MEDCO FORUM®

PRESENTING INNOVATIVE PRODUCTS & SERVICES TO HEALTHCARE PROFESSIONALS

VOLUME 12 NUMBER 10 APRIL 2005

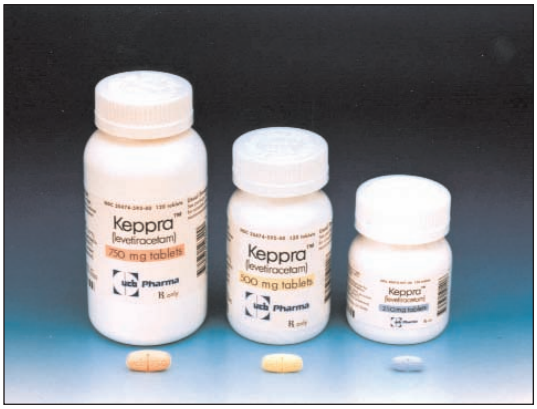
REPRINT

KEPPRA® (LEVETIRACETAM) TABLETS—ORAL SOLUTION

The #1 Choice for Treating Partial Onset Seizures

Keppra® (**levetiracetam**), a unique antiepileptic drug (AED), is indicated as an adjunctive therapy in the treatment of adults with partial-onset seizures—one of the most common forms of epilepsy. Keppra has a novel activity and pharmacokinetic profile that contributes to seizure control without concern for drug interactions. Keppra's limited metabolism is not dependent on any liver cytochrome P450 isoenzymes. It is excreted primarily by the kidneys and circulates largely unbound to plasma proteins.

Since its launch, Keppra, which was developed by the global research-based pharmaceutical sector of **UCB S.A.** (worldwide headquarters in Brussels, Belgium), is marketed in the United States by **Georgia-based UCB Pharma, Inc.**, has had more than 500,000 unique patient starts in the United States (*1*) and has the highest refill rate of second-generation AEDs (*2*). Keppra is approved for use in more than 50 countries, and is available in 250-, 500-, or 750-mg tablets, and as a grape-flavored 100-mg/mL oral solution for those who prefer a liquid or have difficulty swallowing tablets. Keppra can be taken with or without food and does not require blood level tests. The recommended starting dose (1,000 mg/day) is effective at the outset, which is good news for patients who often have to begin medication at a subtherapeutic level to minimize adverse effects. A retrospective analysis examined the time to onset of action after initiation of levetiracetam 1,000 mg in adult patients with refractory partial seizures. The results confirmed a rapid onset of action and indicated a significant increase in the proportion of seizure-free patients as of day +1 after initiation of therapy, when compared with placebo (*3*).



The aim of drug therapy is to improve quality of life by controlling seizures, while minimizing side effects. Clinical studies have shown Keppra has achieved significant response rates within 2 weeks, and is generally well tolerated. Keppra has pharmacokinetic properties that make it easy to start and easy to manage. Michael Smith, MD, Director, Rush Epilepsy Center (Chicago, IL), says, "Keppra is a unique anticonvulsant with a novel mechanism of action. It has minimal liver metabolism. It is well tolerated with a good adverse effects profile. The combination of strong efficacy [and] good tolerability, without affecting other medications, makes Keppra a logical choice for the treatment of partial epilepsy."

In addition to reducing seizure frequency, and severity, AEDs should ideally give patients freedom from seizures. Keppra has been proven to provide excellent seizure freedom rates. One study concluded that more patients responded (minimum 50% reduction in partial seizure frequency) to levetiracetam than placebo, with rates of 33% in the 1,000-mg/day group and 39.8% in the 3,000-mg/day group, compared with 10.8% in the placebo group ($p < 0.001$). Of 199 patients receiving levetiracetam, 11 became seizure-free, while no patient in the placebo group did so (*4*). In addition to providing superior freedom from seizure, Keppra has been shown to provide sustained long term

efficacy—up to 4.5 years (*5*). An additional publication revealed that according to Kaplan–Meier survival analysis, the estimated long-term continuation rate was 60% after 1 year; 37% after 3 years; and 32% after 5 years (*6*).

In the KEEPER™ Phase IV Community Based Trial with 1,030 patients, which collected information regarding efficacy and safety in a community setting, results showed that 20% of patients achieved seizure freedom overall (with 40% achieving seizure freedom during a 6-week period of stable dosing) and overall, 58% of patients responded (*7*). In a retrospective analysis of a subset of patients greater than or equal to 65 years of age, 77% were ≥ 50% responders, 57% were ≥ 75% responders, and 40% were 100% responders (*8*).

According to Gregory K. Bergey, MD, Professor of Neurology, Director, Johns Hopkins Epilepsy Center, Johns Hopkins University School of Medicine and Hospital (Baltimore, MD), "levetiracetam is an agent with an excellent cognitive profile that can be introduced at therapeutic doses. With over 500,000 patient exposures in the United States and more worldwide, there have been no safety-related concerns, and this was reflected in the recent 2004 American Academy of Neurology guidelines for second generation AEDs. It does not produce hepatic induction and has no significant interactions with other medications, making it an excellent choice for patients on multiple medications (e.g. elderly) or those patients on medications which would be adversely affected by hepatic induction (e.g. chemotherapy, protease inhibitors, other AEDs). Although the approved indications are for partial seizures, a growing number of clinical reports suggest it may have a broad spectrum of efficacy. Because it is a non-sedating AED that can be rapidly introduced when necessary, it is expected that levetiracetam will see increasing use in acute seizure management."

UCB Pharma has filed for approval of a pediatric indication for the oral dosage form of Keppra to include use by children down to four years of age. The application is based on trial results, which showed excellent efficacy and safety in 198 children aged 4—16 years with refractory epilepsy (*9*). Seven percent of the children who took Keppra became seizure-free, compared with the 1% taking placebo (*9*). There was a 50% or greater reduction in seizures in 45% of the children on Keppra versus 20% on placebo ($p = 0.0002$) (*9*). Many of the participants had tried eight or nine different medications before trying Keppra. Approval is being sought for an intravenous form of Keppra for use when oral administration is not feasible.

Keppra use is associated with the occurrence of central nervous system adverse events, including somnolence and fatigue, coordination difficulties and behavioral abnormalities, and hematological abnormalities. Keppra dosing must be individualized according to renal function status. In well-controlled clinical studies, the most frequently reported adverse events associated with the use of Keppra in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection, and dizziness, and most appeared to occur predominantly during the first 4 weeks of treatment.

For more information concerning Keppra or other UCB Pharma products, call Medical Information at 1-800-477-7877, ext. 9, or visit UCB Pharma's Web sites at www.keppra.com and www.pharma.ucb-group.com.

References:

1. Verispan Scott-Levin Retail Pharmacy Database, August 2004.
2. IMS Health, National Prescription Audit Plus, May 2004.
3. French, J *et al. Epilepsia*, 2005: (2):324-26.
4. Cereghino, JJ *et al. Neurology,* 2005;55: 236-42.
5. Ben-Menachem, E *et al. Epilepsy Research* 2003;53:57-64.
6. Krakow, K *et al. Neurology* 2001;56: 1772-74.
7. Morrell, MJ *et al. Epilepsy Research* 2003;54:153-61.
8. Ferrendelli, JA *et al. Epilepsy & Behavior* 2003;4;702-09.
9. Glauser, TA *et al.*, Pediatric Study Group. *Epilepsia* 2004;45(supplement 7):186(B.03).