Evaluating the New Antiepileptic Drugs: Balancing Benefits and Adverse Effects

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ABSTRACT

Eight new antiepileptic drugs (AEDs) have been introduced since 1993 and clinicians are now faced with a complex array of treatment choices. In evaluating the newly available drugs, it is important to analyze the different aspects of these agents. Some of the more important characteristics to be aware of are efficacy, adverse effects, pharmacokinetics, and mechanisms of action.

One of the factors complicating treatment choice is the absence of comparative head-to-head clinical trials between the new AEDs. While in some cases it is possible to draw conclusions from the results of randomized, controlled trials that have tested medications against placebo or older drugs, often physicians have to rely on open-label data or personal experiences in selecting the right medications for specific cases.

Trends suggest that the new AEDs are more efficacious compared to the older AEDs, but the major potential benefits of the new drugs are their better safety, tolerability, and cognitive profiles and more desirable pharmacokinetics.

It is obvious that there is a need to redefine the concept of "successful" treatment of epilepsy. Patients need to be individually evaluated and, in addition to controlling seizures, tolerability should be taken into consideration in finding the most appropriate treatment regimen.

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Introductory Remarks

Eight new antiepileptic drugs (AEDs) have been introduced since 1993. This is a major improvement, as prior to that the last anticonvulsant drugs were approved by the Food and Drug Administration (FDA) in 1978. Many of the new drugs show great promise in the different areas of epilepsy treatment. We now have many more choices available for our patients; however, it is difficult to select the right medication for a given seizure type from among so many choices, none of which are perfect. In evaluating the newly available drugs, it is important to look at and analyze the different aspects of these agents. Some of the more important characteristics to be aware of are efficacy, adverse effects, pharmacokinetics, and mechanisms of action.

One of the major factors complicating the matter of making treatment choices is the absence of head-to-head randomized controlled trials among the new AEDs. Before 1993, when selecting from among the older antiepileptics we were able to rely on data from the Veterans Affairs Cooperative Studies (VA studies) that were done in the 1980s. These studies analyzed medications like phenytoin, phenobarbital, primidone, carbamazepine, and valproate in head-to-head trials where patients were randomized to one treatment or another. There have been no head-to-head trials like this among the new AEDs. All the new antiepileptics have been tested against placebo in refractory partial seizure patients. Some of the new antiepileptics have been directly compared against the older antiepileptics in randomized controlled trials in patients with new-onset seizures or generalized-onset seizures. There has not been, however, a major study in which one of the new drugs was placed in a head-to-head trial with another agent.

When we try to find the right medications for specific cases, we have to rely on data from the randomized controlled trials that tested AEDs against placebo, or from head-to-head trials of the newer drugs against the older drugs. However, there are many instances when we have to make judgments without having any randomized, controlled trial data. In these situations, physicians have to rely on open-label data or personal experiences about the efficacy of these drugs in treating less common syndromes and be aware of the possibilities of less common adverse effects.

Efficacy of the New AEDs

The efficacy of the new AEDs can be viewed in three different areas—partial seizures, generalized-onset seizures, and new-onset seizures. In treating partial seizures, each of these drugs has shown efficacy in randomized clinical trials against placebo. This is the standard required by the FDA in order for the drug to be approved. We do not have head-to-head studies to rely on when we analyze efficacy. However, we can try to look at meta-analyses of these drugs for more information. Meta-analyses combine or integrate results of several independent clinical trials. They do not replace comparative clinical trials, but they do provide data for quantitative comparison. Rigorous meta-analysis of the randomized controlled trial data shows trends that some drugs are more effective than others, but there are no statistically significant differences using standard approaches. Furthermore, trials of older drugs compared to the newer drugs usually show no detectable differences in efficacy, but it has become apparent that newer drugs seem to be consistently better tolerated and have fewer side effects. This is important from the patients' point of view and is most evident when patients who have previously been using some of the older antiepileptics are switched to a different, newer medication.

Some of the new AEDs appear to be efficacious against generalized seizures. For example, there are some randomized, controlled trials of topiramate in generalized-onset tonic-clonic seizures. Topiramate has also been tested in Lennox-Gastaut syndrome. Lamotrigine has been studied in primary generalized seizures, especially in Lennox-Gastaut syndrome. There are some strong open-label data suggesting that among the newer drugs levetiracetam and zonisamide may also be effective in generalized-onset seizures. Felbamate is effective in generalized seizures, but its use is limited by hepatic and hematologic toxicity. The drugs that have been shown to be effective against new onset seizures in comparative equivalency trials against a standard drug include lamotrigine, oxcarbazepine, and topiramate. One study of gabapentin showed evidence that it could be efficacious as monotherapy.

There is still a long way to go until we know enough about the new antiepileptics to draw any final conclusions about how and when they can be best used. After new drugs are approved by the FDA and are used more widely in the real world, the results can often be quite different from those of early trials, in terms of efficacy and adverse effects. It is important to critically analyze how and with what objectives the clinical trials have been conducted in order to best interpret their results.

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Adverse Effects of the New AEDs

Many of the newer AEDs seem to have better tolerability, more beneficial safety and cognitive profiles, and fewer drug interactions. Safety is the most significant factor in adapting new treatment methods. There is a significant risk of developing aplastic anemia and hepatic failure with the use of felbamate; however, if a patient has used it for about a year, it appears to be much safer. There has been extensive patient exposure (over 5 million) with gabapentin and it has proven to be an extremely safe agent, possibly the safest AED available at this time. Lamotrigine also has had quite an extensive patient exposure (over 2 million). There is a risk of developing serious rash (toxic epidermal necrolysis; Stevens-Johnson syndrome), but if the titration rate is very slow, the risk is between 1:2,000 to 1:5,000 adults, which is not much different than the risk with phenytoin or carbamazepine use. Topiramate has also had a reasonably good patient exposure (over 1 million), and there have been no safety concerns to date. Tiagabine and levetiracetam have had fairly modest patient exposures, but so far there have been no safety concerns with these drugs. Oxcarbazepine has had a reasonably good patient exposure (over 200,000) and there seems to be no associated risk of aplastic anemia or agranulocytosis. Oxcarbazepine can be associated with skin rash, but the rate may be lower than with carbamazepine use. Zonisamide also has had reasonable patient exposure. With this drug there is a slightly increased risk of developing a serious rash. Even though there have been no reports of aplastic anemia or agranulocytosis in the United States, a few instances have been reported in Japan.

There is some interesting information available about the cognitive effects of the newer AEDs. A number of new agents (gabapentin, lamotrigine, levetiracetam) will probably fit into the very best categories with regard to cognitive profiles. Zonisamide and topiramate tend to have more effects on cognitive function, but with slow titration rates these effects can be more easily controlled.

One can also talk in terms of central nervous system (CNS) side effects. Many of the AEDs will have nonspecific CNS side effects, particularly with the introduction of a new therapeutic agent. Most of these profiles parallel with the cognitive profiles and, again, many of the effects can be minimized with slower introduction.

Beyond safety-related concerns, there are other selected non-CNS side effects that can be attributed to the use of new AEDs. With gabapentin use there is a slight potential for weight gain, experienced by less than 10% of patients, and for mild peripheral edema. Lamotrigine has occasionally been associated with insomnia. Topiramate use results in a slightly increased potential for renal stones (around 1%). This is rarely a safety-related issue and, in fact, in the double-blind, controlled trials, 75% of the patients who had renal stones elected to stay on topiramate. Weight loss is very common with topiramate, particularly if the patient is being switched from valproate. Tiagabine use can occasionally lead to weight gain, and it can also cause spike-wave stupor in some patients. Oxcarbazepine use can induce hyponatremia, which should be monitored, especially in elderly patients. There is a potential for personality changes with levetiracetam use. These changes occur in only about 10% of cases and generally manifest as irritability. This risk can be minimized with a slightly slower introduction of the drug. Zonisamide use can result in renal stones in about 1% of patients. Very rare occurrences of leukopenia have been reported, and the drug has also been associated with weight loss and decreased sweating. The use of felbamate is associated with weight loss, which can either be favorable or unfavorable, depending on the individual patient. Occasional symptoms of gastrointestinal irritation can also occur.

It is also important to think of special patient subgroups, such as women of childbearing age and the elderly. We do not have enough data yet about the safety of the new AEDs in pregnant women. Since some of these drugs do not induce liver enzymes, they may ultimately be the preferential treatment choice in female patients. With the limited data that we have gathered so far, there has been no suggestion of increased risk to the fetus compared to the older AEDs, but it is too early to draw any definitive conclusions. Elderly patients tend to be very sensitive to cognitive side effects as a result of their baseline polypharmacy. It is probable that the newer AEDs will be extensively used in the elderly population.

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Pharmacokinetics of the New AEDs

The pharmacokinetic aspect of the new AEDs is one of the major areas of improvement over the older medications. The pharmacokinetic aspects of importance are the half-life of the drugs, level of protein binding, and hepatic metabolism (which, if present, often means there are more drug-drug interactions).

The serum half-life and biological half-life of some of the medications can be different—even though some of them have short serum half-lives, their biological effects might be much more prolonged. For example, gabapentin, tiagabine, and levetiracetam all have relatively short serum half-lives, and while it could be expected that there would be a need to give them in multiple doses per day, it appears that their biological half-lives are a lot longer.

Other medications, such as felbamate, lamotrigine, topiramate, and zonisamide, all have quite long serum half-lives, especially in uninduced patients. However, when an inducing agent is included, the half-lives of felbamate, zonisamide, oxcarbazepine, and tiagabine can be cut in half.

Therefore, one of the key advantages of the new AEDs is that they do not have to be given to patients that frequently. The second major advantage is that some of these medications are not primarily metabolized by the liver, and therefore drug-drug interactions and effects of other medications that the patient might be taking are not that relevant. The drugs that still have significant hepatic metabolism (around 50%) are felbamate, lamotrigine, oxcarbazepine, tiagabine, and zonisamide. Usually the effect on other drugs is mimicked by those that have hepatic metabolism, so these anticonvulsants are all affected by other drug-drug interactions and they affect the other AEDs that are being used. This is not that much of an issue with tiagabine, because about 96% of it is protein-bound and there is very little of it found freely in the serum plasma.

Mechanisms of Action

The majority of the new AEDs affect the sodium channel (Na^+ channel), much like the older medications. Zonisamide, lamotrigine, felbamate, and topiramate exhibit significant sodium channel blockade, and therefore would be expected to affect the spread of the seizure. Levetiracetam, gabapentin, and tiagabine have no effect on the Na^+ channel. Tiagabine increases γ-aminobutyric acid (GABA) by blocking GABA reuptake. The exact mechanisms of action of levetiracetam and gabapentin are unknown. Levetiracetam decreases interneuronal calcium and gabapentin most likely affects both inhibitory and excitatory amino acids. Even though AEDs primarily act by blocking Na^+ channels, a number of them have other unique mechanisms. Zonisamide has calcium channel (Ca^+ -T) blocking ability and is a free radical scavenger. Lamotrigine's broad clinical spectrum of action suggests that it has other mechanisms of action. Lamotrigine also blocks presynaptic Na^+ channels, decreasing glutamate release. This may be important in preventing excitotoxic damage and providing neuronal protection. How lamotrigine affects absence seizures and myoclonic seizures remains unclear.

In general, it can be said that in patients with difficult-to-control seizures, a drug with multiple mechanisms of action vs a single mechanism of action is preferred, because the development of resistance or tolerance to this AED will take longer. This same principle holds true with the addition of one agent to another. Rational polypharmacy suggests that AEDs with different and unique mechanisms of action should be combined, rather than adding another AED with similar mechanisms of action.

Question & Answer Forum

Q: What were some of the problems with the FDA trials of the new AEDs?

Michael Smith: One of the problems with the FDA trials was the differences in dosing. Some of the pharmaceutical houses went out to try to prove how safe their drugs were, like gabapentin and lamotrigine, while with others, like topiramate, the goal was to prove how efficacious they were. If we were using standardized doses of all the major medications, the trends indicating that some drugs were more efficacious than others might not turn out to be totally true.

Michael Privitera: That is a good point. All of these trials were designed to show that the new drug was more efficacious than placebo and had acceptable tolerability. However, when the trials were designed, the optimal dose was not known. Decisions had to be made that balanced efficacy and tolerability.

A related issue is titration rate. Even if the doses are picked correctly, sometimes a trial can be designed that actually has a titration rate that is too fast, and there is an increased dropout rate from the trial. It is only later realized that the results could have been much better if the titration rate had been about half as fast.

Q: One of the exciting things about the new wave of AEDs is that a number of them have a broad spectrum of potential efficacy. When they go through trials, the trials tend to be fairly restrictive. How does the practitioner begin to intelligently use these agents seizure types other than complex-partial or simple-partial?

Michael Privitera: The first wave of open-label studies should be looked at. Very often, the drugs have been studied in double-blind, randomized, controlled trials for partial seizures, and then they will undergo other studies for FDA approval. The FDA typically requires exposure in at least several thousand people, and patients with any type of epilepsy might be included.

First, the clinician can look at Phase III (preapproval) studies and try to identify subgroups that have generalized seizures. After a drug is approved, Phase IV studies will usually begin and will sometimes include people with generalized seizures. Often, small case series may be published of patients who have generalized epilepsy treated with the new AED.

The first step in evaluating whether a drug has a broad spectrum of efficacy is to find out if the drug makes any seizure types worse. When a drug is added on and it does not help somebody, that is not so bad, but if a drug is added on and it actually makes the seizures worse, that is something we need to know about ahead of time. We have had similar experiences with carbamazepine in atypical absence seizures, for example. The ideal thing to do would be to conduct a randomized, controlled trial. It is difficult to ask practitioners to comb through the data from published open-label studies for information on subgroups of interest. We should try to encourage the pharmaceutical companies to find the data.

Gregory Bergey: In terms of knowing what drugs can make seizures worse, we should start to develop lists of agents that should not be used in certain circumstances.

Q: How do we decide when to reassess treatment and switch the patient to a different medication because of the side-effect profile, and not because they are breaking through with seizures?

Gregory Bergey: This is why it is important to know how the drugs work and what the typical efficacy and side-effect profiles are. We are going to have to try to evaluate each case individually, talk to each patient and see what the needs and concerns are. There is always a slight risk of a breakthrough with crossover, but we should actually encourage the patients to potentially switch if either the projected side-effect profile may not be best for that patient or if they are complaining of side effects. Ten or 15 years ago we probably were more likely to tell a patient to be glad that their seizures are controlled and to try to tolerate some of the side effects. Now, with more choices, the mere fact that a patient's symptoms are controlled is not always a reason to keep treating them with the same drug, when there might be better choices. The treating physicians, who do not deal with epilepsy day in and day out, are still a little reluctant to make a change in the treatment plan when a patient comes to them with totally controlled seizures but has mild side effects.

Slide Library

Choosing Among Antiepileptic Drugs: Balancing Pros and Cons

01.6.01

- Eight new AEDs approved by the FDA since 1993
- Clinicians are faced with a complex array of choices
- Possible to evaluate the choices from four approaches:
  - Efficacy
  - Adverse effects
  - Mechanisms of action
  - Pharmacokinetics

AED=antiepileptic drug; FDA=Food and Drug Administration.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

Choosing AEDs: Comparing Efficacy

01.6.02

- No head-to-head comparison trials exist for the newer AEDs
- Each new AED proved superior to placebo as add-on in partial seizures
- Some new drugs were superior or equivalent to standard AEDs in monotherapy

AED=antiepileptic drug.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

Results of Meta-Analysis of the New AEDs

01.6.03

- All AEDs significantly better than placebo for partial seizures
- Non-significant trend that topiramate, levetiracetam, and tiagabine are most effective (at doses tested)
- AEDs with highest efficacy tend to have highest dropout rate, except for levetiracetam

AED=antiepileptic drug.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

New AED Safety Profiles

01.6.04

- Felbamate
  - Definite risk of aplastic anemia, hepatic failure
- Gabapentin
  - Extensive patient exposure (> 5 million)
  - Extremely favorable profile
- Lamotrigine
  - Extensive patient exposure (>2 million)
  - Risk of serious rash (TEN, SJS) 1:2000 to 1:5000 adults, with slow titration; 1:200 children
- Topiramate
  - Good patient exposure (>1 million)
  - No safety concerns to date

AED=antiepileptic drug; TEN=toxic epidermal necrolysis; SJS=Steven's Johnson syndrome.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

New AED Safety Profiles (cont.)

01.6.05

- Tiagabine
  - Modest patient exposure
  - No safety concerns to date
- Levetiracetam
  - Limited patient exposure (~60,000)
  - No safety concerns to date
- Oxcarbazepine
  - Reasonable patient exposure (>200,000)
  - No apparent increased risk of aplastic anemia
  - No increased leukopenia
- Zonisamide
  - Reasonable patient exposure (>200,000, Japan)
  - Slight increased risk of serious rash
  - Very slight risk of aplastic anemia or agranulocytosis

AED=antiepileptic drug.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

AEDs: Cognitive Profiles

01.6.06

- Best
  - Felbamate
  - Gabapentin
  - Lamotrigine
  - Levetiracetam
  - Valproate
- Intermediate
  - Carbamazepine
  - Phenytoin
  - Oxcarbazepine
  - Tiagabine
  - Zonisamide
- Least favorable
  - Phenobarbital
  - Primidone
  - Topiramate*

AED=antiepileptic drug. * May be better at lower doses.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

Slide Library

New AEDs: Selected Side Effects*

01.6.07

- Felbamate
  - Weight loss
  - Gastrointestinal upset
- Gabapentin
  - Weight gain (<10 %)
  - Peripheral edema (mild)
- Lamotrigine
  - Insomnia (uncommon)
- Topiramate
  - Renal stones (1%)
  - Weight loss
  - Cognitive

AED=antiepileptic drug. *Excluding safety-related and nonspecific CNS effects.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

New AEDs: Selected Side Effects* (cont.)

01.6.08

- Tiagabine
  - Weight gain
  - Spike-wave stupor
- Oxcarbazepine
  - Hyponatremia
- Levetiracetam
  - Personality changes (<10%)
- Zonisamide
  - Renal stones
  - Leukopenia (rare)
  - Weight loss
  - Decreased sweating

AED=antiepileptic drug. *Excluding safety-related and nonspecific CNS effects.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

Mechanisms of Action of the New AEDs

01.6.09

	Na^+ channel	Ca^+ -T channel	GABA	Glutamate	Other
Felbamate	++		+	+	
Gabapentin					++
Lamotrigine	++				
Tiagabine			++		
Topiramate	++		+	+	
Zonisamide	++	++			+
Levetiracetam					++
Oxcarbazepine	++				

AED=antiepileptic drug; Na^+=sodium; Ca^+ -T=calcium; GABA=γ-aminobutyric acid.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

Pharmacokinetic Characteristics of the New AEDs

01.6.10

	Protein Binding	Hepatic Metabolism
Felbamate	25%	+
Gabapentin	–	–
Lamotrigine	55%	+
Tiagabine	96%	++
Topiramate	12%	+
Zonisamide	50%	++
Levetiracetam	–	–
Oxcarbazepine	50%	+

AED=antiepileptic drug.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

The Potential Promise of New AEDs vs Older AEDs

01.6.11

- Improved efficacy	?
- More desirable pharmacokinetics	✓
- Fewer drug interactions	✓
- Better safety profile	✓
- Better tolerability	✓
- Better cognitive profile	✓
- Less need for serum monitoring	✓
- Nonepilepsy uses	✓

AED=antiepileptic drug.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

Epilepsy Treatment 2001

01.6.12

- Need to revisit and redefine the concept of "successful" treatment
- Initial therapy should strongly consider tolerability rather than just the selection of the perceived "strongest" or most effective agent
- Some of the new AEDs have improved side-effect profiles compared to the older agents
- In nonresponders, alternative monotherapy may have equal efficacy and better tolerability than polypharmacy

AED=antiepileptic drug.
Privitera MD, Bergey GK, Smith MC. *CNS Spectrums.* Vol 6, No 7 (suppl 6). 2001.

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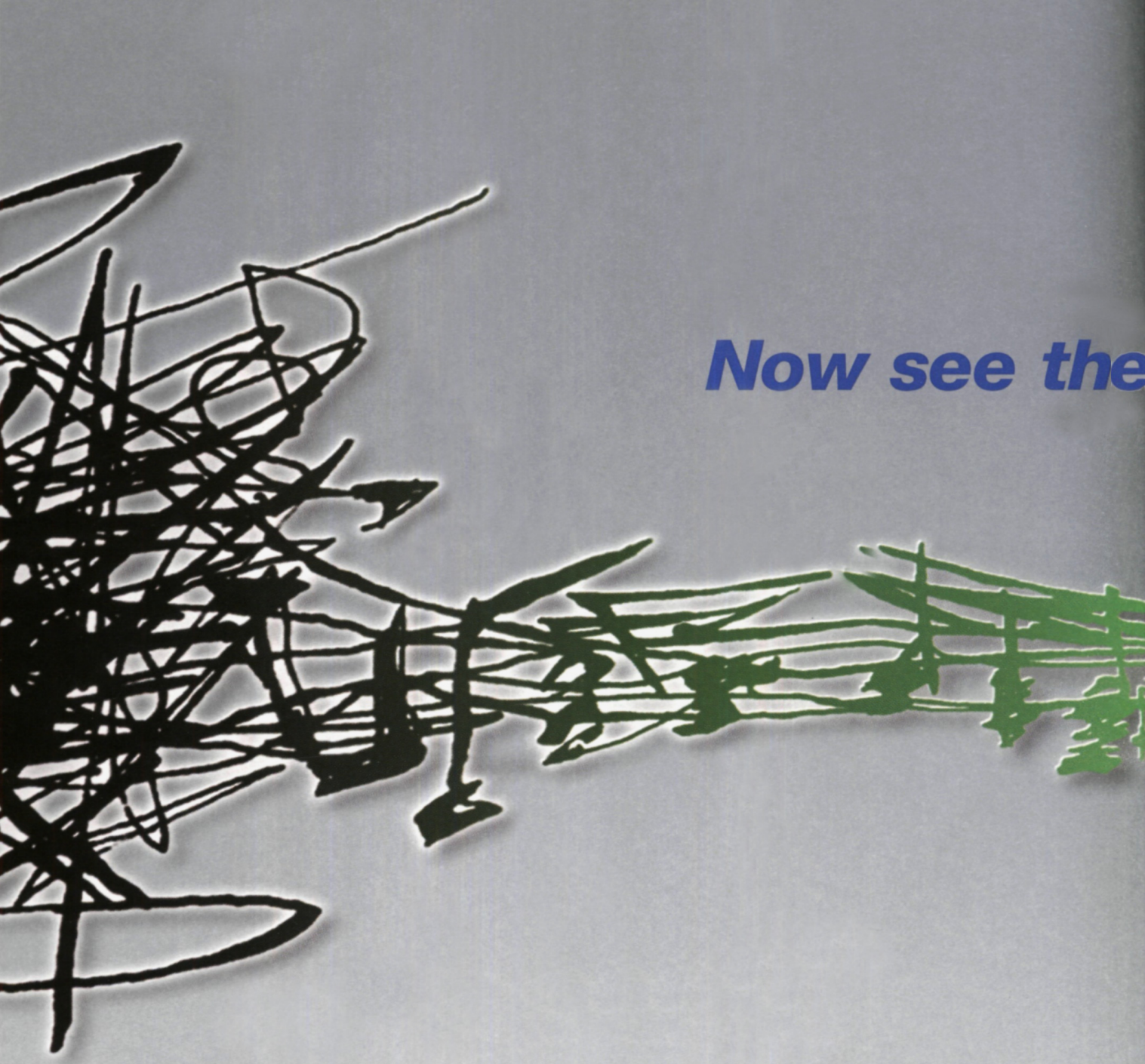
You've seen the world of schizophrenia...



GEODON is indicated for the treatment of schizophrenia. When deciding among the alternative treatments available for this condition, the prescriber should consider the finding of GEODON's greater capacity to prolong the QT/QT_C interval compared to several other antipsychotic drugs. Prolongation of the QT_C interval is associated in some other drugs with the ability to cause torsade de pointes–type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether GEODON will cause torsade de pointes or increase the rate of sudden death is not yet known. GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with other QT-prolonging drugs.

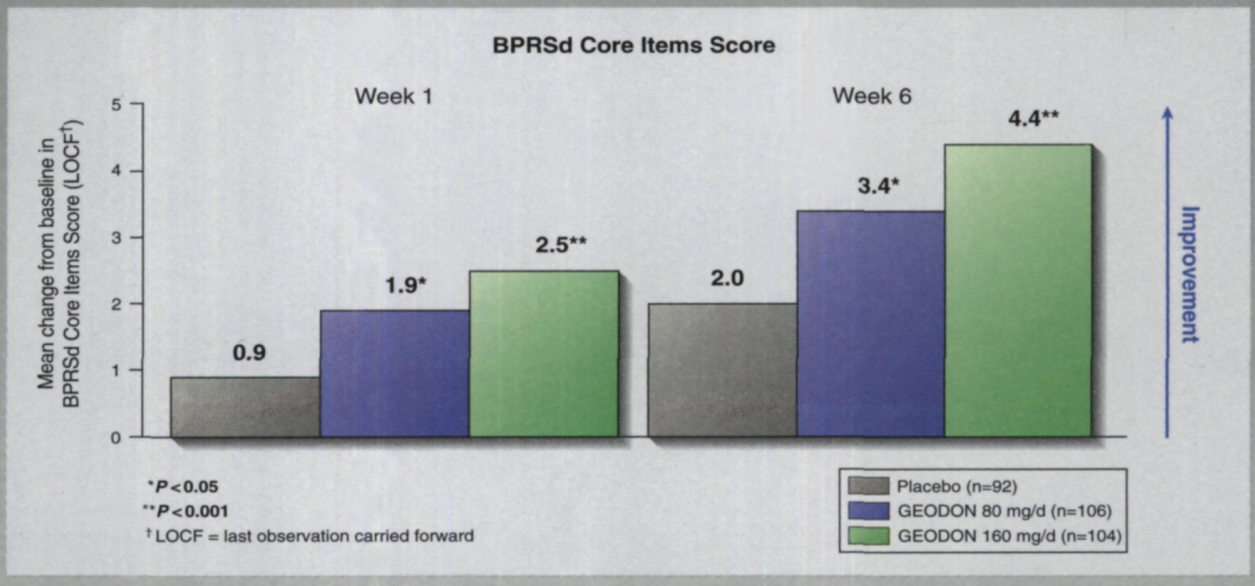
In short-term trials, the most commonly observed adverse events associated with GEODON at an incidence of ≥5% and at least twice the rate of placebo were somnolence (14% vs 7%), respiratory disorders (8% vs 3%), of which >90% were cold symptoms or upper respiratory infections, and EPS (5% vs 1%).

Please see brief summary of prescribing information on last page.

NEW GEODON—
See the difference in the acute phase

OVERALL PSYCHOPATHOLOGY—Controls symptoms across the dose range[2,A,B]

POSITIVE SYMPTOMS—Improvement as early as Week 1[1,2,A,B]



A 6-week, double blind, placebo-controlled, multicenter study of 302 inpatients with an acute exacerbation of schizophrenia or schizoaffective disorder (DSM-III-R). After a 3- to 7-day washout period, patients were randomized to receive either GEODON 80 mg/day on Days 1–41; 80 mg/day on Days 1 and 2, followed by 160 mg/day on Days 3-41; or placebo. All GEODON doses were administered twice daily with food.[2]

NEGATIVE SYMPTOMS—Significant improvement at Weeks 1 and 6[1,2,A,B]

In short-term trials, 4.1% of GEODON-treated patients discontinued treatment due to adverse events, compared to 2.2% on placebo. The most common adverse event associated with discontinuation was rash, 1% (GEODON-treated patients) vs 0% (placebo-treated patients).

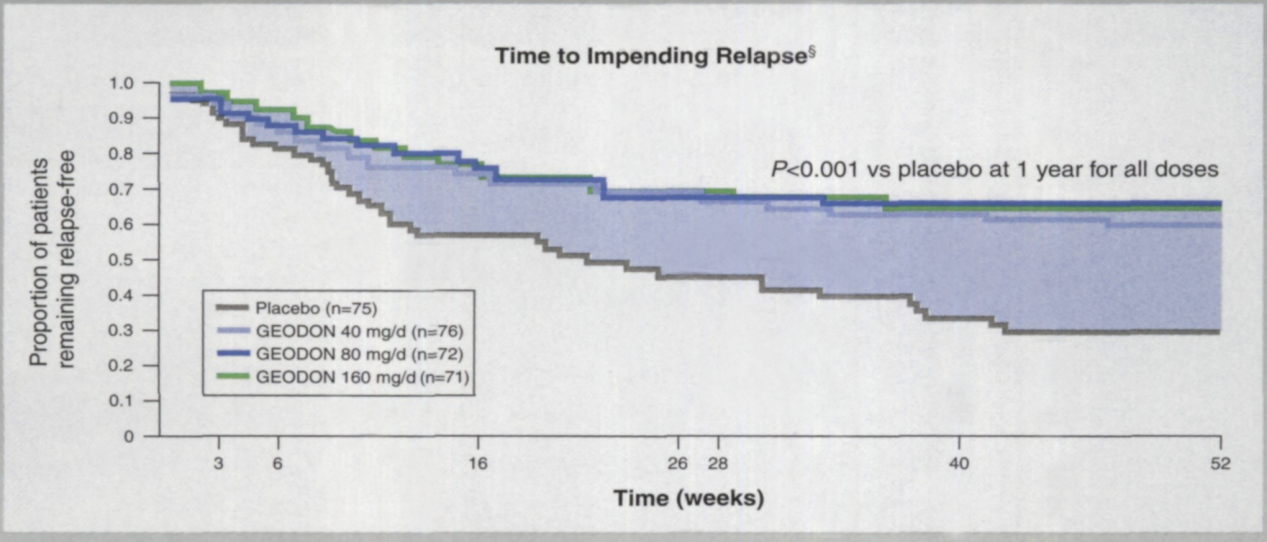
[A] In a 6-week, double-blind trial (n=419), GEODON 40 and 120 mg/day were statistically significant ($P<0.05$) vs placebo at Weeks 1 and 6 on the Brief Psychiatric Rating Scale derived (BPRSd) Total Score and on the BPRSd Core Items Score. A trend toward statistical significance was achieved with 120 mg/day ($P=0.06$) in the Positive and Negative Syndrome Scale (PANSS) Negative Subscale Score. Statistical significance was not achieved with the 40 mg/day dose on the PANSS Negative Subscale Score.[2]

[B] In a 6-week, double-blind trial (n=302), GEODON 80 and 160 mg/day were both statistically significant ($P<0.05$) vs placebo at Weeks 1 and 6 in the BPRSd Total Score and the PANSS Negative Score.[1]

Please see brief summary of prescribing information on last page.

NEW GEODON—
See the difference over time

RELAPSE PREVENTION—Proven delay in both time to and rate of relapse in a 1–year, placebo-controlled trial[2]



A prospective, 1-year, double-blind, placebo-controlled, multicenter study of 294 inpatients with chronic stable schizophrenia (DSM-III-R) hospitalized for at least 2 months. Prior to enrollment, patients were withdrawn from antipsychotic and anticholinergic medication over a 3-day, single-blind, placebo run-in period. Patients then were randomized to receive either GEODON 40 mg/day, 80 mg/day, or 160 mg/day, or placebo for 1 year. All GEODON doses were administered twice daily with food. Patients were immediately withdrawn and treated openly if they reached the endpoint of impending relapse.[2]

LOW DISCONTINUATION RATES—Rates of discontinuation due to adverse events were low and similar to placebo across the dose range in this trial[2¶]

— there was no pattern of adverse events associated with discontinuation

As with other antipsychotics, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia.

§ Impending relapse was defined as Clinical Global Impression (CGI) Improvement Score of ≥6 and/or a score of ≥6 on PANSS items P7 (hostility) and G8 (uncooperativeness) on 2 successive days. Patients with CGI Improvement Score of 5 (minimally worse) were continually monitored until the score either improved (patients remained in study) or deteriorated to ≥6 (patients were withdrawn from the study).[2]

¶ Discontinuation rates for GEODON 40, 80, and 160 mg/day, and placebo were 7.9%, 8.3%, 1.4%, and 8.0%, respectively.[2]

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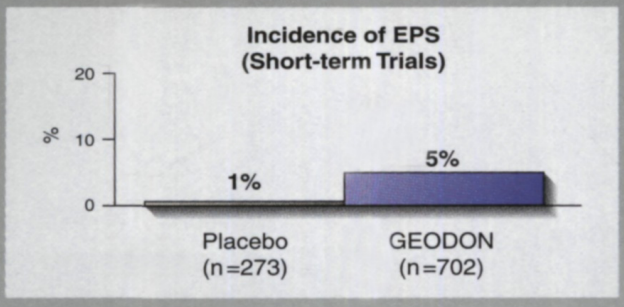
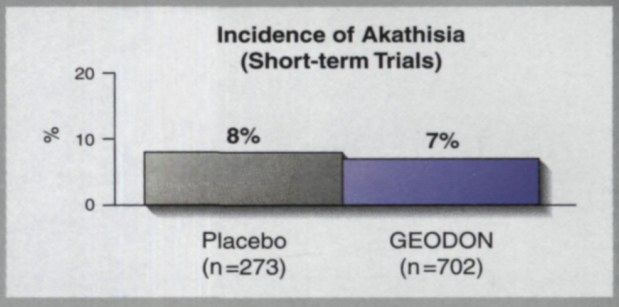
NEW GEODON—
See the difference GEODON can make

LOW INCIDENCE OF EPS*†— Comparable to placebo[2]



Pooled data from short-term, fixed-dose, placebo-controlled, oral-dosing, phase II/III 4- and 6-week studies across a dose range of 10-200 mg/day.



Pooled data from short-term, fixed-dose, placebo-controlled, oral-dosing, phase II/III 4- and 6-week studies across a dose range of 10-200 mg/day.

- No dose-related EPS or akathisia by objective measures
- EPS was one of the most common adverse events in short-term trials‡
- In a long-term trial, the incidence in GEODON-treated patients vs placebo for EPS was 4% vs 7% and for akathisia was 10% vs 5%

EFFECT ON PROLACTIN— Comparable to placebo[2]

- Median change from baseline to last observation in all phase II/III studies was –3.3 ng/mL for GEODON-treated patients vs –1.2 ng/mL for placebo

Patients who are at risk for significant electrolyte disturbances, eg, low serum potassium and/or magnesium, should have baseline measurements performed before initiating GEODON. Hypokalemia may result from diuretic therapy, diarrhea, and other causes and may increase the risk of QT prolongation and arrhythmia. Patients on diuretics should be monitored.

In short-term trials, some patients experienced orthostatic hypotension (1%). In premarketing trials, some patients experienced syncope (0.6%). Seizures occurred infrequently (0.4%); confounding factors may have contributed to many of these cases. As with other antipsychotics, GEODON should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

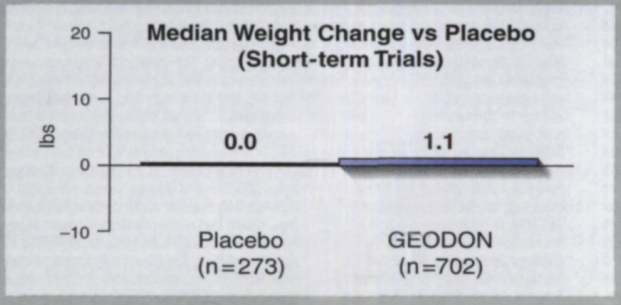
* EPS = extrapyramidal syndrome.

† As measured by Simpson-Angus Rating Scale, Abnormal Involuntary Movement Scale, and Barnes Akathisia Scale.

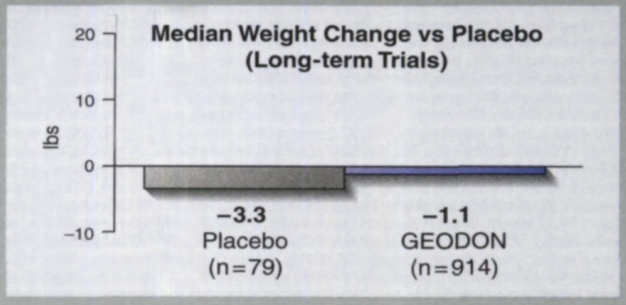
‡ ≥5% and at least twice the rate of placebo.

Please see brief summary of prescribing information on last page.

WEIGHT-NEUTRAL PROFILE—*Weight change comparable to placebo*[2]



Pooled data from short-term, fixed-dose, placebo-controlled, oral-dosing, phase II/III 4- and 6-week studies across a dose range of 10-200 mg/day.



Pooled data from maintenance oral-dosing, phase II/III studies across a dose range of 10-160 mg/day. Includes a 1-year, placebo-controlled study.

- In short-term clinical trials, 10% of GEODON-treated patients experienced a weight gain of ≥7% of body weight vs 4% for placebo
- In long-term clinical trials, the mean weight change for patients with "low" body mass index (BMI) was +3.1 lbs, with a "normal" BMI was 0 lbs, and with a "high" BMI was -2.9 lbs

GEODON Dosing

BID Dosing With Food*

Initiate Control
40 mg/d

Evaluate

Optimize Response
40-160 mg/d

Evaluate

Sustain Improvement
40-160 mg/d

*Absorption of GEODON is increased with food.

Available strengths: 20-mg, 40-mg, 60-mg, and 80-mg capsules

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REFERENCES: 1. Daniel DG, Zimbroff DL, Potkin SG, et al, and the Ziprasidone Study Group. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacology*. 1999;20:491-505. **2.** Data on file. Pfizer Inc., New York, NY.

GEODON™ (ziprasidone HCl) Capsules BRIEF SUMMARY
[SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION]

CONTRAINDICATIONS —*QT Prolongation:* Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs (see **WARNINGS**), GEODON should not be used with other drugs that prolong the QT interval, including (not a complete list) quinidine, dofetilide, pimozide, sotalol, thioridazine, moxifloxacin, and sparfloxacin. Because GEODON prolongs the QT interval, it is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). **WARNINGS —*QT Prolongation and Risk of Sudden Death:*** **A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. GEODON use should be avoided in combination with other drugs that are known to prolong the QT_c interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see *Drug Interactions* under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c measurements >500 msec.** ***Neuroleptic Malignant Syndrome (NMS):*** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. ***Tardive Dyskinesia (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. **PRECAUTIONS —*General:*** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and Orthostatic Hypotension in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. *Ketoconazole*, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. *Cimetidine*, 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS —*Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on a pool of two 6-week and two 4-week placebo-controlled trials in which GEODON was administered in doses ranging from 10-200 mg/day. ***Adverse Events Associated with Discontinuation:*** 4.1% (29/702) of GEODON patients vs 2.2% (6/273) of placebo patients. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) vs no placebo patients (see **PRECAUTIONS**). ***Adverse Events at an Incidence ≥1%:*** The most commonly observed adverse events associated with GEODON (≥ 5% and at least twice the rate of placebo) were somnolence (14%), respiratory disorder (8%), and extrapyramidal syndrome (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in ≥1% of GEODON patients and at a greater incidence than in placebo. Body as a Whole—asthenia, accidental injury. Cardiovascular—tachycardia, postural hypotension. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Musculoskeletal—myalgia. Nervous—somnolence, akathisia, dizziness, extrapyramidal syndrome, dystonia, hypertonia. Respiratory—respiratory disorder (cold symptoms and upper respiratory infection account for >90%), rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, diarrhea, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled trials was 5% vs 1% for placebo patients. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients.There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT_c interval (see **WARNINGS**). GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Body as a Whole — *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System — *Frequent:* hypertension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System : *Frequent:* vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine — *Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System — *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders — *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phophatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System — *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System — *Frequent:* agitation, tremor, dyskinesia, hostility, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delerium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System — *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages — *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses —*Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System —*Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **DRUG ABUSE AND DEPENDENCE—*Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/75).

10% TOTAL RECOVERED FIBER
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