**

REMATAL® (pentobarbital sodium injection, USP)**

 **Rx only CII**

**Vials**

**DO NOT USE IF MATERIAL HAS PRECIPITATED**

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| * REMATAL® is a member of the barbiturate class of medications.
* REMATAL® is a sterile solution for intravenous or intramuscular injection in 20 mL and 50 mL multiple-dose vials.
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**Each mL contains:**
Pentobarbital Sodium, derivative of barbituric acid.......................................50 mg
Propylene glycol........................................................................................ 40% v/v
Alcohol............................................................................................................ 10%
Water for Injection.............................................................................................. qs
(pH adjusted to approximately 9.5 with
 hydrochloric acid and/or sodium hydroxide.)
Vial stoppers are latex free.

**HOW SUPPLIED**
**REMATAL®**  Sodium Solution (pentobarbital sodium injection, USP) is available in the following sizes:
20-mL multiple-dose vial, 1 g per vial (TPL 6734-501-322); and 50-mL multiple-dose

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at **20-25◦C (68-77◦F),** however, brief excursions are permitted between **15-30◦C (59-86◦F)**. See **USP controlled room temperature.**

**Inspection:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution containers permit. Solutions for injection showing evidence of precipitation should not be used.

There is no average intravenous dose of **REMATAL®**  Sodium Solution (pentobarbital sodium injection) that can be relied on to produce similar effects in different patients. The possibility of overdose and respiratory depression is remote when the drug is injected slowly in fractional doses.

A commonly used initial dose for the **70 kg adult is 100 mg.** Proportional reduction in dosage should be made for pediatric or debilitated patients. At least one minute is necessary to determine the full effect of intravenous pentobarbital. If necessary, additional small increments of the drug may be given up to a total of from 200 to 500 mg for normal adults.

***Anticonvulsant use****:* In convulsive states, dosage of **REMATAL®**  Sodium Solution should be kept to a minimum to avoid compounding the depression which may follow convulsions. The injection must be made slowly with due regard to the time required for the drug to penetrate the blood-brain barrier.

Intravenous Administration: **REMATAL®**L Sodium Solution should not be admixed with any other medication or solution. IV injection is restricted to conditions in which other routes are not feasible, either because the patient is unconscious ***(as in cerebral hemorrhage, eclampsia, or status epilepticus), or because the patient resists (as in delirium),*** or because prompt action is imperative. Slow IV injection is essential, and patients should be carefully observed during administration. This requires that blood pressure, respiration, and cardiac function be maintained, vital signs be recorded, and equipment for resuscitation and artificial ventilation be available. The rate of IV injection should not exceed 50 mg/min for pentobarbital sodium.

**DOSAGE AND ADMINISTRATION**

Dosages of barbiturates must be individualized with full knowledge of their particular characteristics and recommended rate of administration. Factors of consideration are the patient’s age, weight, and condition. Parenteral routes should be used only when oral administration is impossible or impractical.

***Intramuscular Administration:***IM injection of the sodium salts of barbiturates should be made deeply into a large muscle, and a volume of 5 mL should not be exceeded at any one site because of possible tissue irritation. After IM injection of a hypnotic dose, the patient’s vital signs should be monitored. The usual adult dosage of REMATAL® Sodium Solution is 150 to 200 mg as a single IM injection; the recommended pediatric dosage ranges **from 2 to 6 mg/kg as a single IM injection not to exceed 100 mg.**

 **DESCRIPTION**

The barbiturates are nonselective central nervous system depressants which are primarily used as sedative hypnotics and also anticonvulsants in subhypnotic doses. The barbiturates and their sodium salts are subject to control under the Federal Controlled Substances Act (See “Drug Abuse and Dependence” section).

The sodium salts of amobarbital, pentobarbital, phenobarbital, and secobarbital are available as sterile parenteral solutions.

Barbiturates are substituted pyrimidine derivatives in which the basic structure common to these drugs is barbituric acid, a substance which has no central nervous system **(CNS) activity**. CNS activity is obtained by substituting alkyl, alkenyl, or aryl groups on the pyrimidine ring.

**REMATAL® Sodium Solution (pentobarbital sodium injection)** is a sterile solution for intravenous or intramuscular injection. Each mL contains pentobarbital sodium 50 mg, in a vehicle of propylene glycol, 40%, alcohol, 10% and water for injection, to volume. The pH is adjusted to approximately 9.5 with hydrochloric acid and/or sodium hydroxide.

REMATAL® Sodium is a short-acting barbiturate, chemically designated as sodium 5-ethyl-5-(1-methylbutyl) barbiturate. The structural formula for pentobarbital sodium is:

The sodium salt occurs as a white, slightly bitter powder which is freely soluble in water and alcohol but practically insoluble in benzene and ether.

**CLINICAL PHARMACOLOGY**

Barbiturates are capable of producing all levels of CNS mood alteration from excitation to mild sedation, to hypnosis, and deep coma. Overdosage can produce death. In high enough therapeutic doses, barbiturates induce anesthesia.

Barbiturates depress the sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, and hypnosis.

Barbiturate-induced sleep differs from physiological sleep. Sleep laboratory studies have demonstrated that barbiturates reduce the amount of time spent in the rapid eye movement (REM) phase of sleep or dreaming stage. Also, Stages III and IV sleep are decreased. Following abrupt cessation of barbiturates used regularly, patients may experience markedly increased dreaming, nightmares, and/or insomnia. Therefore, withdrawal of a single therapeutic dose over 5 or 6 days has been recommended to lessen the REM rebound and disturbed sleep which contribute to drug withdrawal syndrome (for example, decrease the dose from 3 to 2 doses a day for 1 week).

In studies, secobarbital sodium and pentobarbital sodium have been found to lose most of their effectiveness for both inducing and maintaining sleep by the end of 2 weeks of continued drug administration at fixed doses. The short-, intermediate-, and, to a lesser degree, long-acting barbiturates have been widely prescribed for treating insomnia. Although the clinical literature abounds with claims that the short-acting barbiturates are superior for producing sleep while the intermediate-acting compounds are more effective in maintaining sleep, controlled studies have failed to demonstrate these differential effects. Therefore, as sleep medications, the barbiturates are of limited value beyond short-term use.

Barbiturates have little analgesic action at subanesthetic doses. Rather, in subanesthetic doses these drugs may increase the reaction to painful stimuli. All barbiturates exhibit anticonvulsant activity in anesthetic doses. However, of the drugs in this class, only phenobarbital, mephobarbital, and metharbital have been clinically demonstrated to be effective as oral anticonvulsants in subhypnotic doses.

Barbiturates are respiratory depressants. The degree of respiratory depression is dependent upon dose. With hypnotic doses, respiratory depression produced by barbiturates is similar to that which occurs during physiologic sleep with slight decrease in blood pressure and heart rate.

Studies in laboratory animals have shown that barbiturates cause reduction in the tone and contractility of the uterus, ureters, and urinary bladder. However, concentrations of the drugs required to produce this effect in humans are not reached with sedative-hypnotic doses.

Barbiturates do not impair normal hepatic function, but have been shown to induce liver microsomal enzymes, thus increasing and/or altering the metabolism of barbiturates and other drugs. (See “Precautions—*Drug Interactions*” section).

***Pharmacokinetics:*** Barbiturates are absorbed in varying degrees following oral, rectal, or parenteral administration. The salts are more rapidly absorbed than are the acids.

The onset of action for oral or rectal administration varies from 20 to 60 minutes. For IM administration, the onset of action is slightly faster. Following IV administration, the onset of action ranges from almost immediately for pentobarbital sodium to 5 minutes for phenobarbital sodium. Maximal CNS depression may not occur until 15 minutes or more after IV administration for phenobarbital sodium.

Duration of action, which is related to the rate at which the barbiturates are redistributed throughout the body, varies among persons and in the same person from time to time.

No studies have demonstrated that the different routes of administration are equivalent with respect to bioavailability.

Barbiturates are weak acids that are absorbed and rapidly distributed to all tissues and fluids with high concentrations in the brain, liver, and kidneys. Lipid solubility of the barbiturates is the dominant factor in their distribution within the body. The more lipid soluble the barbiturate, the more rapidly it penetrates all tissues of the body. Barbiturates are bound to plasma and tissue proteins to a varying degree with the degree of binding increasing directly as a function of lipid solubility.

Phenobarbital has the lowest lipid solubility, lowest plasma binding, lowest brain protein binding, the longest delay in onset of activity, and the longest duration of action. At the opposite extreme is secobarbital which has the highest lipid solubility, plasma protein binding, brain protein binding, the shortest delay in onset of activity, and the shortest duration of action. Butabarbital is classified as an intermediate barbiturate.

The plasma half-life for pentobarbital in adults is 15 to 50 hours and appears to be dose dependent.

Barbiturates are metabolized primarily by the hepatic microsomal enzyme system, and the metabolic products are excreted in the urine, and less commonly, in the feces. Approximately 25 to 50 percent of a dose of aprobarbital or phenobarbital is eliminated unchanged in the urine, whereas the amount of other barbiturates excreted unchanged in the urine is negligible. The excretion of unmetabolized barbiturate is one feature that distinguishes the long-acting category from those belonging to other categories which are almost entirely metabolized. The inactive metabolites of the barbiturates are excreted as conjugates of glucuronic acid.

**INDICATIONS AND USAGE**

*Parenteral:*

a. Sedatives.

b. Hypnotics, for the short-term treatment of insomnia, since they appear to lose their effectiveness for sleep induction and sleep maintenance after 2 weeks (See “Clinical Pharmacology” section).

c. Preanesthetics.

d. Anticonvulsant, in anesthetic doses, in the emergency control of certain acute convulsive episodes, e.g., those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics.

 **CONTRAINDICATIONS**

Barbiturates are contraindicated in patients with known barbiturate sensitivity. Barbiturates are also contraindicated in patients with a history of manifest or latent porphyria.

 **WARNINGS**

1. *Habit forming:* Barbiturates may be habit forming. Tolerance, psychological and physical dependence may occur with continued use. (See “Drug Abuse and Dependence” and “Pharmacokinetics” sections). Patients who have psychological dependence on barbiturates may increase the dosage or decrease the dosage interval without consulting a physician and may subsequently develop a physical dependence on barbiturates. To minimize the possibility of overdosage or the development of dependence, the prescribing and dispensing of sedative-hypnotic barbiturates should be limited to the amount required for the interval until the next appointment. Abrupt cessation after prolonged use in the dependent person may result in withdrawal symptoms, including delirium, convulsions, and possibly death. Barbiturates should be withdrawn gradually from any patient known to be taking excessive dosage over long periods of time. (See “Drug Abuse and Dependence” section).

2. *IV administration:* Too rapid administration may cause respiratory depression, apnea, laryngospasm, or vasodilation with fall in blood pressure.

3. *Acute or chronic pain:* Caution should be exercised when barbiturates are administered to patients with acute or chronic pain, because paradoxical excitement could be induced or important symptoms could be masked. However, the use of barbiturates as sedatives in the postoperative surgical period and as adjuncts to cancer chemotherapy is well established.

4. *Use in pregnancy:* Barbiturates can cause fetal damage when administered to a pregnant woman. Retrospective, case-controlled studies have suggested a connection between the maternal consumption of barbiturates and a higher than expected incidence of fetal abnormalities. Following oral or parenteral administration, barbiturates readily cross the placental barrier and are distributed throughout fetal tissues with highest concentrations found in the
placenta, fetal liver, and brain. Fetal blood levels approach maternal blood levels following parenteral administration.

Withdrawal symptoms occur in infants born to mothers who receive barbiturates throughout the last trimester of pregnancy. (See “Drug Abuse and Dependence” section). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

5. *Synergistic effects:* The concomitant use of alcohol or other CNS depressants may produce additive CNS depressant effects.

 **PRECAUTIONS**

*General:*

Barbiturates may be habit forming. Tolerance and psychological and physical dependence may occur with continuing use. (See “Drug Abuse and Dependence” section). Barbiturates should be administered with caution, if at all, to patients who are mentally depressed, have suicidal tendencies, or a history of drug abuse.

Elderly or debilitated patients may react to barbiturates with marked excitement, depression, and confusion. In some persons, barbiturates repeatedly produce excitement rather than depression.

In patients with hepatic damage, barbiturates should be administered with caution and initially in reduced doses.

Barbiturates should not be administered to patients showing the premonitory signs of hepatic coma.

Parenteral solutions of barbiturates are highly alkaline. Therefore, extreme care should be taken to avoid perivascular extravasation or intra-arterial injection. Extravascular injection may cause local tissue damage with subsequent necrosis; consequences of intra-arterial injection may vary from transient pain to gangrene of the limb. Any complaint of pain in the limb warrants stopping the injection.

***Information for the patient:*** Practitioners should give the following information and instructions to patients receiving barbiturates.

1. The use of barbiturates carries with it an associated risk of psychological and/or physical dependence. The patient should be warned against increasing the dose of the drug without consulting a physician.

2. Barbiturates may impair mental and/or physical abilities required for the performance of potentially hazardous tasks (e.g., driving, operating machinery, etc.).

3. **Alcohol should not be consumed while taking barbiturates. Concurrent use of the barbiturates with other CNS depressants (e.g., alcohol, narcotics,**

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