto REDACTED - LTC-NAM@abbott.com]
Sent: Monday, January 05, 2004 7:16 PM
To: REDACTED - LTCPP-NDCPD
Subject: REDACTED - LTCPP mailing-follow up questions

Thanks REDACTED for the examples.

- I would like to put together a proposed budget for the mailing ASAP. How does this work? I guess we need to target the top high prescibers of benzodiapines and atypicals. How many would that be would you guess? I would guess that in addition to your cover/positioning letter you would need the Depakote ER package insert. Would you also include a clinical reprint as well to reinforce the cover/positioning letter?
  - How long does it take to set up and complete a mailing? I would like to get it done ASAP
    - On an unrelated note, we definately want to sponsor the April program for REDACTED with the customer (REDACTED) you mentioned when we met in Tampa. Who do I work with to get the program set up? I know that I can run the program funding through you.

Thanks

REDACTED - LTC-NAM
LTC National Account Manager
Abbott Laboratories
Phone: REDACTED
Fax: REDACTED
REDACTED - LTC-NAM@abbott.com

"REDACTED - LTCPP-NDCPD@REDACTED - LTCPP.com>

12/19/2003 01:58 PM

To: REDACTED - LTC-NAM (E-mail)" REDACTED - LTC-NAM
cc:
Subject: REDACTED - LTCPP mailer - examples

REDACTED - LTC-NAM
As we discussed:
<REDACTED mailer cover letter FINAL.doc>>
<< REDACTED .pdf>>

REDACTED - LTCPP-NDCPD
REDACTED - LTCPP
National Dir.of Clinical Program Development
REDACTED ext REDACTED

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REDACTED

REDACTED - LTCPP-CPM

From: REDACTED - LTCPP-NDCPD
Sent: Tuesday, February 03, 2004 9:12 AM
To: REDACTED - LTCPP-CPM
Subject: RE: permission to reprint article

REDACTED - LTCPP-CP,

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-----Original Message-----
From: REDACTED - LTCPP-CPM
Sent: Friday, January 30, 2004 10:42 AM
To: REDACTED - LTCPP-NDCPD
Subject: FW: permission to reprint article

REDACTED - LTCPP-NDCPD

I understand permission was granted to reprint the article, however can you be specific as to what I need to do with REDACTED at Mail Marketing with this?

REDACTED - LTCPP-CPM
Clinical Project Manager
REDACTED - LTCPP

-----Original Message-----
From: REDACTED @ascp.com]
Sent: Thursday, January 29, 2004 4:48 PM
To: REDACTED - LTCPP-CPM
Subject: Re: permission to reprint article

REDACTED - LTCPP-CP,
Sorry for the delay in responding to your request. We are granting you permission to reprint the article. Please see the terms below.

American Society of Consultant Pharmacists
Reprint Permission Terms

I am pleased to grant your recent request for permission to reprint the article(s) listed below from The Consultant Pharmacist :

September 2003 issue of the Consultant Pharmacist on: Divalproex Sodium Use in the Elderly: A New Formulation Offers New Opportunities. This article was written by Thomas C. Snader, PharmD.

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Thank you for your interest in ASCP's publications.

REDACTED

American Society of Consultant Pharmacists REDACTED

REDACTED

America's Senior Care Pharmacists (tm)

From: "REDACTED - LTCPP-CPM" <CMC4211@REDACTED - LTCPP.com>
Date: Wed, 21 Jan 2004 10:49:44 -0500
To: REDACTED
Subject: permission to reprint article

REDACTED,

I am requesting permission to reprint an article in the September 2003 issue of the Consultant Pharmacist on: Divalproex Sodium Use in the Elderly: A New Formulation Offers New Opportunities. This article was written by Thomas C. Snader, PharmD. The purpose is to copy this article and sent it out in a mailer to our pharmacists.

Thank you.

REDACTED - LTCPP-CPM

Clinical Project Manager

REDACTED - LTCPP

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REDACTED

REDACTED - LTCPP

January 2004

Dear Health Care Professional:

As you are aware, REDACTED - LTCPP has developed a geriatric-specific drug formulary. We would like to share some important information about our Select Formulary with you. Our preferred pharmaceutical products are selected through a three-tier evaluation process that begins with review by an expert external national Pharmacy and Therapeutics (P&T) Committee. Based on the P&T Committee's evaluation and further analysis of pharmacoeconomic and cost data, REDACTED - LTCPP selects the most appropriate products for elderly residents to include within the Select Formulary.

Depakote and its derivatives have FDA approval for a variety of indications including bipolar disorder, seizure disorders, and migraine headache prophylaxis. In addition to these uses, Depakote and Depakote-ER are being used with increasing frequency to treat/manage agitation, anger, and hostility associated with dementia in the elderly. For elderly residents requiring therapy for a dementia related behavior disorder, **Depakote ER®** has been granted preferred status on the PharMerica's formulary. Depakote ER® is a logical cost-effective choice for treating elderly patients with these challenging behavioral symptoms.

Depakote ER® should be considered for patients with dementia related behaviors including:

- Initial therapy for patients with agitation anger, and hostility symptoms
- Adjunctive therapy for patients partially responsive to an atypical antipsychotic (antipsychotic can be tapered to a lower dose or eliminated after stabilization of behaviors)
- Replacement therapy for patients receiving benzodiazepines

- **Depakote ER®** can be dosed once daily and has improved side effects profiles vs the original Depakote DR (delayed release) with significant decreases in sedation and gastrointestinal complaints.

- **Depakote ER®** 500mg costs less than equivalent doses of the original Depakote DR (delayed release) with additional pharmacoeconomic savings in decreased med-passes and increased quality of life.

- Use of **Depakote ER®** instead of atypical antipsychotics and benzodiazepines can also positively impact the nursing facilities Quality Indicator Report.

Physician prescribing in compliance with the formulary can maintain or improve resident outcomes while containing costs. This also will minimize the number of calls and interventions from nursing and pharmacy to change prescriptions to formulary-preferred drugs. We appreciate your support of these formulary preferences for our long-term care patients.
Enclosed you will find complete prescribing information that will be helpful.

If you have any questions, please contact the REDACTED - LTCPP consultant pharmacist in the facility where you practice.

Sincerely,

REDACTED - LTCPP-NDCPD

National Director of Clinical Program Development
Chair, P&T Liaison Committee

Disclaimer: Information contained in this letter is for general guidelines only. Prescribing and dosing should be based on individual patient conditions. Portions of the accompanying literature have been supported by an unrestricted educational grant from Abbott Laboratories.