**PRESCRIBING INFORMATION**
**PRODUCT MONOGRAPH**

# CELONTIN

**(Methsuximide Capsules U.S.P.)**

**300 mg**

**ANTICONVULSANT**

ERFA Canada 2012 Inc.

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Montréal, QC
Canada, H4P 2P5

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**Control number : 162468**

# PRESCRIBING INFORMATION

## CELONTIN*

**(Methsuximide Capsules U.S.P.)**

**300 mg**

## THERAPEUTIC CLASSIFICATION

**Anticonvulsant**

## ACTION AND CLINICAL PHARMACOLOGY

CELONTIN (methsuximide) elevates the seizure threshold in the cortex and basal ganglia and reduces synaptic response to low frequency repetitive stimulation. The paroxysmal spike and wave pattern of the EEG, common in petit mal seizure, is suppressed.

Methsuximide suppresses the paroxysmal three cycles per second spike and wave activity associated with lapses of consciousness which is common in absence (petit mal) seizures. The frequency of epileptiform attacks is reduced, apparently by depression of the motor cortex and elevation of the threshold of the central nervous system to convulsive stimuli.

Limited studies indicate that the drug is metabolized via N-demethylation to N-demethylmethsuximide (NDM). Profound CNS depression following methsuximide overdose has been attributed to this metabolite, and it is probable that the anticonvulsant effects of the drug are due to NDM. In one study, which measured methsuximide and NDM levels simultaneously in plasma of patients who were receiving methsuximide chronically, the concentration of NDM was 700 times greater than the concentration of methsuximide. On the basis of this study, a tentative therapeutic plasma level of 10 to 40 µg/ml of NDM has been proposed.

Less than 1% of a dose of methsuximide is excreted unchanged in the urine; although a number of as yet unidentified metabolites are excreted in urine.

## INDICATIONS AND CLINICAL USAGE

CELONTIN (methsuximide) is used for the control of absence (petit mal) seizures refractory to other drugs.

## CONTRAINDICATIONS

Methsuximide should not be used in patients with a history of hypersensitivity to succinimides, methsuximide or any component of this medication.

## WARNINGS

General

Proceed slowly when increasing or decreasing dosage, as well as when adding or eliminating other medication. Abrupt withdrawal of anticonvulsant medications may precipitate petit mal status.

Methsuximide, when used alone in mixed types of epilepsy, may increase the frequency of grand mal seizures in some patients.

Hematopoietic Effect

Blood dyscrasias, including some with fatal outcome, have been reported to be associated with the use of succinimides; therefore, periodic blood counts should be performed. Patients should be instructed to promptly contact their physician if they develop signs and/or symptoms suggesting an infection (eg. Sore throat, fever); blood counts should be considered at that point.

Hepatic/Renal Impairment

It has been reported that succinimides, including methsuximide, have produced morphological and functional changes in animal liver. For this reason, administer methsuximide with extreme caution to patients with known liver or renal disease. Periodic urinalysis and liver function studies are advised for all patients receiving the drug.

Autoimmune Disorders

Cases of systemic lupus erythematosus have been reported with the use of methsuximide. The physician should be alerted to this possibility.

Psychiatric

It is recommended that the physician withdraw the drug slowly on the appearance of unusual depression, aggression, or other behavioral alterations.

Lamotrigine: Methsuximide may lower the serum concentrations of lamotrigine. When methsuximide is used in combination with lamotrigine, adjustment of the lamotrigine dose may be necessary when methsuximide is started or stopped.

*Pregnancy*: Recent reports indicate an association between the use of anticonvulsant drugs and an elevated incidence of birth defects in children born to epileptic women taking such medications during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women this incidence may be increased 2- to 3-fold. The increase is largely due to specific defects, e.g., congenital malformations of the heart, and cleft lip and/or palate. Nevertheless, the great majority of mothers receiving anticonvulsant medications deliver normal infants.

Data are more extensive with respect to phenytoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsants, including trimethadione and paramethadione. However, the possibility also exists that other factors, e.g., genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.

Anticonvulsant drugs should not be discontinued 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 risk to both the mother and the unborn child. With regard to drugs given for minor seizures, the risk of discontinuing medications prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Epileptic women of childbearing age should be encouraged to seek professional counsel and should report the onset of pregnancy promptly to their physician. Where the necessity for continued use of the antiepileptic medication is in doubt, appropriate consultation might be indicated.

The preceding considerations should be borne in mind and methsuximide should be used in women of childbearing potential only when the expected benefits to the patients warrant the possible risk to a fetus.

*Lactation*: Methsuximide is excreted in human breast milk. Because the effects of methsuximide on the nursing infant are unknown, caution should be exercised when methsuximide is administered to a nursing mother. Methsuximide should be used in nursing mothers only if the benefits clearly outweigh the risks.

**Suicidal Ideation and Behavior**

Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for sign of suicidal ideation and behavior and appropriate treatment should be considered.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behavior in patients treated with these drugs. The mechanism of this risk is not known.

There were 43892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy

patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behavior reported from the metanalysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behavior for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

## PRECAUTIONS

Information for Patients

*Occupational Hazards*:

Methsuximide may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a motor vehicle or other such activity requiring alertness; therefore the patient should be cautioned accordingly.

Patients taking methsuximide should be advised of the importance of adhering strictly to the prescribed dosage regimen.

Patients should be instructed to promptly contact their physician if they develop signs and/or symptoms (e.g., sore throat, fever) suggesting an infection.

*Drug Interactions:* Since CELONTIN (methsuximide) may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of these drugs may be necessary (eg, methsuximide may increase the plasma concentrations of phenytoin and phenobarbital).

*ADVICE TO THE PHARMACIST AND PATIENT:* Since methsuximide has a relatively low melting temperature (51.1 °C), storage conditions which may promote high temperatures (closed cars, delivery vans, or storage near steam pipes) should be avoided. Do not dispense or use capsules that are not full or in which contents have melted. Effectiveness may be reduced. Protect from excessive heat (40.0 °C).

## ADVERSE REACTIONS

**Body as a Whole:** Abdominal pain, fever, headache and systemic lupus erythematosus (see **PRECAUTIONS**, Autoimmune Disorders).

**Digestive System:** Anorexia, constipation, diarrhea, epigastric pain, nausea, vomiting.

**Hemic and Lymphatic System:** Eosinophilia, leukopenia, monocytosis, pancytopenia with or without bone marrow suppression (see **PRECAUTIONS**, Hematopoietic Effect).

**Metabolism and Nutrition:** Porphyria, weight loss.

**Nervous System:** Aggression, ataxia, auditory hallucinations, depression, dizziness, drowsiness, insomnia, irritability, nervousness, psychosis.

Drowsiness, ataxia, and dizziness have been the most frequent adverse effects noted.

Psychological abnormalities have included confusion, instability, mental slowness, depression, hypochondriacal behavior, and aggression. There have been rare reports of psychosis, suicidal behavior and auditory hallucinations (see PRECAUTIONS, Psychiatric).

**Respiratory System:** Hiccups

**Skin/Appendages:** Rash, Stevens-Johnson syndrome, urticaria.

**Special Senses:** Blurred vision, photophobia.

**Urogenital:** Microscopic hematuria, proteinuria.

**Miscellaneous:** Periorbital edema, hyperemia.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute overdoses may produce nausea, vomiting, and CNS depression including coma with respiratory depression. Methsuximide poisoning may follow a biphasic course. Following an initial comatose state, patients have awakened and then relapsed into a

coma within 24 hours. It is believed that an active metabolite of methsuximide, N-desmethylmethsuximide, is responsible for this biphasic profile. It is important to follow plasma levels of N-desmethylmethsuximide in methsuximide poisonings. Levels greater than 40 mcg/ml have caused toxicity, and coma has been seen at levels of 150 mcg/ml. (see **ACTION AND CLINICAL PHARMACOLOGY**)

**Treatment:** Treatment should include emesis (unless the patient is or could rapidly become obtunded, comatose, or convulsing) or gastric lavage, activated charcoal, cathartics, and general supportive measures. Charcoal hemoperfusion may be useful in removing the N-desmethyl metabolite of methsuximide. Forced diuresis and exchange transfusions are ineffective.

## DOSAGE AND ADMINISTRATION

Optimal dosage (that which is just sufficient to control seizures without causing disturbing side effects) must be determined by trial and should be individualized according to the needs of each patient. A suggested schedule is 300 mg daily for the first week. If required, the daily dosage may be increased at weekly intervals by 300 mg/day for the 3 weeks following to a daily dosage of 1200 mg.

### Capsule Composition

Each yellow capsule with orange cap contains: methsuximide 300 mg. Nonmedicinal ingredients: cornstarch; capsule shell: D&C Yellow No. 10, FD&C Red No. 3, FD&C Yellow No. 6 and gelatin. Energy: 1.57 kJ (0.38 kcal). Gluten-, lactose-, paraben-, sodium-, sulfite- and tartrazine-free.

### Stability and Storage Recommendation

Store CELONTIN (methsuximide) between 15 and 30°C. Protect from light, moisture and excessive heat.

## AVAILABILITY OF DOSAGE FORMS

CELONTIN (methsuximide) capsules are available in the dosage strength of 300 mg per capsule.
Each capsule with yellow body and orange cap is imprinted with “Parke-Davis”.
Available in bottles of 100.

## PHARMACEUTICAL INFORMATION

**Drug Substance**

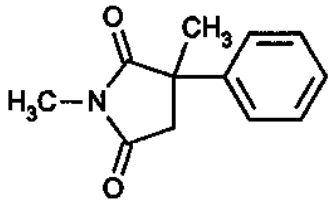
Proper Name: Methsuximide

Chemical Name: (±)-1,3-dimethyl-3-phenylpyrrolidine-2,5-dione

Empirical Formula: $C_{12}H_{13}NO_2$

Molecular Weight: 203.24

Structural Formula:




Melting Range: $50^{o}$ to $56^{o}$C

## IMPORTANT: PLEASE READ

**CONSUMER INFORMATION**

**CELONTIN®**
**(Methsuximide)**
**300 mg Capsules USP**

**Read this information each time you refill your prescription in case new information has been added. This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CELONTIN.**
**Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**

CELONTIN® is used to control absence (petit mal) seizures when it resists treatment with other drugs.

**What it does:**

CELONTIN® is an anti-epileptic drug. It is used to treat epilepsy. The exact mechanism of action is not entirely understood.

**When it should not be used:**

**DO NOT TAKE CELONTIN® if you have any of the following medical conditions:**

- **Known allergy to methsuximide (CELONTIN®) or any component of this medication.**
- **Allergy (hypersensitivity) to succinimides or components of these products.**

**What the medicinal ingredient is:**

**Methsuximide**

**What the non medicinal ingredients are:**

Cornstarch; capsule shell: D&C Yellow No. 10, FD&C Red No. 3, FD&C Yellow No. 6 and gelatin.

**What dosage forms it comes in:**

Capsule, 300 mg

## WARNING AND PRECAUTIONS

Before you use CELONTIN talk to your doctor or pharmacist if you:

- have liver or kidney disease
- have or have had depression, aggression, or mood problems
- have or had grand mal seizures *or lupus* .
- have any other medical conditions
- are pregnant or plan to become pregnant. When pregnant women use anticonvulsant drugs such as CELONTIN®, there may be a higher risk of birth defects in the baby. Tell your healthcare provider right away if you become pregnant while taking CELONTIN®. You and your healthcare provider should decide if you should take CELONTIN® while you are pregnant. Talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. The purpose of this registry is to collect information about the safety of medicines used to treat seizures during pregnancy. You can enroll in this registry by calling 1-888-233-2334. Information on the registry can also be found on the following website: http://aedpregnancyregistry.org/.
- are breast-feeding or plan to breast-feed. CELONTIN® passes into breast milk.

Some people have thoughts of suicide or hurting themselves while taking medications to prevent seizures such as CELONTIN®. Talk to your doctor right away if this happens to you.

**Driving and using machines:** Before you perform tasks which may require special attention, wait until you know how you respond to CELONTIN®.

**This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.**

## INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or

alternative medicines.

Do not start or stop other medicines without talking to your healthcare provider. The blood level of CELONTIN® and any other antiepileptic drugs may need to be checked by the doctor in a blood test.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

Drugs that may interact with CELONTIN include:

- Lamotrigine, an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder.
- Anticonvulsivants (antiepileptic drugs) such as phenytoin, phenobarbital or valproic acid

## PROPER USE OF THIS MEDICATION

You should never discontinue this medication without consulting your physician. Some conditions may become worse when the drug is suddenly stopped. Your dose may need to be gradually decreased.

Take CELONTIN® exactly as instructed by your doctor.

It is important to keep your appointments for medical checkups.

Dosage is individualised. Your doctor will start you on a low dose and slowly increase your dose. It may take several weeks or months to reach the best dose for you and to get the full benefit from this medication. To help you remember, use it at the same time(s) each day.

CELONTIN® may be taken with or without food.

**Usual Dose**

300 mg a day for the first week.
If needed, the dosage can be gradually increased by the doctor to 1200 mg a day.

**Missed Dose**

Do not abruptly stop taking your medicine because of the risk of increasing your epileptic seizures.
If a dose is missed, you should take it as soon as you remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

**Overdose**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Nausea, diarrhea, vomiting, indigestion.
- Drowsiness, dizziness, lethargy, sedation
- Euphoria, hyperactivity

**If any of these affects you severely, tell your doctor or pharmacist.**

CELONTIN can cause abnormal urine and blood test results. Your doctor will decide when to perform urine and blood tests and will interpret the results.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| Symptom | | talk to your physician or pharmacist right away | | Seek emergency medical attention IMMEDIATELY |
|---|---|---|---|---|
| | | Only in severe cases | In all cases | |
| Uncommon | Thoughts of suicide or hurting yourself | | ✔ | |
| | **Allergic reaction** (symptoms include swelling in the eyes, lips, mouth, tongue, face and throat, itching, rash, hives) | | | ✔ |
| | **Decreased platelets in the blood,** fatigue, weakness, bleeding or bruising more easily than normal, nose bleeds | | ✔ | |

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|---|---|---|---|---|
| | **Decreased white blood cells** fatigue, fever, aches, pains and flu-like symptoms | | ✔ | |
| | **Psychotic disorders** Hallucinations (hearing things that are not there), psychosis aggression | | ✔ | |
| | Severe skin rash that causes blistering | | | ✔ |
| | Pain and inflammation of the joints | | ✔ | |
| | **Porphyria** (abdominal pain,light sensitivity causing rashes, blistering or scaring of the skin, seizures, mental disturbances or nerve damage) | | | ✔ |
| | **Ataxia** Lack of voluntary coordination of muscle movements | | ✔ | • • • |

***This is not a complete list of side effects. For any unexpected effects while taking*** CELONTIN®***, contact your doctor or pharmacist.***

## HOW TO STORE IT

**Do NOT keep outdated medicine or medicine no longer needed.** Any outdated or unused medicine should be returned to your pharmacist.

Keep the capsules in a dry place at normal room temperature (15°C- 30°C) in the packaging that they come in.

**Keep out of reach and sight of children.**

## MORE INFORMATION

This document plus the full product monograph prepared for health professionals can be found at http://www.ECI2012.net or by contacting the sponsor, ERFA Canada 2012 Inc. at 1-888-922-3133.

This leaflet was prepared by ERFA Canada 2012 Inc.

Last revised: March 14th 2013.

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

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**Report online at www.healthcanada.gc.ca/medeffect**
**Call toll-free at 1-866-234-2345**
**Complete a Canada Vigilance Reporting Form and:**
**- Fax toll-free to 1-866-678-6789, or**
**- Mail to: Canada Vigilance Program**
**Health Canada**
**Postal Locator 0701D**
**Ottawa, Ontario**
**K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***