Stiripentol was approved by the Food and Drug Administration (FDA) on August 20, 2018 as adjunctive therapy with clobazam for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. It is not currently approved as monotherapy. Dravet syndrome, also referred to as severe myoclonic epilepsy of infancy, is a rare disorder characterized by seizures unresponsive to most antiepileptics, motor impairment, and developmental disabilities. Nearly a quarter of patients die during childhood. Approximately 70% of patients have a mutation in the sodium channel alpha-1 subunit gene (SCN1A) leading to malfunction or loss of function in GABAergic neurons. As a treatment for a rare disorder, stiripentol has been designated as an orphan drug by both the European Medicines Agency and the FDA. It has been approved for use in Europe for more than a decade, with more recent approvals in Canada and Japan.

**Mechanism of Action**

Stiripentol, an aromatic allylic alcohol, is unrelated to other currently available antiepileptics. It is a racemic mixture, with an R enantiomer approximately 2.5 times more active than the S enantiomer. The mechanism by which stiripentol produces its antiseizure effect has not been fully defined. It acts as a direct allosteric modulator of GABA	extsubscript{A} receptors and increases GABA levels in neural tissue by preventing its reuptake and metabolism. Stiripentol also inhibits lactate dehydrogenase, activating ATP-sensitive potassium channels and reducing neuronal action potential firing. Seizure control may be further enhanced by its inhibition of clobazam metabolism in patients taking the drugs concomitantly, resulting in higher concentrations of both clobazam and norclobazam (N-desmethylclobazam), its active metabolite.

**Pharmacokinetics**

In a study of stiripentol pharmacokinetics in healthy adults, oral doses of 500, 1,000, and 2,000 mg produced median maximum peak plasma concentrations of 2, 6.5, and 14.1 mg/L between 2 and 4 hours post-dose. The drug is highly protein bound (99%), with an estimated elimination half-life of 5 to 13 hours. Although the metabolism of stiripentol has not been fully delineated, it is known to be a substrate for CYP1A2, CYP2C19, and CYP3A4. As a result of its reliance on both hepatic and renal clearance, use of stiripentol in patients with moderate to severe hepatic or renal impairment is not recommended.

The first published study to evaluate stiripentol plasma concentrations enrolled 10 children and adolescents from 6 to 16 years of age with refractory atypical absence seizures. The patients received a mean maintenance dose of 57 mg/kg/day (range 34-78 mg/kg/day) during the 4-week trial, which produced a mean minimum plasma concentration of 12 mg/L (4-22 mg/L). Although identification of a potential dose-concentration relationship was limited by concurrent use of drugs that inhibit or induce the metabolism of stiripentol, this report provided preliminary information on potential target plasma concentrations. Additional data has come from a randomized placebo-controlled add-on trial conducted by Chiron and colleagues. Forty-one children with Dravet syndrome already taking valproate and clobazam were randomized to receive stiripentol 50 mg/kg/day, with titration up to 100 mg/kg/day if needed, or placebo for up to 22 months. At week 7, the treated patients were receiving a mean dose of 50 mg/kg/day and had a mean minimum plasma concentration of 10 mg/L (range 8.3-11.7 mg/L), similar to the earlier paper. Fifteen (71%) of the 21 stiripentol patients had a 50% or greater reduction in seizure frequency, compared to no improvement in the controls.

Peigné and colleagues developed a population pharmacokinetic model for stiripentol with 139 plasma concentrations obtained from 35 children with Dravet syndrome. All patients were receiving a dose of 50 mg/kg/day in addition to clobazam and valproate. The data were best
described with a one-compartment model with zero-order absorption and first-order elimination. The mean population estimate for apparent volume of distribution (Vd/F) was 82 L, with a mean apparent clearance (CL/F) of 4.2 L/hr. The authors found a 300% increase in area under the concentration time curve (AUC) when body weight increased from 10 to 70 kg. These findings reflect a dose-dependent non-linearity and support the proposed dosing regimen of 50 mg/kg/day for younger children, but suggest that a lower weight-based dose be considered in adolescents and adults to avoid toxicity.

Clinical Experience
Several clinical trials of stiripentol published within the past 5 years have added to our understanding of its safety and efficacy in treating refractory seizure disorders. In 2000, Wirrell and colleagues conducted a retrospective evaluation of 82 pediatric patients in the United States treated with stiripentol obtained under a special access permit between 2005 and 2012. The median age at the start of stiripentol therapy was 6.9 years. A total of 103 treatment courses were grouped into stiripentol with clobazam (35), stiripentol with valproate (14), stiripentol with both clobazam and valproate (48), and stiripentol alone (6). Sixty-eight percent of patients experienced a reduction in seizure frequency, with half having a marked reduction. All 35 of the patients with prolonged seizures (defined as those lasting more than 15 minutes) had significant improvement. Emergency department and hospital visits also declined. The group receiving the combination of stiripentol and clobazam had the greatest improvement, followed by those receiving stiripentol, clobazam, and valproate. Eighty-eight percent of patients and families reported an improvement in quality of life after starting stiripentol. The most common adverse effects were somnolence, reported in 18% of patients, and decreased appetite, reported in 8.5%. Four patients discontinued therapy for adverse effects and two for lack of efficacy.

In 2015, Inoue and Ohtsuka, writing for the STP-1 Study Group in Japan, described the results of their multicenter open-label study of stiripentol in children and young adults with Dravet syndrome. Patients up to 30 years of age were eligible to enroll in the study if they were having four or more clonic or tonic-clonic seizures per month while receiving both clobazam and valproate. Stiripentol was initiated at a dose of 50 mg/kg/day for 16 weeks. Patients experiencing improvement were continued on the protocol for up to an additional 40 weeks. Of the 24 patients enrolled, 21 were treated for more than 16 weeks and 19 completed the study. Fifty-four percent of the patients were responders, achieving a 50% or greater reduction in seizure frequency. Two patients became seizure free. Twenty-two patients had one or more adverse effects, most commonly somnolence (in 79% of patients), loss of appetite (67%), ataxia (58%), and elevated glutamyltransferase levels (38%). Nine patients required a dose reduction, but there were no patients who discontinued treatment.

A single-center cross-sectional study from the Necker Enfants Malades Hospital in Paris was published in 2016. De Liso and colleagues assessed the outcomes of 54 patients (ages 2.5 to 22 years) with Dravet syndrome and the SCN1A mutation treated at their hospital during 2013. The mean age of seizure onset was 5 months (range 2-9 months). Treatment was initiated with valproate in 83% of the patients, at a mean age of 7 months. Stiripentol was prescribed in 96% of patients, with a mean age at initiation of 20 months (range 3-6 months). Doses ranged from 35 to 50 mg/kg/day, with a mean of 42 mg/kg/day. The median duration of treatment was 8 years. At the last follow-up visit, 96% of the patients were receiving triple-therapy with stiripentol, valproate, and clobazam. Although all but two of the patients continued to have seizures, both frequency and duration were reduced. The majority (62%) were having less than 1 seizure per week. Higher seizure frequency, reflecting a less robust response to treatment, was associated with an earlier age at seizure onset (p = 0.06) and a later time to initiation of stiripentol (p = 0.07). Seizure duration also improved, with only two patients having seizures longer than 5 minutes.

Three additional stiripentol studies were published earlier this year. Myers and colleagues conducted a multicenter prospective, open-label study of stiripentol. A total of 41 patients between 11 months and 22 years of age were enrolled. The mean number of other antiepileptics patients were receiving at the time of stiripentol initiation was 2.8 (range 2-8), with the most common agents being clobazam in 80% of patients, valproate in 71%, and topiramate in 61%. Stiripentol was titrated to a mean effective dose of 67 mg/kg/day, with a maximum dose of 4 grams/day. The median duration of treatment was 37 months, with a range of 2 to 141 months. Twenty of the patients (48%) had a 50% or greater reduction in the frequency of tonic-clonic seizures. There was a similar reduction in 11 (48%) of the 23 patients with focal seizures. The frequency of status epilepticus decreased by 50% or greater in 11 (42%) of 26 patients. Only one patient had an increase in their seizures. The most common adverse effects attributed to stiripentol were sedation, anorexia, weight loss, and behavioral changes.

While most studies have assessed patients of all ages as a single group, Chiron and colleagues published a study evaluating the ability of stiripentol in combination with valproate and clobazam, to provide a sustained reduction in seizures as patients with Dravet syndrome became adults. The longitudinal study included 40 children placed on stiripentol prior to 15 years of age. Patients remained in the study to a median
age of 23 years, with a range of 18 to 40 years at the time of their last assessment. Clobazam was being given concomitantly in 40 patients; valproate in 39; and topiramate in 21. Thirty-seven of the 40 patients were still having generalized tonic-clonic seizures at the time of their last follow-up, but none were still having episodes of status epilepticus. As in previous studies of Dravet syndrome, the frequency and duration of seizures decreased as the patients approached adulthood. The greatest benefit in seizure reduction occurred in the patients who started stiripentol prior to 15 years of age. Adverse effects were reported as mild, with loss of appetite in 15 patients (38%). The authors concluded that triple therapy continued to be effective in minimizing seizure frequency and duration into adulthood.

The efficacy of stiripentol has also been compared in patients with or without known SCN1A pathogenic variants. Cho and colleagues studied 32 patients with Dravet syndrome: 15 with known SCN1A pathogenic variants and 17 with benign variants or variants of unknown significance (VUOS). There were no differences in the clinical status of the patient groups at the start of treatment. The addition of stiripentol reduced seizure frequency by 72.53% ± 23% in the known pathogenic variant group compared to 50.58% ± 40.14% in the benign variant/VUOS group (p = 0.004). Stiripentol was also found to be more effective in patients with missense errors than in those with truncation errors. The number of patients was too small to determine the relative effect of a pathogenic variant at different locations. Continued research in this area may eventually lead to more precise drug and dose selection for children with Dravet syndrome, allowing for earlier initiation of effective therapy.

**Warnings and Precautions**

Stiripentol is known to produce significant decreases in neutrophil count. A clinically significant decrease (< 1,500 cells/mm³) was observed in 13% of patients in clinical trials. A clinically significant decrease in platelet count (< 150,000/μL) was also reported in more than 10% of patients. The manufacturer recommends hematologic laboratory testing prior to stiripentol initiation and every 6 months during treatment.

Abrupt discontinuation of stiripentol may result in withdrawal symptoms. When stopping treatment, the dose should be gradually reduced to minimize the risk for a sudden increase in seizure frequency or the development of status epilepticus. In cases where a more rapid termination is necessary, such as with the development of a serious adverse effect, appropriate monitoring is recommended. For some patients, this may involve hospitalization.

As with other antiseizure drugs, the stiripentol prescribing information includes a warning regarding an increased risk for suicidal ideation, suicide attempts, new or worsening depression, agitation, aggression, oppositional behaviors, anxiety, and panic attacks. Families should be aware of the need to immediately contact a healthcare provider for any unusual changes in mood or behavior, signs of depression, suicidal thoughts or behavior, or self-harm.

**Adverse Effects**

The safety profile of stiripentol was established in two randomized double-blind, placebo-controlled studies conducted by the manufacturer in 64 children, adolescents, and young adults (33 patients given stiripentol and 31 given placebo). Adverse effects observed in 10% or more of the patients given stiripentol are provided in Table 1. Similar results have been observed in several other studies.

<table>
<thead>
<tr>
<th>Table 1. Stiripentol Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stiripentol</strong></td>
</tr>
<tr>
<td>Somnolence</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Ataxia</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Hypotonia</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Tremor</td>
</tr>
<tr>
<td>Dysarthria</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
</tbody>
</table>

**Drug Interactions**

Stiripentol is both an inhibitor and inducer of CYP1A2, CYP2B6, and CYP3A4 and an inhibitor of CYP2C8, CYP2C19, P-glycoprotein, and Breast Cancer Resistance Protein (BCRP). Dose adjustments may be necessary for drugs metabolized by these enzymes, such as caffeine, clobazam, midazolam, sertraline, and quinidine, when given with stiripentol. Administration of stiripentol and clobazam, a substrate for CYP2C19, results in a reduction in the rate of clobazam metabolism and subsequent increases in plasma concentrations of both clobazam and norclobazam. In the study by Chiron published in 2000, the mean clobazam dose in the patients receiving stiripentol had been reduced from 0.5 mg/kg/day at baseline to 0.38 mg/kg/day at study completion (p = 0.001) in response to the development of clobazam-associated adverse effects. Patients receiving this combination should be closely monitored for clobazam adverse effects indicating the need for dose adjustment. Some investigators have suggested an empiric clobazam dose reduction of 50%.

A similar interaction occurs with stiripentol and valproate. In a recent study of 28 patients (ages 1-35 years) with Dravet syndrome, those taking valproate experienced a significant increase in their serum concentrations after stiripentol was added, with a rise in mean valproate concentration to dose ratio from 4.0 ± 1.3 (mcg/mL)/mg/kg to
4.6 ± 1.7 (mcg/mL)/mg/kg, p = 0.006. As with clobazam, patients taking valproate and stiripentol should be closely monitored for signs of valproate toxicity. Valproate serum concentrations should be monitored to assist in dose adjustment.15

Coadministration of drugs that induce CYP1A2, CYP3A4, or CYP2C19, such as carbamazepine, rifampin, phenobarbital, or phenytoin, may produce lower serum stiripentol concentrations and reduce efficacy.2 These combinations should be avoided whenever possible. The FDA has requested that the manufacturer conduct a series of studies to better define the significance of stiripentol drug interactions.5 Data from these studies may be available by the end of 2020. Central nervous system depressants may potentiate the somnolence caused by stiripentol and should be used with caution.

Availability
Stiripentol will be available in 250 mg and 500 mg capsules, as well as a 250 mg and 500 mg fruit-flavored powder packets for oral suspension.2 The manufacturer has not yet provided pricing information. The capsules and powder packets should be stored at room temperature in their original container to protect the drug from exposure to light. Stiripentol powder for oral suspension contains phenylalanine. In patients with phenylketonuria, use of the capsules is recommended. If the oral suspension is necessary, the family should know that each 250 mg packet contains 1.4 mg phenylalanine and each 500 mg packet contains 2.8 mg phenylalanine in order to determine total daily exposure.

Dosing Recommendations
The recommended dose for stiripentol is 50 mg/kg/day divided and given in two or three doses, with a maximum dose of 3,000 mg/day.2 Capsules must be swallowed whole with a glass of water during a meal. They should not be opened or crushed. The powder for oral suspension should be mixed with 100 mL of water and taken immediately after mixing. The manufacturer recommends adding another 25 mL of water to the cup and having the patient drink this as well to ensure the full dose has been administered. The oral suspension should not be stored for future use. Both the capsules and oral suspension should be taken during a meal.

Summary
Stiripentol offers an additional option for the treatment of refractory seizures in children and adults with Dravet syndrome. While most widely studied in combination with clobazam or valproate in these patients, it may also be useful in patients with other types of refractory seizures. Research is currently underway to identify clinically significant drug interactions and better define the role of stiripentol as adjunctive therapy for seizures in the pediatric population.

References