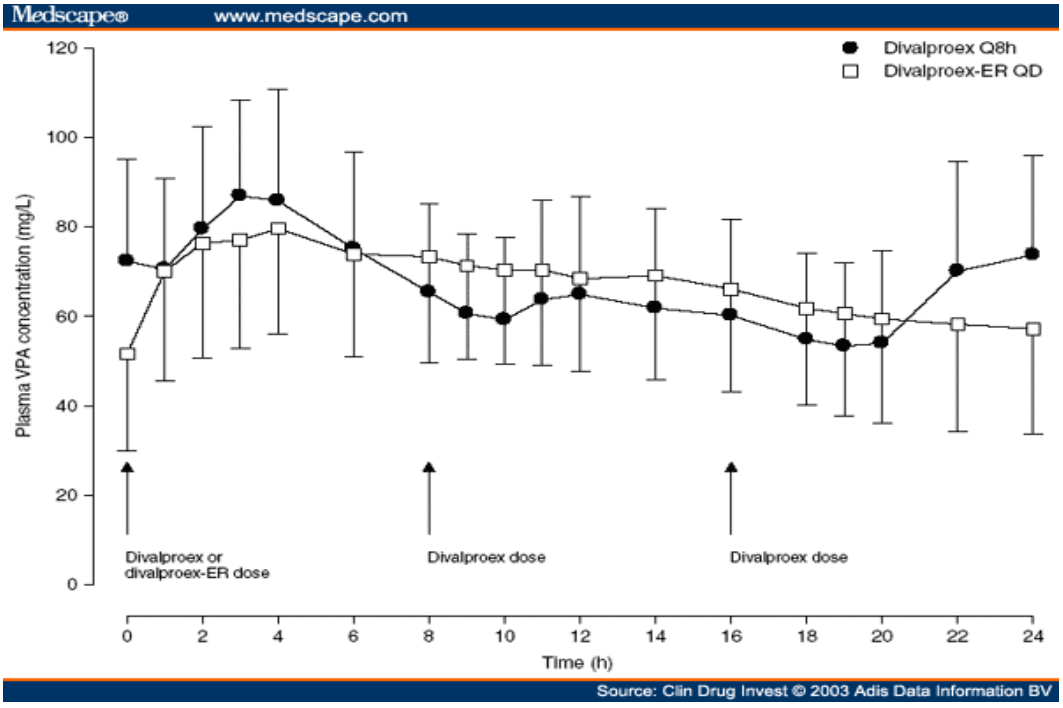
Depakote EC versus Depakote ER (NDF Name Depakote SA)
VA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient.

There are currently two oral formulations of divalproex sodium available. The first agent on the market (1983) was an enteric coated tablet (Divalproex-EC), which results in a delayed-release pharmacokinetic profile and requires multiple daily doses. In 2002, a sustained release formulation (Divalproex-SA for NDF orderable item), allowing once daily administration, was approved. Divalproex sodium is routinely used in various epilepsy disorders[1], prophylaxis of migraine headache, as well as for treatment of mania associated with bipolar disorder. [1,2] Patient compliance is a critical component of therapy for these disease states. The once-daily administration of medication has been shown to substantially enhance patient compliance compared with more frequent administration[3,4]. Thus, divalproex sodium- sustained release (SA) may provide advantages in certain patient populations. However, there is a risk associated with product confusion due to the similar names and indications for the delayed and extended release preparations.

A multicenter, randomized, cross over trial in 76 epilepsy patients compared the bioavailability of the two divalproex sodium preparations. Additionally, the study patients were receiving concomitant enzyme inducing antiepileptic agents (carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate or primidone).[5] The results of the pharmacokinetic analysis can be seen in Figure 1 where a comparison of plasma levels between the EC and SA formulations is described. The results of the trial demonstrated that patients with epilepsy taking Divalproex-EC may switch to 8–20% higher doses of divalproex-SA and have equivalent divalproex exposure, lower fluctuation in serum concentrations, and similar tolerability. The specific divalproex dose across a wide range of doses used in epilepsy and the presence of a concomitant enzyme-inducing AED did not have a statistically significant effect on divalproex-ER/divalproex relative bioavailability. These findings, in both epilepsy and bipolar disease, have been corroborated by other investigators as well.[6-10]

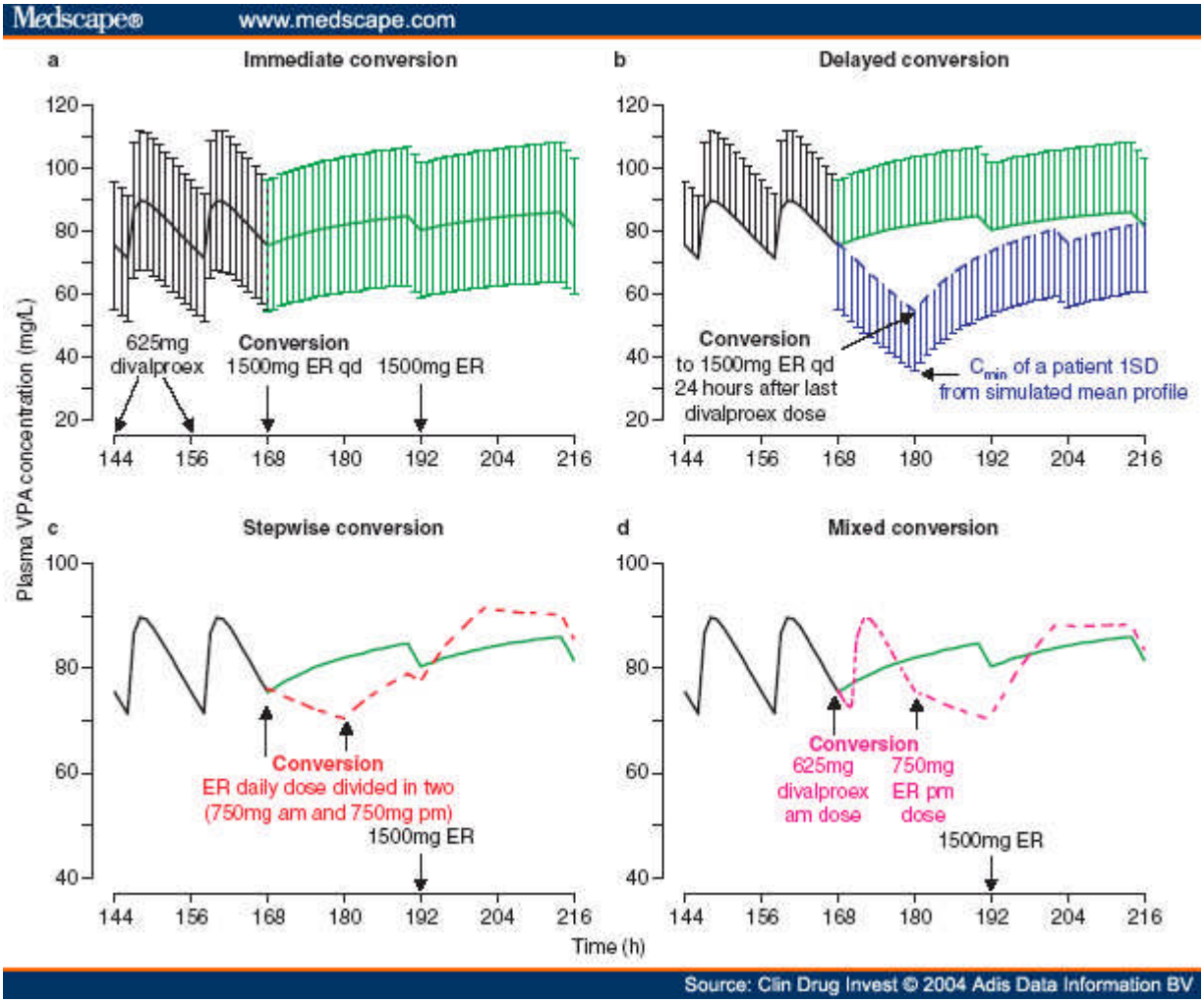
Figure 1: Mean plasma valproic acid concentration time profiles



Note in graphic Divalproex ER is the same as Divalproex SA in the text

Reed and colleagues conducted a computer simulation of conversion for divalproex EC to SA.[12] The four possible divalproex q12h to once-daily divalproex ER formulation conversion strategies selected for study were the following: immediate conversion 12 hours after the last divalproex dose; delayed conversion 24 hours after the last divalproex dose; stepwise conversion, i.e. half the divalproex SA daily dose in both the morning and evening for 1 day; and mixed conversion, i.e. half divalproex daily dose in the morning and half divalproex SA daily dose in the evening for 1 day, prior to converting to once-daily divalproex SA. The results of the models demonstrated that the process to convert between EC and SA products does not require a stepwise conversion or withdrawal phase. If these techniques are implemented patients will undergo the largest changes in plasma concentrations which may result in loss of therapeutic effect. Employing a one time immediate conversion was shown to result in the least amount of plasma concentration variability and would likely be the most convenient for patients. Figure 2 provides an example from the computer model that shows the result so various conversion techniques.

Figure 2: Mean plasma valproic acid concentration over time



Note in graphic Divalproex ER is the same as Divalproex SA in the text

The conversion of divalproex EC to SA has been shown to be safe and effective. Patients should be converted with an increase in dose of 8-20% when going to the SA product. For example, a patient receiving 1000 mg/day of the EC product could convert to 1250 mg of the SA product. Table 1 is the manufacturer's recommended conversion doses. Conversion can be done as a one time change and need not be titrated. Plasma levels should be monitored according to the clinical condition of the patient.

Table 1:Dose Conversion

Depakote (total daily dose in mg)	Depakote SA (total daily dose in 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

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