BARBITURATES (Systemic)

Introduction

Revised: 08/15/95

This monograph includes information on the following:1) Amobarbital ; 2) Aprobarbital b; 3) Butabarbital ; 4) Mephobarbital ; 5) Metharbital a, b; 6) Pentobarbital ; 7) Phenobarbital ; 8) Secobarbital ; 9) Secobarbital and Amobarbital.

VA CLASSIFICATION (Primary)
Amobarbital
Oral¾CN301
Parenteral¾CN301/CN400
Aprobarbital
Oral¾CN301
Butabarbital
Oral¾CN301
Mephobarbital
Oral¾CN400
Metharbital
Oral¾CN400
Pentobarbital
Oral¾CN301
Parenteral¾CN301/
Phenobarbital
Oral¾CN301/; GA900
Parenteral¾CN301/; GA900
Secobarbital
Oral¾CN301
Parenteral¾CN301/

Note: Controlled substance classification¾Note: Controlled substances in the U.S. and Canada as follows 69, 70, 90, 95, 115, 117, 120 :

Drug	U.S.	Canada
Amobarbital	II	C
Aprobarbital	III	
Butabarbital	III	C
Mephobarbital	IV	C
Pentobarbital	II	C
Oral		
Parenteral	II	C
Rectal	III	C
Phenobarbital	IV	C

Secobarbital	II	C
Oral		
Parenteral	II	
Secobarbital and Amobarbital	II	C

Commonly used brand name(s):Alurate2; Amytal1; Ancalixir7; Barbita7; Busodium3; Butalan3; Butisol3; Gemonil5; Luminal7; Mebaral4; Nembutal6; Nova Rectal6; Novopentobarb6; Novosecobarb8; Sarisol No. 23; Seconal8; Solfoton7; Tuinal9.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

a Not commercially available in the U.S.

b Not commercially available in Canada.

Category

Sedative-hypnotic¾Amobarbital; Aprobarbital; Butabarbital; Pentobarbital; Phenobarbital (parenteral only); Secobarbital.

Anticonvulsant¾Amobarbital (parenteral only); Mephobarbital; Metharbital; Pentobarbital (parenteral only); Phenobarbital; Secobarbital (parenteral only).

Antihyperbilirubinemic¾Phenobarbital.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Anesthesia, adjunct¾Amobarbital, butabarbital, pentobarbital, phenobarbital (parenteral), and secobarbital are indicated for use as preoperative medication to help reduce anxiety and facilitate induction of anesthesia 46, 51, 69, 70, 92, 99A, 105, 106, 108, 115, 117, 119, 164.

Narcoanalysis¾Amobarbital (parenteral) may be indicated in narcoanalysis 30, 46, 114.

Epilepsy, tonic-clonic seizure pattern (treatment) or

Epilepsy, simple partial seizure pattern (treatment)¾Phenobarbital 55, 56, 95 , a long-acting barbiturate, is indicated as long-term anticonvulsant therapy for the treatment of generalized tonic-clonic and simple partial (cortical focal) seizures; mephobarbital 33, 49, 50 and metharbital, also long-acting barbiturates, may be indicated as alternatives to phenobarbital 84, 86, 107, 117, 119.

Convulsions (treatment)

Seizures (prophylaxis and treatment)

Status epilepticus (treatment) or

Tetanus (treatment adjunct)¾Parenteral barbiturates 91, 114 , especially phenobarbital, are indicated in the emergency treatment of certain acute convulsive episodes such as those associated with status epilepticus, eclampsia, meningitis, and toxic reactions to strychnine. They are also indicated as adjunctive treatment for acute convulsive episodes associated with tetanus. 36, 51, 54, 55, 56, 58, 107, 117, 119

Phenobarbital is used in the prophylaxis and treatment of febrile seizures 55, 117, 119.
*

[Hyperbilirubinemia (prophylaxis and treatment)] *¾Phenobarbital (oral and parenteral) is used in the prevention and treatment of hyperbilirubinemia in neonates. It is used also to lower bilirubin concentrations in patients with congenital nonhemolytic unconjugated hyperbilirubinemia or chronic intrahepatic cholestasis. 113

[Ischemia, cerebral (treatment)] * or

[Hypertension, cerebral (treatment)] *¾Pentobarbital (parenteral) is used for induction of coma to protect the brain from various states, including ischemia and increased intracranial pressure that follow stroke and head trauma; however, this use is controversial and further studies are needed.

Amobarbital, aprobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital, and secobarbital and amobarbital have been used for the short-term treatment of insomnia; however, they generally have been replaced by benzodiazepines. If barbiturates are used, they are not recommended for long-term use since they appear to lose their effectiveness in sleep induction and maintenance after 2 weeks or less. 28, 46, 47, 48, 50, 51, 52, 55, 56, 57, 58, 59, 60, 69, 70, 73, 90, 92, 95, 99A, 105, 106, 107, 108, 115, 116, 117, 119, 120, 121, 164

Amobarbital, aprobarbital, butabarbital, mephobarbital, pentobarbital, phenobarbital, and secobarbital have also been used for routine sedation to relieve anxiety, tension, and apprehension 95, 105, 106, 107, 108, 115, 117, 164 ; however, barbiturates generally have been replaced by benzodiazepines for daytime sedation 46, 47, 48, 52, 55, 56, 57, 58.

Unaccepted

Amobarbital (parenteral) has been used as a diagnostic aid in schizophrenia 114 but it generally has been replaced by other agents 30.

Amobarbital (parenteral) has also been used in the management of catatonic and negativistic reactions 114 ; however, phenothiazines generally are more appropriate therapy for catatonic reactions. It has also been used in the management of manic reactions, although benzodiazepines and lithium are usually preferred. 30

[Phenobarbital (oral and parenteral) has been used in the treatment of familial, senile, or essential action tremors; however, it generally has been replaced by other agents, such as benzodiazepines and beta-adrenergic blockers.]

* Not included in Canadian product labeling.

Pharmacology/Pharmacokinetics

See Table 1.

Physicochemical characteristics:

Molecular weight¾Amobarbital: 226.27

Amobarbital sodium: 248.26

Aprobarbital: 210.23

Butabarbital sodium: 234.23

Mephobarbital: 246.27

Metharbital: 198.22

Pentobarbital: 226.27

Pentobarbital sodium: 248.26

Phenobarbital: 232.24

Phenobarbital sodium: 254.22

Secobarbital sodium: 260.27

Mechanism of action/Effect:

Barbiturates act as nonselective depressants of the central nervous system (CNS), capable of producing all levels of CNS mood alteration from excitation to mild sedation, hypnosis, and deep coma 90, 92, 99A, 116, 117, 119, 120.

In sufficiently high therapeutic doses, barbiturates induce anesthesia. Recent studies have suggested that the sedative-hypnotic and anticonvulsant effects of barbiturates may be related to their ability to enhance and/or mimic the inhibitory synaptic action of gamma-aminobutyric acid (GABA). 51, 52, 55, 56, 57, 58, 84, 114, 115

Sedative-hypnotic¾ Barbiturates depress the sensory cortex, decrease motor activity, alter cerebral function, and produce drowsiness, sedation, and hypnosis 99A, 116, 120.

Although the mechanism of action has not been completely established, the barbiturates appear to have a particular effect 26 at the level of the thalamus where they inhibit ascending conduction in the reticular formation, thus interfering with the transmission of impulses to the cortex.

The mechanism of action of pentobarbital in protecting the brain from ischemia and intracranial pressure is not completely understood; however, it is related to pentobarbital's anesthetic action (produced by sufficiently high dosage) and possibly to the depression of neuronal activity and metabolism 90.

Anticonvulsant¾ Barbiturates are believed to act by depressing monosynaptic and polysynaptic transmission in the CNS. They also increase the threshold for electrical stimulation of the motor cortex.

Antihyperbilirubinemic¾ Phenobarbital lowers serum bilirubin concentrations probably by induction of glucuronyl transferase, the enzyme which conjugates bilirubin.

Other actions/effects:

Barbiturates have little analgesic action at subanesthetic doses and may increase reaction to painful stimuli 51, 52, 53, 55, 56, 57, 90, 92, 95, 99A.

Although phenobarbital, mephobarbital, and metharbital are the only barbiturates effective as anticonvulsants in subhypnotic doses, all of the barbiturates exhibit anticonvulsant activity in anesthetic doses 31, 51, 56, 57, 90, 99A, 117, 119.

Barbiturates are respiratory depressants; the degree of respiratory depression is dose-dependent 48, 49, 51, 52, 53, 55, 56, 57, 60, 84, 90, 92, 99A, 115, 116, 117, 119, 120.

Barbiturates have been shown to reduce the rapid eye movement (REM) phase of sleep or dreaming stage. Also, Stages III and IV sleep (slow-wave sleep, SWS) are decreased. 48, 51, 52, 53, 55, 56, 57, 60, 99A, 115, 116, 117, 119, 120

Animal studies have shown that barbiturates cause reduction in the tone and contractility of the uterus, ureters, and urinary bladder; however, concentrations required to produce this effect in humans are not attained with sedative-hypnotic doses 49, 51, 52, 53, 55, 56, 90, 117, 119.

Barbiturates have been shown to induce liver microsomal enzymes, thereby increasing and altering the metabolism of 62 other medications or compounds 48, 49, 50, 51, 52, 53, 55, 56, 57, 84, 90, 92, 95, 99A, 115, 117, 118, 119, 120.

Absorption:

Absorbed in varying degrees following oral, parenteral, or rectal administration 48, 49, 51, 52, 53, 55, 57, 90, 117.

Barbiturate sodium salts are absorbed more rapidly than the free acids because of rapid dissolution 48, 51, 52, 53, 57, 90, 92, 116, 117, 119.

The rate of absorption is increased if barbiturates are taken well diluted or on an empty stomach 48, 51, 52, 53, 55, 57, 115, 116, 117, 119.

Distribution:

Rapidly distributed to all tissues and fluids with high concentrations in the brain, liver, and kidneys 48, 49, 51, 52, 53, 55, 56, 57, 58, 60, 84, 99A, 115, 116, 117, 119, 120.

Lipid solubility is the primary factor in distribution within the body. The more lipid soluble the barbiturate, the more rapidly it penetrates all tissues of the body; phenobarbital has the lowest lipid solubility and secobarbital the highest 49, 51, 52, 53, 55, 56, 60, 84, 90, 92, 99A, 117, 119, 120.

Biotransformation:

Hepatic, primarily by the hepatic microsomal enzyme system 46, 47, 48, 51, 52, 53, 55, 56, 59, 90, 92, 95, 113, 114, 115, 116, 117, 119.

About 75% of a single oral dose of mephobarbital is metabolized to phenobarbital in 24 hours 49, 84.

Metharbital is metabolized to barbital 50, 86.

Onset of action:

Oral or rectal¾Varies from 20 to 60 minutes 52, 53, 55, 58.

Intramuscular¾Slightly faster than for oral or rectal 52, 53, 55, 58.

Intravenous¾Ranges from almost immediately for pentobarbital sodium to 5 minutes for phenobarbital sodium 52, 53, 55, 56, 58.

Therapeutic serum concentration

Anticonvulsant¾Phenobarbital: 10 to 40 mcg per mL (43 to 172 micromoles/L) 172.

Note: The optimal blood phenobarbital concentration should be determined by response in seizure control and the appearance of toxic effects.

To achieve blood concentrations considered therapeutic in children, higher-per-kg dosages of phenobarbital and most other anticonvulsants generally are required 117, 119.

Time to peak effect:

Phenobarbital¾Maximal CNS depression may not occur for 15 minutes or more after intravenous administration of phenobarbital sodium 51, 55, 56, 117, 119.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to one of the barbiturates may be sensitive to other barbiturates also.

Carcinogenicity/Tumorigenicity/Mutagenicity

For butabarbital and secobarbital¾No long-term studies in animals have been done to determine the carcinogenic and mutagenic potential of butabarbital or secobarbital 48, 58, 115, 116.

For pentobarbital¾Adequate studies have not been done in humans or animals to determine the carcinogenic potential of pentobarbital 51, 52, 53, 90, 92.

For phenobarbital¾Studies in animals have shown that phenobarbital is carcinogenic in mice and rats following lifetime administration. It produced benign and malignant liver cell tumors in mice and benign liver cell tumors very late in life in rats. A study in humans did not provide sufficient evidence that phenobarbital is carcinogenic in humans. 31, 55, 56, 117, 120

Pregnancy/Reproduction

Fertility¾For butabarbital: No long-term studies in animals have been done to determine the effects of butabarbital on fertility 48.

Pregnancy¾Barbiturates readily cross the placenta following oral or parenteral administration. They are distributed throughout fetal tissues, the highest concentrations being found in the placenta, fetal liver, and brain. 84, 115, 116, 120 Following parenteral administration, fetal blood concentration approaches maternal blood concentration 48, 49, 50, 51, 52, 53, 55, 56, 58, 60, 84, 90, 92, 120.

Barbiturates have been shown to cause an increased incidence of fetal abnormalities. Risk-benefit must be carefully considered when the medication is required in life-threatening situations or in serious diseases for which other medications cannot be used or are ineffective. 31, 55, 56, 57, 60, 84, 90, 92, 99A, 115, 116, 117, 118, 119, 120, 121

Third trimester: Use of barbiturates throughout the last trimester of pregnancy may cause physical dependence with resulting withdrawal symptoms in the neonate. In infants suffering from long-term exposure in utero, the acute withdrawal syndrome of seizures and hyperirritability has been reported to occur from birth to a delayed onset of up to 14 days. 48, 51, 52, 53, 55, 56, 57, 60, 84, 99A, 115, 116, 120

Use of long-acting barbiturates, especially phenobarbital, as anticonvulsants during pregnancy is reportedly associated with a neonatal coagulation defect that may cause bleeding during the early neonatal period (usually within 24 hours of birth). This coagulation defect is characterized by decreased concentrations of vitamin K-dependent clotting factors and prolongation of the prothrombin time and/or the partial thromboplastin time. Vitamin K should be given to the mother during delivery and to the infant (intramuscularly or subcutaneously) immediately after birth. 49, 50, 51, 52, 53, 56, 57, 84

Also, one study in humans has suggested that prenatal exposure to barbiturates may be associated with an increased incidence of brain tumors 49, 51, 52, 53, 55, 56, 57, 84, 90, 92, 117, 119.

FDA Pregnancy Category D 31, 55, 56, 57, 60, 84, 90, 92, 99A, 115, 116, 117, 118, 119, 120, 121.

Labor and delivery¾Barbiturates in hypnotic doses do not appear to inhibit uterine activity; however, full anesthetic doses of barbiturates decrease the force and frequency of uterine contractions 31, 48, 51, 52, 53, 55, 56, 60, 84, 90, 92, 99A, 117, 119, 120.

Use of barbiturates during labor may cause respiratory depression in the neonate, especially the premature neonate, because of immature hepatic function 30, 47, 49, 51, 52, 53, 55, 56, 59, 60, 69, 70, 84, 90, 99A, 115, 116, 117, 119, 120, 121.

If barbiturates are used during labor and delivery, it is recommended that resuscitation equipment be readily available 31, 51, 52, 53, 55, 56, 60, 84, 90, 92, 99A, 115, 116, 117, 119, 120.

Breast-feeding

Barbiturates are distributed into breast milk; use by nursing mothers may cause CNS depression in the infant 48, 49, 51, 52, 53, 55, 56, 59, 84, 99A, 115, 116, 117, 119, 120.

Pediatrics

Some children may react to barbiturates with paradoxical excitement.

Geriatrics

Geriatric patients may react to usual doses of barbiturates with excitement, confusion, or mental depression 28, 29, 46, 47, 48, 49, 53, 55, 56, 57, 58, 59, 69, 70, 84, 90, 92, 95, 99A, 114, 115, 117, 118, 119, 120, 121.

The risk of barbiturate-induced hypothermia may be increased in elderly patients, especially with high doses or in acute overdose of barbiturates.

In addition, elderly patients are more likely to have age-related hepatic or renal function impairment, which may require a reduction of dosage in patients receiving a barbiturate 84, 90, 95, 99A, 115, 116, 120.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Acetaminophen

(therapeutic effects of acetaminophen may be decreased when the medication is used concurrently in patients receiving chronic barbiturate therapy because of increased metabolism resulting from induction of hepatic microsomal enzymes; also, risk of hepatotoxicity with single toxic doses or

prolonged use of high doses of acetaminophen may be increased in alcoholics or in patients regularly using hepatic enzyme inducers such as barbiturates 45, 122, 179, 180, 182)

Addictive medications, other, especially CNS depressants with habituating potential

(prolonged concurrent use may increase the risk of habituation; caution is recommended 45)

>> Adrenocorticoids, glucocorticoid and mineralocorticoid 28, 29, 31, 45, 48, 49, 51, 54, 55, 59, 84, 90, 92, 95, 99A, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 179, 180 or

Chloramphenicol 172, 174, 175, 179, 180 or

>> Corticotropin 45, 48, 49, 51, 52, 53, 54, 55, 57, 59, 60, 124 or

Cyclosporine 125, 180 or

Dacarbazine 126 or

Digitalis glycosides 120, 127, 179, 180 or

Metronidazole 172, 173, 176, 177, 178, 179, 180 or

Quinidine 129, 179, 180

(effects may be decreased when these medications are used concurrently with barbiturates, especially phenobarbital, because of enhanced metabolism resulting from induction of hepatic microsomal enzymes; dosage adjustment of these medications, with the exception of digoxin, may be necessary 28, 29, 45, 46, 69, 70, 95, 114, 115, 123, 124)

>> Alcohol 84, 90, 92, 99A, 115, 116, 117, 118, 119, 120, 121, 179, 180 or

>> CNS depression-producing medications, other (See Appendix II)

(concurrent use may increase the CNS depressant effects of either these medications or barbiturates; caution is recommended and dosage of one or both agents should be reduced 28, 29, 31, 45, 46, 47, 48, 49, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 90, 92, 95, 114, 115, 116, 121, 179, 180)

Amphetamines 130

(concurrent use may cause a delay in the intestinal absorption of phenobarbital 45, 130)

Anesthetics, halogenated hydrocarbon 131, 180

(chronic use of barbiturates prior to enflurane, halothane, or methoxyflurane anesthesia may increase anesthetic metabolism leading to increased risk of hepatotoxicity 45, 131)

(chronic use of barbiturates prior to methoxyflurane anesthesia may increase formation of nephrotoxic metabolites leading to increased risk of nephrotoxicity 45, 131)

>> Anticoagulants, coumarin- or indandione-derivative 132, 179, 180

(effects may be decreased when these medications are used concurrently with barbiturates because of increased metabolism resulting from induction of hepatic microsomal enzymes; also, bleeding may result when the barbiturate is discontinued 62 ; periodic prothrombin-time determinations may be required to determine if dosage adjustments of anticoagulants are necessary 28, 29, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, 60, 69, 70, 90, 92, 95, 99A, 114, 115, 116, 117, 118, 119, 120, 121, 132)

Anticonvulsants, hydantoin 133, 179, 180

(concurrent use with barbiturates appears to produce variable and unpredictable effects on the metabolism of hydantoin anticonvulsants; blood concentrations of hydantoin anticonvulsants should be closely monitored when these medications are used concurrently 31, 45, 48, 49, 51, 52, 53, 55, 60, 84, 90, 92, 115, 116, 117, 119, 120, 133)

Anticonvulsants, succinimide or 61, 134

>> Carbamazepine 166, 179, 180

(concurrent use with barbiturates may result in increased metabolism, leading to decreased serum concentrations and reduced elimination half-lives of carbamazepine or succinimide anticonvulsants because of induction of hepatic microsomal enzyme activity; monitoring of serum concentrations as a guide to dosage is recommended, especially when carbamazepine or a succinimide anticonvulsant is added to or withdrawn from an existing regimen 45, 61, 62, 63, 134, 166)

Antidepressants, tricyclic 135, 179, 180

(effects of tricyclic antidepressants may be decreased when these medications are used concurrently with barbiturates, especially phenobarbital, because of increased metabolism resulting from induction of hepatic microsomal enzymes 45, 135)

Calcium channel blocking agents 137, 179, 180

(caution is advised during titration of calcium channel blocker dosage for those patients taking medication known to promote hypotension, such as barbiturate preanesthetics, since the combination may result in excessive hypotension 45, 137)

Carbonic anhydrase inhibitors 138

(osteopenia induced by barbiturates, especially phenobarbital, may be enhanced when carbonic anhydrase inhibitors are used concurrently; it is recommended that patients receiving concurrent therapy be monitored for early signs of osteopenia and that the carbonic anhydrase inhibitor be discontinued and appropriate treatment initiated if necessary 45, 138)

>> Contraceptives, estrogen-containing, oral 31, 139

(concurrent use with barbiturates, especially phenobarbital, may result in reduced contraceptive reliability because of accelerated estrogen metabolism caused by induction of hepatic microsomal enzymes; use of a nonhormonal method of birth control or a progestin-only oral contraceptive may be necessary 45, 48, 49, 51, 52, 53, 55, 60, 84, 90, 92, 115, 116, 117, 119, 120, 139, 179, 180, 181)

Cyclophosphamide 140, 179

(concurrent use with barbiturates, especially phenobarbital, may induce microsomal metabolism to increase formation of alkylating metabolites of cyclophosphamide, thereby reducing the half-life and increasing the leukopenic activity of cyclophosphamide 140)

Disopyramide 141

(concurrent use with barbiturates, especially phenobarbital, may reduce serum disopyramide to ineffective concentrations; therefore, monitoring of its serum concentrations is necessary during concurrent therapy 141)

>> Divalproex sodium 144 or

>> Valproic acid 144, 179, 180

(concurrent use may decrease the metabolism of barbiturates, resulting in increased serum 62 concentrations, which may lead to increased CNS depression and neurological toxicity; barbiturate serum 62 concentrations should be monitored to determine if dosage adjustment is necessary when these medications are used concurrently; also, the half-life of valproic acid may be decreased and dosage adjustment may be necessary 48, 49, 51, 52, 53, 60, 84, 90, 92, 115, 116, 117, 119, 120)

(in addition, phenobarbital may enhance valproic acid hepatotoxicity, presumably through the formation of hepatotoxic valproate metabolites 62, 64)

Doxycycline 145, 179, 180

(half-life of doxycycline may be shortened when this medication is used concurrently with barbiturates, especially phenobarbital, probably because of increased metabolism resulting from induction of hepatic microsomal enzymes; this effect may continue for up to 2 weeks after barbiturate therapy is discontinued; adjustment of doxycycline dosage during and after therapy or substitution of another tetracycline may be necessary 31, 48, 49, 51, 52, 53, 55, 60, 84, 90, 92, 115, 116, 117, 119, 120, 145)

Fenoprofen 146, 180

(concurrent use with phenobarbital may decrease the elimination half-life of fenoprofen, possibly because of increased metabolism resulting from induction of hepatic microsomal enzyme activity; fenoprofen dosage adjustment may be required 146)

Griseofulvin 148, 179, 180

(absorption may be decreased when this medication is used concurrently with barbiturates, especially phenobarbital, resulting in decreased serum concentrations; although the effect of decreased serum 62 concentrations on therapeutic response has not been established, concurrent use preferably should be avoided 31, 48, 49, 51, 52, 53, 55, 84, 90, 92, 115, 116, 117, 119, 120, 148)

Guanadrel 142 or

Guanethidine 143

(concurrent use with barbiturates may aggravate orthostatic hypotension 142, 143)

Haloperidol 149, 180

(concurrent use with barbiturate anticonvulsants may cause a change in the pattern and/or frequency of epileptiform seizures; dosage adjustments of anticonvulsants may be necessary; serum concentrations of haloperidol may be significantly reduced 149)

Hypothermia-producing medications, other (See Appendix II)

(concurrent use with barbiturates in high doses or acute overdose may increase the risk of hypothermia)

Ketamine 150

(concurrent use of ketamine, especially in high doses or when rapidly administered, with barbiturate preanesthetics may increase the risk of hypotension and/or respiratory depression 150)

Leucovorin 151

(large doses may counteract the anticonvulsant effects of barbiturate anticonvulsants 151)

Levothyroxine 152

(concurrent use of barbiturates may increase hepatic degradation of levothyroxine, which may result in increased requirements; dosage adjustment may be necessary 45, 152)

Loxapine 153 or

Phenothiazines 154, 179, 180 or

Thioxanthenes 155

(may lower the seizure threshold; dosage adjustment of barbiturate anticonvulsants may be necessary 153, 154, 155)

(concurrent use of chlorpromazine with phenobarbital has been shown to increase the metabolism 62 of chlorpromazine; therefore, phenobarbital may decrease serum concentrations of phenothiazines when used concurrently 24, 154, 179)

Maprotiline 156

(in addition to possibly enhancing CNS depressant effects, concurrent use of maprotiline may lower the convulsive threshold, at high doses, and decrease the effects of barbiturate anticonvulsants 156)

Methylphenidate 157

(concurrent use may increase serum concentrations of barbiturate anticonvulsants, especially phenobarbital, because of metabolism inhibition, possibly resulting in toxicity; dosage adjustment of the barbiturate anticonvulsant may be necessary 157)

Mexiletine 158

(concurrent use with barbiturates may accelerate metabolism and result in decreased plasma concentrations of mexiletine; plasma concentrations of mexiletine should be monitored during concurrent use to ensure efficacy is maintained 27, 158)

Monoamine oxidase (MAO) inhibitors, including furazolidone, pargyline, and procarbazine 159, 179, 180

(concurrent use may prolong the CNS depressant effects of barbiturates, probably because metabolism of the barbiturate is inhibited 48, 49, 51, 52, 53, 55, 57, 84, 90, 92, 99A, 115, 116, 159)

(concurrent use with barbiturate anticonvulsants may cause a change in the pattern of epileptiform seizures; dosage adjustment of the barbiturate anticonvulsant may be necessary 31, 159)

Phenylbutazone 147, 179, 180

(concurrent use may decrease the efficacy of barbiturates by inducing hepatic microsomal enzymes and increasing their metabolism; also, hepatic enzyme inducers such as barbiturates may increase phenylbutazone metabolism and decrease its half-life 45, 147)

Posterior pituitary 160

(concurrent use with barbiturates may increase the risk of cardiac arrhythmias and coronary insufficiency 160)

Primidone 161, 179

(although concurrent use with barbiturate anticonvulsants is rarely indicated, since primidone is metabolized to phenobarbital 62 , it may cause a change in the pattern of epileptiform seizures because of altered medication metabolism and also increase the sedative effect of either primidone or the barbiturate anticonvulsant 62 ; decreases in primidone dosage may be necessary 161)

Rifampin 170, 179, 180

(concurrent use with rifampin may enhance the metabolism of hexobarbital by induction of hepatic microsomal enzymes, resulting in lower serum concentrations; there are conflicting data on rifampin's effect on phenobarbital; dosage adjustment may be required)

Vitamin D 162

(effects may be reduced by barbiturates, especially phenobarbital, because of accelerated metabolism by hepatic microsomal enzyme induction; vitamin D supplementation may be required in patients on long-term barbiturate anticonvulsant therapy to prevent osteomalacia, although rickets is rare 49, 84, 162)

Xanthines, such as 163, 179, 180 :

Aminophylline

Caffeine

Oxtriphylline

Theophylline

(concurrent use with barbiturates, especially phenobarbital, may increase metabolism of the xanthines [except dyphylline] by induction of hepatic microsomal enzymes, resulting in increased theophylline clearance; also, concurrent use may antagonize hypnotic effects of barbiturates 45, 163)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

With diagnostic test results

Cyanocobalamin Co 57

(absorption of radioactive cyanocobalamin may be impaired by concurrent use of barbiturate anticonvulsants, especially phenobarbital)

Metyrapone test

(increased metabolism of metyrapone by an hepatic enzyme inducer such as a barbiturate may decrease the response to metyrapone 169)

Phentolamine test

(barbiturates may cause a false-positive phentolamine test; it is recommended that all medications be withdrawn at least 24 hours, preferably 48 to 72 hours, prior to a phentolamine test)

With physiology/laboratory test values

Bilirubin, serum

(concentrations may be decreased in neonates, in patients with congenital nonhemolytic unconjugated hyperbilirubinemia, and in epileptics; this effect is presumably due to induction of glucuronyl transferase, the enzyme responsible for the conjugation of bilirubin)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problem exists

>> Porphyria, acute intermittent or variegata, or history of

(barbiturates may aggravate symptoms by inducing enzymes responsible for porphyrin synthesis 28, 29, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 84, 90, 91, 92, 95, 99A, 114, 115, 116, 117, 118, 119, 120, 121)

Risk-benefit should be considered when the following medical problems exist

Anemia, severe

(may be complicated by barbiturate-induced respiratory depression, especially with phenobarbital)

Asthma, history of

(hypersensitivity reactions such as bronchospasm more likely to occur in these patients 28, 29, 47, 48)

Diabetes mellitus, especially with phenobarbital

>> Drug abuse or dependence, history of

(predisposition of patient to habituation and dependence 28, 29, 46, 47, 51, 54, 56, 57, 58, 69, 70, 95, 99A, 114, 115, 116, 118, 120, 121)

>> Hepatic coma, premonitory signs of, or

Hepatic function impairment

(barbiturates metabolized in liver; medication should be administered with caution and, initially, in reduced dosage 28, 29, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 90, 92, 95, 99A, 114, 115, 116, 117, 118, 119, 120, 121)

Hyperkinesis

(condition may be exacerbated)

Hyperthyroidism

(symptoms may be exacerbated because barbiturates displace thyroxine from plasma proteins)

Hypoadrenalism, borderline

(systemic effects of exogenous hydrocortisone and endogenous cortisol may be diminished by barbiturates 28, 29, 46, 47, 59, 69, 70, 95, 99A, 114, 118, 121)

Mental depression and/or

Suicidal tendencies

(condition may be exacerbated, especially in elderly patients 48, 49, 54, 57, 59, 69, 70, 90, 95, 115, 116, 118, 120, 121)

>> Pain, acute or chronic

(paradoxical excitement may be induced or important symptoms may be masked 28, 29, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 69, 70, 84, 90, 92, 95, 99A, 114, 115, 116, 117, 118, 121)

Renal function impairment, especially with intermediate- and long-acting barbiturates

(barbiturates excreted primarily by kidneys; dosage reduction may be necessary 84, 116, 120)

>> Respiratory disease involving dyspnea or obstruction, particularly status asthmaticus

(serious ventilatory depression may occur 28, 29, 46, 47, 48, 49, 52, 53, 57, 58, 69, 70, 84, 95, 99A, 114, 118, 121)

>> Sensitivity to barbiturate prescribed

(in patients sensitive to barbiturates, severe hepatic damage can occur from ordinary doses and is usually associated with dermatitis and involvement of parenchymatous organs 69, 70, 90, 92, 95, 99A, 114, 115, 116, 117, 118, 119, 120, 121)

Caution should be used also in debilitated patients because they may react to usual doses with marked excitement, mental depression, and confusion 69, 70, 84, 90, 92, 95, 99A, 115, 116, 117, 118, 119, 120, 121

For parenteral dosage forms only

Cardiac disease

(adverse circulatory reactions may occur with intravenous administration, especially with too-rapid administration)

Hypertension

(hypotension may occur with intravenous administration, especially in these patients; slow administration usually prevents this occurrence)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):

Folate concentrations, serum

(determinations recommended periodically because of increased folate requirements of patients on long-term anticonvulsant therapy with phenobarbital and possibly mephobarbital 171)

Hematopoietic function and

Hepatic function and

Renal function

(determinations recommended at periodic intervals during prolonged barbiturate therapy 31, 48, 49, 51, 52, 53, 55, 57, 60, 84, 90, 92, 99A, 115, 116, 117, 119, 120)

Barbital concentrations, serum

(determinations recommended when clinically indicated during metharbital therapy)

Phenobarbital concentrations, serum

(determinations recommended as clinically indicated when phenobarbital or mephobarbital is used as an anticonvulsant)

Side/Adverse Effects

Note: Exfoliative dermatitis and Stevens-Johnson syndrome, possibly fatal, may occur rarely as hypersensitivity reactions to barbiturates. If dermatologic reactions occur, the barbiturate should be discontinued.

Severe respiratory depression, apnea, laryngospasm, bronchospasm, or hypertension may occur with intravenous administration of barbiturates, especially if administered too rapidly 30, 47, 55, 58, 114, 117, 119.

Prolonged barbiturate therapy may result in osteopenia or rickets 49.

Barbiturate dependence may occur, especially following prolonged use of high doses. The characteristics of dependence include: a strong desire or need to continue taking the barbiturate; a tendency to increase the dose; a psychological dependence on the effects of the medication; and a physical

dependence on the effects of the medication requiring its presence for maintenance of homeostasis and resulting in an abstinence syndrome when the barbiturate is discontinued. Symptoms of withdrawal are related to the pharmacokinetics of the specific barbiturate and can be severe and may even cause death. 48, 55, 57, 84, 90, 92, 116, 117, 119, 120

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Those indicating need for medical attention

Incidence less frequent

Sensitivity to barbiturates (confusion)¾especially in geriatric or debilitated patients 84, 90, 92, 115, 116; mental depression¾especially in geriatric or debilitated patients; paradoxical reaction (unusual excitement)¾especially in children or geriatric or debilitated patients 28, 29, 46, 47, 84, 90, 92, 95, 115, 116

Incidence rare

Agranulocytosis (sore throat and/or fever); allergic reaction (skin rash or hives; swelling of eyelids, face, or lips; wheezing or tightness in chest)¾especially in patients who have asthma, urticaria, angioedema, and similar conditions; exfoliative dermatitis (fever; red, thickened, or scaly skin); hallucinations; hypotension or megaloblastic anemia (unusual tiredness or weakness)¾with chronic barbiturate use; Stevens-Johnson syndrome (bleeding sores on lips; chest pain; muscle or joint pain; painful sores, ulcers, or white spots in mouth; skin rash or hives; sore throat or fever) 95; thrombocytopenia (unusual bleeding or bruising); thrombophlebitis (soreness, redness, swelling, or pain at injection site)¾for parenteral dosage forms only

With prolonged or chronic use

Hepatic damage (yellow eyes or skin); osteopenia or rickets (bone pain, tenderness, or aching; loss of appetite; muscle weakness; unusual weight loss) 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Clumsiness or unsteadiness; dizziness or lightheadedness; drowsiness; "hangover" effect

Incidence less frequent

Anxiety or nervousness; constipation; feeling faint; headache; irritability; nausea or vomiting; nightmares or trouble in sleeping 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 84, 90, 92, 95, 115, 116, 118

Those indicating possible barbiturate withdrawal and need for medical attention if they occur after medication is discontinued

Minor symptoms¾may occur within 8 to 12 hours and usually occur in the following sequence:Anxiety or restlessness; muscle twitching; trembling of hands; weakness; dizziness; vision problems; nausea; vomiting; trouble in sleeping, increased dreaming, or nightmares; orthostatic hypotension (feeling faint; lightheadedness)

Major symptoms¾may occur within 16 hours and last up to 5 daysConvulsions; hallucinations 69, 70, 84, 90, 92, 95, 115, 121

Note: Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days 90, 92, 115.
46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 84, 90, 92, 99A, 115, 116, 121 69, 70, 84, 90, 92, 95, 99A, 114, 115, 116, 117, 118, 119, 120, 121

Overdose

For specific information on the agents used in the management of barbiturate overdose, see:
· Charcoal, Activated (Oral-Local) monograph; and/or
· Ipecac (Oral-Local) monograph.

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Acute

Confusion, severe; decrease in or loss of reflexes 40; drowsiness, severe; fever 40; hypothermia (low body temperature) 40; shortness of breath or slow or troubled breathing; slow heartbeat; slurred speech; staggering; unusual movements of the eyes; weakness, severe 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 95, 99A, 114, 115, 116, 117, 118, 119, 120, 121

Note: In acute barbiturate overdosage, CNS and respiratory depression may progress to Cheyne-Stokes respiration, areflexia, slight constriction of the pupils (in severe toxicity, pupils may be dilated), oliguria, tachycardia, lowered body temperature, and coma. Typical shock syndrome (apnea, circulatory collapse, respiratory arrest, and death) may occur. 55, 57, 115, 116, 117, 119

In extreme barbiturate overdosage, all electrical activity in the brain may cease. In this case an electroencephalogram (EEG) may be "flat,"" but this does not necessarily indicate clinical death since, unless hypoxic damage occurs, this effect is fully reversible. 48, 55, 57, 84, 90, 92, 95, 115, 116, 117, 119

Complications in barbiturate overdosage such as pneumonia, pulmonary edema, cardiac arrhythmias, congestive heart failure, and renal failure may occur 55, 57, 84, 90, 92, 95, 115, 117, 119.

In acute overdosage, the blood barbiturate concentration for some of the barbiturates relative to the degree of CNS depression in nontolerant persons is as follows:

See Table 2.

Chronic

Confusion, severe; irritability, continuing; poor judgment; trouble in sleeping 84, 90, 92, 99A, 115, 116, 117

Treatment of overdose

Treatment of barbiturate overdose is primarily supportive and consists of the following 46, 48, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 84, 90, 92, 95, 99A, 114, 115, 116, 117, 118, 119, 120, 121

To decrease absorption¾ If the patient is conscious and has not lost the gag reflex, emesis may be induced with ipecac syrup; care should be taken to prevent pulmonary aspiration of vomitus. After vomiting is completed, 30 90, 92 to 60 grams of activated charcoal in a glass of water or sorbitol may be administered to prevent absorption and increase excretion of the barbiturate. 84, 90, 92, 95, 115, 116

If emesis is contraindicated, gastric lavage may be performed with a cuffed endotracheal tube in place with the patient face down 69, 70, 84, 90, 92, 95, 114, 115.

Activated charcoal should be left in the stomach and a saline cathartic may be administered 84, 115, 116.

To enhance elimination¾ If renal function is normal, forced diuresis may help to eliminate the barbiturate 84, 90, 92, 115, 116.

Alkalinization of the urine increases renal excretion of some barbiturates, especially phenobarbital, also aprobarbital, and mephobarbital (which is metabolized to phenobarbital) 84, 90, 92, 95.

Although hemodialysis 90, 92 or hemoperfusion is not recommended as a routine procedure, it may be used in severe barbiturate poisoning or if the patient is anuric or in shock 69, 70, 84, 90, 92, 95, 114, 116.

Monitoring¾ Vital signs and fluid balance should be monitored 84, 90, 92, 115, 116.

Supportive care¾ An adequate airway should be maintained, with assisted respiration and administration of oxygen as needed 69, 70, 84, 90, 92, 95, 115, 116.

Blood pressure and body temperature should be maintained 40, 69, 70, 95, 114.

Fluid therapy and other standard treatment for shock should be administered, if necessary 69, 70, 84, 90, 92, 95, 114, 115, 116.

A vasopressor may be required if hypotension occurs 95.

Fluid or sodium overload should be avoided, especially if cardiovascular status is decreased.

Chest physiotherapy should be administered.

If pneumonia is suspected, appropriate cultures should be taken and antibiotics should be administered 69, 70, 84, 90, 92, 114, 115, 116.

Also, appropriate care should be taken to prevent hypostatic pneumonia, decubiti, aspiration, and other complications that may occur with altered states of consciousness 84, 90, 92, 115, 116.

Patients in whom intentional overdose is known or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Barbiturates (Systemic).

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Sensitivity to barbiturates

Pregnancy¾Barbiturates readily cross placenta; increase in incidence of fetal abnormalities (FDA Pregnancy Category D); use during third trimester of pregnancy may cause physical dependence with resulting withdrawal symptoms in neonate; long-acting barbiturates associated with neonatal coagulation defect that may cause bleeding during early neonatal period; use during labor may cause respiratory depression in neonate

Breast-feeding¾Barbiturates distributed into breast milk; use by nursing mothers may cause CNS depression in infant

Use in children¾Children may react to barbiturates with paradoxical excitement

Use in the elderly¾Elderly patients may react to usual doses of barbiturates with excitement, confusion, or mental depression; risk of barbiturate-induced hypothermia may be increased in elderly patients; elderly patients more likely to have age-related hepatic or renal function impairment, which may require a dosage reduction of barbiturates

Other medications, especially alcohol, adrenocorticoids, corticotropin, other CNS depression-producing medications, coumarin- or indandione-derivative anticoagulants, carbamazepine, divalproex sodium, estrogen-containing contraceptives, or valproic acid

Other medical problems, especially history of drug abuse or dependence, premonitory signs of hepatic coma, acute or chronic pain, or respiratory disease involving dyspnea or obstruction (particularly status asthmaticus)

Caution if any laboratory tests required; possible interference with results of metyrapone test.

Proper use of this medication

>> Importance of not using more medication than the amount prescribed because of habit-forming potential

>> Not increasing dose if medication appears less effective after a few weeks; checking with physician 46, 47, 48

>> For anticonvulsant use: Compliance with therapy; not missing any doses

>> Proper dosing

Missed dose: If on scheduled dosing regimen¾Taking as soon as possible; not taking if almost time for next dose; not doubling doses

Proper administration

For extended-release dosage form

Swallowing capsule or tablet whole

Not breaking, crushing, or chewing

For suppository dosage form

Proper administration technique

>> Proper storage

Precautions while using this medication

Regular visits to physician to check progress during prolonged therapy

Checking with physician before discontinuing medication after prolonged use; gradual dosage reduction may be necessary to avoid the possibility of withdrawal symptoms

>> Avoiding use of alcohol or other CNS depressants

>> Suspected psychological or physical dependence: Checking with physician

>> Suspected overdose: Getting emergency help at once

>> Caution if dizziness, lightheadedness, or drowsiness occurs

>> Use of another or additional method of contraception if taking estrogen-containing oral contraceptives concurrently

Side/adverse effects

Signs of potential side effects, especially allergic reaction or intolerance to barbiturate, blood dyscrasias, exfoliative dermatitis, hallucinations, hepatic damage (with prolonged or chronic use), mental depression, paradoxical reaction, osteopenia or rickets (with prolonged or chronic use), or Stevens-Johnson syndrome

Unusual excitement may be more likely to occur in children and in elderly or very ill patients

Confusion and mental depression may be more likely to occur in elderly or very ill patients

General Dosing Information

Dosage of the barbiturates must be individualized, based on the patient's age, weight, and condition 48, 49, 50, 51, 52, 53, 90, 92.

In patients with impaired hepatic function, lower doses should be used initially. Lower doses may be required also in patients with impaired renal function. 31, 49, 51, 52, 53, 55, 90, 92, 99A

Patients on dialysis may require an increase in dosage.

Tolerance may occur with repeated administration of the barbiturates, especially of the long-acting ones and with large doses of the shorter-acting ones 51, 55, 56, 57, 60, 84, 90, 92, 115, 116, 117, 119, 120, 121.

Prolonged administration of barbiturates as hypnotics generally is not recommended because they have not been shown to be effective for a period of more than 2 weeks 46, 47, 51, 52, 53, 69, 70, 84, 115, 116.

Prolonged uninterrupted use of barbiturates, particularly the short-acting ones, may result in psychic or physical dependence 46, 47, 48, 49, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 84, 90, 92, 95, 99A, 114, 115, 116, 117, 118, 119, 120, 121.

Chronic use of barbiturates at doses 3 to 4 times the therapeutic concentration will usually produce physical dependence in about 75% of patients.

Daily administration in excess of 400 mg of pentobarbital or secobarbital for approximately 90 days is likely to produce some degree of physical dependence; a dosage of 600 to 800 mg taken for at least 35 days is sufficient to produce withdrawal seizures. The average daily dose for the barbiturate addict generally is about 1.5 grams. 51, 52, 53, 55, 57, 84, 90, 92, 115

Barbiturates should be withdrawn gradually in order to avoid the possibility of precipitating withdrawal symptoms 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 84, 90, 92, 99A, 115, 116, 117, 118, 119.

To minimize the possibility of acute or chronic overdosage, the least possible quantity of a barbiturate should be prescribed and dispensed at any one time 84.

The toxic dose of barbiturates varies but generally an oral dose of 1 gram of most barbiturates produces serious poisoning in an adult. Death commonly occurs after 2 to 10 grams of ingested barbiturate. 48, 84, 90, 92

Diet/Nutrition

Patients on long-term anticonvulsant therapy with phenobarbital and possibly mephobarbital may have increased folic acid requirements 171.

In addition, patients on long-term therapy may require supplements of vitamin D to prevent osteomalacia 172.

For parenteral dosage forms only

Prior to administration, parenteral solutions should be inspected visually for particulate matter and discoloration, if possible 52, 55.

For intravenous injections, it is preferable to use the larger veins to minimize the risk of irritation and the possibility of resulting thrombosis. Administration into varicose veins is not recommended because of poor circulation in these veins. 30, 52

Intravenous injections should be administered slowly and patients should be carefully monitored during administration. This requires maintenance of blood pressure, respiration, and cardiac function and recording of vital signs. Equipment for resuscitation and artificial ventilation should be readily available. 52, 55

Intramuscular injections should be administered deeply into large muscles, such as the gluteus maximus or vastus lateralis because superficial intramuscular injection may be painful and may produce sterile abscesses or sloughs. 47, 51, 55, 58, 92, 117, 119

No more than 5 mL, regardless of drug concentration, should be injected intramuscularly at any one site because of possible tissue irritation 30, 47, 55, 114.

Parenteral solutions of barbiturate salts are highly alkaline; therefore, caution should be used to avoid perivascular extravasation or intra-arterial injection, since extravasation may cause local tissue damage with subsequent necrosis and intra-arterial injection may cause spasm, severe pain, and possibly gangrene 55, 56, 114, 117, 119.

For rectal dosage forms only

Barbiturates may be administered rectally when oral or parenteral administration may be undesirable. If the rectal dosage form is not available, the soluble sodium salt of the barbiturate may be incorporated in a retention enema. 117, 119

To assure accuracy in dosage, suppositories should not be divided 53.

Rectal administration of barbiturates is not recommended for status epilepticus; intravenous injection is the preferred route of administration for this condition.

For treatment of dependence

Treatment of dependence consists of the following 84, 90, 92, 99A, 115, 116, 117, 118, 119, 120

· Gradual withdrawal of the barbiturate 90, 115, 116.

· An example of the different withdrawal regimens used (all of which require an extended period of time) involves substituting a 30-mg dose of phenobarbital for each 100- to 200-mg dose of the barbiturate that the patient has been taking. The total daily amount of phenobarbital then is administered as a single dose or in 3 or 4 divided doses, not to exceed 600 mg per day. If signs of withdrawal occur on the first day of treatment, a loading dose of 100 to 200 mg of phenobarbital may be administered intramuscularly in addition to the oral dose. After stabilization on phenobarbital, the total daily dose is decreased by 30 mg a day as long as withdrawal is proceeding smoothly. This regimen may be modified by initiating treatment at the patient's regular dosage level and decreasing the daily dosage by 10% if tolerated by the patient. 48, 49, 51, 52, 53, 54, 55, 56, 57, 60, 84, 115, 116

· For infants physically dependent on barbiturates, initially a dose of 3 to 10 mg of phenobarbital per kg of body weight per day may be given. After withdrawal symptoms (hyperactivity, disturbed sleep, tremors, hyperreflexia) are relieved, the dosage of phenobarbital should be gradually decreased and completely withdrawn over a 2-week period. 48, 49, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 84, 90, 92, 99A, 115, 116

· Also, barbiturate withdrawal may be accomplished with benzodiazepines, such as diazepam 16.

For treatment of adverse effects

For extravasation into subcutaneous tissues¾Recommended treatment includes
· Application of moist heat to affected area.
· Injection of a 0.5% procaine solution into the affected area.For accidental intra-arterial injection¾Recommended treatment includes
· Release of tourniquet or restrictive garments to permit dilution of injected medication.
· Injection of 10 mL of a 1% procaine solution into the artery and, if necessary, brachial plexus block to relieve spasm.
· Anticoagulant therapy may prevent thrombosis.
· Supportive treatment.

AMOBARBITAL

Summary of Differences

Category¾ Parenteral amobarbital also may be indicated as an anticonvulsant.

Indications¾ Parenteral amobarbital also may be indicated in narcoanalysis; and has been used in diagnosis of schizophrenia and for catatonic, negativistic, and manic reactions, but generally has been replaced by other agents.

Pharmacology/pharmacokinetics¾ Long-acting barbiturate:
Onset of action: 60 minutes or longer.
Duration of action: 10 to 12 hours.

Protein binding:
Moderate.

Additional Dosing Information

See also General Dosing Information.

For parenteral dosage forms only

The rate of intravenous injection should not exceed 100 mg per minute for adults or 60 mg per square meter of body surface per minute for children. Faster rates of administration may cause serious respiratory depression. 47, 114

Superficial intramuscular or subcutaneous injections may be painful and may produce sterile abscesses or sloughs.

Oral Dosage Forms

AMOBARBITAL TABLETS USP

Usual adult dose

Sedative-hypnotic¾Hypnotic¾ Oral, 65 to 200 mg at bedtime 1, 2, 69, 70, 117, 119, 164.

Sedative¾ Daytime¾Oral, 50 to 300 mg a day in divided doses 1, 2, 69, 70, 164.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients.

Usual pediatric dose

Sedative-hypnotic¾Hypnotic¾ Dosage has not been established 2.

Sedative¾ Daytime¾Oral, 2 mg per kg of body weight or 60 mg per square meter of body surface three times a day 2, 167.

Preoperative¾Oral, 2 to 6 mg per kg of body weight, up to a maximum of 100 mg per dose 1, 55, 117, 119, 164.

Strength(s) usually available

U.S.¾Not commercially available 69, 71.

Canada¾30 mg (Rx)[Amytal] 104A

100 mg (Rx)[Amytal] 104A

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.

Note: Controlled substance in the U.S. and Canada.

AMOBARBITAL SODIUM CAPSULES USP

Usual adult dose

Sedative-hypnotic¾Hypnotic¾ Oral, 65 to 200 mg at bedtime 1, 2, 29, 55, 70, 117, 119, 164.

Sedative¾ Daytime¾Oral, 50 to 300 mg a day in divided doses 1, 2, 55, 117, 119, 164.

During labor¾Oral, 200 to 400 mg, repeated every one to three hours, if necessary, up to a total dose of 1 gram 3, 29, 70.

Preoperative¾Oral, 200 mg one to two hours before surgery 3, 29, 70, 164.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients.

Usual pediatric dose

Sedative-hypnotic¾Hypnotic¾ Dosage has not been established 2.

Sedative¾ Daytime¾Oral, 2 mg per kg of body weight or 60 mg per square meter of body surface three times a day 2, 167.

Preoperative¾Oral, 2 to 6 mg per kg of body weight, up to a maximum of 100 mg per dose 1.

Strength(s) usually available

U.S.¾200 mg (Rx)[Amytal] [Generic] 70, 71, 72

Canada¾200 mg (Rx)[Amytal] 104A

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.

Note: Controlled substance in the U.S. and Canada.

Parenteral Dosage Forms

AMOBARBITAL SODIUM STERILE USP

Usual adult dose

Sedative-hypnotic¾Hypnotic¾ Intramuscular or intravenous, 65 to 200 mg 1, 47, 114, 117, 119 .

Sedative¾ Intramuscular or intravenous, 30 to 50 mg two or three times a day 55, 117, 119.

Anticonvulsant¾Intravenous, 65 to 500 mg 4, 55.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients.

Usual adult prescribing limits

Intramuscular, up to 500 mg per dose 5, 47, 114.

Intravenous, up to 1 gram per dose 5, 47, 114.

Usual pediatric dose

Sedative-hypnotic¾Hypnotic¾ Children up to 6 years of age:
Intramuscular, 2 to 3 mg per kg of body weight per dose 4, 113.

Children 6 years of age and over:
Intramuscular, 2 to 3 mg per kg of body weight per dose 4, 113.

Intravenous, 65 to 500 mg per dose 2, 4, 114.

Sedative¾ Preoperative:
Intravenous, 65 to 500 mg or 3 to 5 mg per kg of body weight per dose 1, 55, 117, 119.

Anticonvulsant¾Children up to 6 years of age¾ Intramuscular or intravenous, 3 to 5 mg per kg of body weight or 125 mg per square meter of body surface per dose 4, 167.

Children 6 years of age and over¾ Intravenous, 65 to 500 mg per dose 5, 47, 113, 114, 167.

Size(s) usually available:

U.S.¾500 mg (Rx)[Amytal] 71, 114

Canada¾500 mg (Rx)[Amytal] 104A

Packaging and storage:

Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form:

Solutions of amobarbital sodium should be prepared aseptically with sterile water for injection 114.

For preparation of various concentrations of solutions for injection, see the manufacturer's package insert 114.

Stability:

After reconstitution, solution should be used within 30 minutes since amobarbital sodium hydrolyzes in solution or upon exposure to air. Solution should not be used if it does not become absolutely clear within 5 minutes after reconstitution or if a precipitate forms after the solution clears. 47, 114

Note: Controlled substance in the U.S. and Canada.

APROBARBITAL

Summary of Differences

Pharmacology/pharmacokinetics¾ Intermediate-acting barbiturate:
Onset of action: 45 to 60 minutes.
Duration of action: 6 to 8 hours.

Protein binding:
Low.

Oral Dosage Forms

APROBARBITAL ELIXIR

Usual adult dose

Sedative-hypnotic¾Hypnotic: Oral, 40 to 160 mg at bedtime 6, 31, 55, 117, 119.

Sedative: Daytime¾Oral, 40 mg three times a day 6, 55, 117, 119.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients.

Usual pediatric dose

Dosage has not been established 6.

Strength(s) usually available

U.S.¾40 mg per 5 mL (Rx)[Alurate (alcohol 20%) (dextrose) (saccharin) (sorbitol) (sucrose) (FD&C Yellow No. 6) (FD&C Red No. 40)] 73, 73A

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight, light-resistant container, unless otherwise specified by manufacturer. Protect from freezing.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.
· Keep container tightly closed.

Note: Controlled substance in the U.S.

BUTABARBITAL

Summary of Differences

Pharmacology/pharmacokinetics¾ Intermediate-acting barbiturate:
Onset of action: 45 to 60 minutes.
Duration of action: 6 to 8 hours.

Protein binding:

Low.

Oral Dosage Forms

BUTABARBITAL SODIUM ELIXIR USP

Usual adult dose

Sedative-hypnotic¾Hypnotic¾ Oral, 50 to 100 mg at bedtime 7, 32, 48, 55, 77, 105, 115, 116, 117, 119 .

Sedative¾ Daytime¾Oral, 15 to 30 mg three or four times a day 7, 48, 55, 77, 105, 115, 116, 117, 119 .
Preoperative¾Oral, 50 to 100 mg sixty to ninety minutes before surgery 7, 32, 48, 55, 77, 115, 116, 117, 119.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients. 32, 48, 77, 115, 116

Usual pediatric dose

Sedative-hypnotic¾Hypnotic¾ Dosage must be individualized by physician.

Sedative¾ Daytime¾Oral, 2 mg per kg of body weight or 60 mg per square meter of body surface three times a day 2, 4, 77, 105 .
Preoperative¾Oral, 2 to 6 mg per kg of body weight, up to a maximum of 100 mg per dose 7, 48, 55, 77, 115, 116, 117, 119.

Strength(s) usually available

U.S.¾30 mg per 5 mL (Rx)[Busodium] [Butalan] [Butisol (alcohol [by volume] 7%) (tartrazine)] [Generic] 76, 77, 80, 82

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container. Protect from freezing.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.
· Keep container tightly closed.

Note: Controlled substance in the U.S.

BUTABARBITAL SODIUM TABLETS USP

Usual adult dose

See Butabarbital Sodium Elixir USP .

Usual pediatric dose

See Butabarbital Sodium Elixir USP .

Strength(s) usually available

U.S.¾15 mg (Rx)[Busodium] [Butisol (scored)] [Generic]

30 mg (Rx)[Busodium] [Butisol (scored) (tartrazine)] [Sarisol No. 2] [Generic]

50 mg (Rx)[Butisol (scored) (tartrazine)]

100 mg (Rx)[Busodium] [Butisol (scored)] [Generic]

76, 77, 80, 81, 82, 83

Canada¾15 mg (Rx)[Butisol (scored) (sodium 2 mg)]

30 mg (Rx)[Butisol (scored) (sodium 3 mg) (tartrazine)]

100 mg (Rx)[Butisol (scored) (sodium 10 mg)]

105, 106

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.

Note: Controlled substance in the U.S. and Canada.

MEPHOBARBITAL

Summary of Differences

Category¾ Indicated only as an anticonvulsant.

Pharmacology/pharmacokinetics¾ Biotransformation:
About 75% of a single dose metabolized to phenobarbital in 24 hours.

Long-acting barbiturate:
Onset of action: 60 minutes or longer.
Duration of action: 10 to 12 hours.

Patient consultation¾ Compliance with therapy when used as an anticonvulsant.

Additional Dosing Information

See also General Dosing Information. In epilepsy
· Therapy with mephobarbital should begin with small doses, the dosage being gradually increased over a period of 4 to 5 days until the optimum dosage is determined 49, 84.

· When used to replace another anticonvulsant, the dosage of mephobarbital should be gradually increased while the dosage of the other medication is maintained initially and then gradually decreased in order to maintain seizure control 49, 84.

· Mephobarbital may be alternated with phenobarbital therapy 49.

· When used in conjunction with phenytoin, the dose of phenytoin may need to be reduced, but the full dose of mephobarbital may be given 49, 84.

· Mephobarbital should be withdrawn slowly in order to avoid precipitating seizures or status epilepticus. When the dosage is to be reduced to a maintenance level or discontinued, the amount should be reduced over a period of 4 to 5 days or possibly longer. 49, 84

Oral Dosage Forms

MEPHOBARBITAL TABLETS USP

Usual adult dose

Anticonvulsant¾Oral, 200 mg at bedtime to 600 mg a day in divided doses 8, 33, 49, 55, 84, 107, 117, 119.

Sedative-hypnotic¾Sedative: Daytime¾Oral, 32 to 100 mg three or four times a day 8, 49, 55, 84, 107, 117, 119.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients. 84

Usual pediatric dose

Anticonvulsant¾Children up to 5 years of age: Oral, 16 to 32 mg three or four times a day 8, 33, 49, 84, 107, 117 .

Children 5 years of age and over: Oral, 32 to 64 mg three or four times a day 8, 33, 49, 84, 107.

Sedative-hypnotic¾Sedative: Daytime¾Oral, 16 to 32 mg three or four times a day 8, 84, 107.

Strength(s) usually available

U.S.¾32 mg (Rx)[Mebaral (scored) (lactose) (starch) (stearic acid) (talc)]

50 mg (Rx)[Mebaral (lactose) (starch) (stearic acid) (talc)]

100 mg (Rx)[Mebaral (lactose) (starch) (stearic acid) (talc)]

84, 85

Canada¾30 mg (Rx)[Mebaral (lactose 65 mg)] 107

100 mg (Rx)[Mebaral (lactose 59 mg)] 107

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.

Note: Controlled substance in the U.S. and Canada.

METHARBITAL

Summary of Differences

Category¾ Indicated only as an anticonvulsant.

Pharmacology/pharmacokinetics¾ Biotransformation:
Metabolized to barbital.

Long-acting barbiturate:
Onset of action: 60 minutes or longer.
Duration of action: 10 to 12 hours.

Patient consultation¾ Compliance with therapy.

Additional Dosing Information

See also General Dosing Information.

Metharbital should be withdrawn gradually in order to avoid the possibility of precipitating seizures or status epilepticus 50.

When used to replace or supplement other anticonvulsant therapy, the dosage of metharbital should be gradually increased while the dosage of the other medication is maintained initially and then gradually decreased in order to maintain seizure control 50.

Oral Dosage Forms

METHARBITAL TABLETS

Usual adult dose

Anticonvulsant¾Oral, initially 100 mg one to three times a day, the dosage being increased up to 800 mg per day, if necessary 9, 34, 50, 55, 86, 117, 119.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients.

Usual pediatric dose

Anticonvulsant¾Oral, 50 mg one to three times a day; or 5 to 15 mg per kg of body weight per day in divided doses 9, 34, 50.

Strength(s) usually available

U.S.¾Not commercially available.

Canada¾Not commercially available.

In other countries¾100 mg[Gemonil (scored) (lactose)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· Avoid alcoholic beverages.

· May cause drowsiness.

PENTOBARBITAL

Summary of Differences

Category¾ Parenteral pentobarbital also may be indicated as an anticonvulsant.

Indications¾ Parenteral pentobarbital also used to protect brain from ischemia and increased intracranial pressure that follow stroke and head trauma.

Pharmacology/pharmacokinetics¾ Short-acting barbiturate:
Onset of action: 10 to 15 minutes.
Duration of action: 3 to 4 hours.

Protein binding:
Moderate to high.

Additional Dosing Information

See also General Dosing Information.

When administered during labor, doses greater than 200 mg may cause respiratory depression in the newborn.

For parenteral dosage forms only

The injection is for intramuscular or intravenous use only; it is not recommended for subcutaneous administration 36, 52, 92.

Intravenous injections should be made slowly, not to exceed 50 mg per minute, to avoid adverse respiratory and circulatory reactions 36, 52, 92.

Oral Dosage Forms

PENTOBARBITAL ELIXIR USP

Usual adult dose

Sedative-hypnotic¾Hypnotic¾ Oral, 100 mg (pentobarbital sodium) at bedtime 10, 51, 55, 90, 117, 119.

Sedative¾ Daytime¾Oral, 20 mg (pentobarbital sodium) three or four times a day 2, 4, 55, 117, 119.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients. 90

Usual pediatric dose

Sedative-hypnotic¾Hypnotic¾ Dosage must be individualized by physician 51, 90.

Sedative¾ Daytime¾Oral, 2 to 6 mg (pentobarbital sodium) per kg of body weight per day 113.

Preoperative¾Oral, 2 to 6 mg (pentobarbital sodium) per kg of body weight, up to a maximum of 100 mg per dose 10, 51, 55, 90, 117, 119.

Strength(s) usually available

U.S.¾20 mg of pentobarbital sodium (18.2 mg of pentobarbital) per 5 mL (Rx)[Nembutal (alcohol 18%)] 88, 89

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container. Protect from freezing.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.
· Keep container tightly closed.

Note: Controlled substance in the U.S.

PENTOBARBITAL SODIUM CAPSULES USP

Usual adult dose

Sedative-hypnotic¾Hypnotic: Oral, 100 mg at bedtime 10, 35, 51, 55, 90, 108.

Sedative: Preoperative¾Oral, 100 mg 10, 35, 90, 108.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients. 35, 51, 90

Usual pediatric dose

Sedative-hypnotic¾Hypnotic: Dosage must be individualized by physician 10, 51, 90.

Sedative: Preoperative¾Oral, 2 to 6 mg per kg of body weight, up to a maximum of 100 mg per dose 10, 51, 55, 90, 117, 119.

Strength(s) usually available

U.S.¾50 mg (Rx)[Nembutal] [Generic]

100 mg (Rx)[Nembutal (tartrazine)] [Generic]

89, 90, 91

Canada¾100 mg (Rx)[Nembutal (tartrazine)] [Novopentobarb] 108

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.

Note: Controlled substance in the U.S. and Canada.

Parenteral Dosage Forms

PENTOBARBITAL SODIUM INJECTION USP

Usual adult dose

Sedative-hypnotic¾Hypnotic¾ Intramuscular, 150 to 200 mg 1, 10, 36, 37, 52, 55, 92, 117, 119.

Intravenous, 100 mg initially; after one minute, additional small doses may be administered at one-minute intervals, if necessary, up to a total of 500 mg 1, 10, 36, 37, 52, 55, 92, 108, 117, 119.

Sedative¾ Preoperative¾Intramuscular, 150 to 200 mg 4, 113.

Anticonvulsant¾Intravenous, 100 mg initially; after one minute, additional small doses may be administered at one-minute intervals, if necessary, up to a total of 500 mg 10, 36, 37, 52, 92.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients. 92

Usual pediatric dose

Sedative-hypnotic¾Hypnotic¾ Intramuscular, 2 to 6 mg per kg of body weight, up to a maximum of 100 mg per dose 10, 36, 52, 92.

Intravenous, 50 mg initially; after one minute, additional small doses may be administered at one-minute intervals, if necessary, until desired effect is obtained 2, 10, 108.

Sedative¾ Preoperative¾Intramuscular, 2 to 6 mg per kg of body weight, up to a maximum of 100 mg per dose 1, 10, 37, 167.

Anticonvulsant¾Intramuscular or intravenous, 50 mg initially; after one minute, additional small doses may be administered at one-minute intervals, if necessary, until desired effect is obtained 4, 10, 113.

Strength(s) usually available

U.S.¾50 mg per mL (Rx)[Nembutal (alcohol 10%) (propylene glycol 40% v/v)] [Generic] 89, 91, 92

Canada¾50 mg per mL (Rx)[Nembutal (alcohol 10%) (propylene glycol 40%)] 108

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing. 92

Stability:

Do not use if solution is discolored or contains a precipitate 92.

Note: Controlled substance in the U.S. and Canada.

Rectal Dosage Forms

PENTOBARBITAL SODIUM SUPPOSITORIES

Usual adult dose

Sedative-hypnotic¾Hypnotic¾ Rectal, 120 to 200 mg at bedtime 11, 38, 53, 93, 165.

Sedative¾ Daytime¾Rectal, 30 mg two to four times a day 53, 93, 165.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients. 93

Usual pediatric dose

Sedative-hypnotic¾Hypnotic¾ Children up to 2 months of age: Dosage has not been established 11, 38, 53, 93, 165.

Children 2 months to 1 year of age (4.5 to 9 kg): Rectal, 30 mg 11, 38, 53, 93, 165.

Children 1 to 4 years of age (9 to 18 kg): Rectal, 30 or 60 mg 11, 38, 53, 93, 165.

Children 5 to 12 years of age (18 to 36 kg): Rectal, 60 mg 11, 38, 53, 93, 165.

Children 12 to 14 years of age (36 to 50 kg): Rectal, 60 or 120 mg 11, 38, 53, 93, 165.

Sedative¾ Daytime:
Rectal, 2 mg per kg of body weight or 60 mg per square meter of body surface three times a day 4, 53, 165.

Preoperative:
Children up to 2 months of age: Dosage has not been established 1.

Children 2 months to 1 year of age: Rectal, 30 mg 1, 117, 119, 165.

Children 1 to 4 years of age: Rectal, 30 or 60 mg 1, 117, 119, 165.

Children 5 to 12 years of age: Rectal, 60 mg 1, 117, 119, 165.

Children 12 to 14 years of age: Rectal, 60 or 120 mg 117, 119.

Strength(s) usually available

U.S.¾30 mg (Rx)[Nembutal (semisynthetic glycerides)]

60 mg (Rx)[Nembutal (semisynthetic glycerides)]

120 mg (Rx)[Nembutal (semisynthetic glycerides)]

200 mg (Rx)[Nembutal (semisynthetic glycerides)]

89, 93

Canada¾25 mg (Rx)[Nova Rectal (in a polyethylene glycol base)] 165

50 mg (Rx)[Nova Rectal (in a polyethylene glycol base)] 165

Packaging and storage:

Store between 2 and 15 °C (36 and 59 °F), in a well-closed container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· For rectal use only.
· Avoid alcoholic beverages.
· May cause drowsiness.

· Refrigerate.

Note: Controlled substance in the U.S. and Canada.

PHENOBARBITAL

Summary of Differences

Category¾ Also indicated as an anticonvulsant.
Oral and parenteral phenobarbital also used as an antihyperbilirubinemic; and has been used as an antitremor agent, although generally has been replaced by benzodiazepines and beta-adrenergic blockers.

Pharmacology/pharmacokinetics¾ Distribution:
Distributed less rapidly than other barbiturates because it has lowest lipid solubility.

Time to peak effect:
Maximal CNS depression may not occur for 15 minutes or more after intravenous administration.

Long-acting barbiturate:
Onset of action: 60 minutes or longer.
Duration of action: 10 to 12 hours.

Protein binding:
Low to moderate.

Patient consultation¾ Compliance with therapy when used as an anticonvulsant.

Additional Dosing Information

See also General Dosing Information.

In epilepsy
· In children, higher-per-kg dosage of phenobarbital and most other anticonvulsants generally are required to achieve blood concentrations considered therapeutic.
· Several weeks of phenobarbital therapy may be required to achieve maximum antiepilepsy effects.
· Phenobarbital should be withdrawn slowly in order to avoid precipitating seizures or status epilepticus.
· When phenobarbital is replaced by another anticonvulsant, the dosage of phenobarbital should be maintained initially and then reduced gradually while, at the same time, the dosage of the replacement medication is increased gradually in order to maintain seizure control.
· When administered intravenously, phenobarbital sodium may require 15 minutes or more to attain peak concentrations in the brain; therefore, it is important to use the minimal dosage required and to wait for the anticonvulsant effect to develop before administering a second dose, in order to avoid the possibility of severe barbiturate-induced depression 55.

For parenteral dosage forms only

Sterile phenobarbital sodium may be administered subcutaneously after reconstitution, but phenobarbital sodium injection is not recommended for subcutaneous use.

The rate of the intravenous injection should not exceed 60 mg per minute. Faster rates of administration may cause serious respiratory depression. 55, 117

Following intravenous administration, up to 30 minutes may be required for maximum effect.

Bioequivalence information

For phenobarbital tablets¾ Bioavailability differences between generic products from different manufacturers have been reported in the past 183, 184.

However, no controlled studies systematically comparing the large number of tablets commercially available from different manufacturers have been conducted. In two studies published in 1979 and 1984 comparing phenobarbital tablets from different manufacturers in male volunteers, there were no significant differences in mean peak plasma concentrations (C max) or relative area under the plasma concentration-time curve (AUC); however, statistically significant delays in reaching time of peak concentration (t max) were demonstrated among products 183, 184.

In response to the potential problem of bio-inequivalence, official dissolution standards were changed 185 , and problems have not been documented in the years following establishment of these standards 185.

The current standard excludes slow-dissolving tablets 185.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

PHENOBARBITAL CAPSULES

Usual adult dose

Anticonvulsant¾Oral, 60 to 250 mg (base) per day, as a single dose or in divided doses 1, 39, 55, 95, 117, 119 .

Sedative-hypnotic¾Hypnotic: Oral, 100 to 320 mg (base) at bedtime 1, 12, 39, 55, 95, 117, 119 .

Sedative: Daytime¾Oral, 30 to 120 mg (base) in two or three divided doses a day 1, 12, 55, 95, 117, 119 .

[Antihyperbilirubinemic] *¾Oral, 30 to 60 mg (base) three times a day 4, 113.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients.

Usual pediatric dose

Anticonvulsant¾Oral, 1 to 6 mg (base) per kg of body weight per day, as a single dose or in divided doses 12, 167.

Sedative-hypnotic¾Hypnotic¾ Dosage must be individualized by physician.

Sedative¾ Daytime¾Oral, 2 mg (base) per kg of body weight or 60 mg per square meter of body surface three times a day 12, 95, 113.

Preoperative¾Oral, 1 to 3 mg (base) per kg of body weight 4, 39, 55, 117, 119.

[Antihyperbilirubinemic] *¾Neonates: Oral, 5 to 10 mg (base) per kg of body weight per day for the first few days after birth 13, 113 .

Children up to 12 years of age: Oral, 1 to 4 mg (base) per kg of body weight three times a day 4, 113.

Strength(s) usually available

U.S.¾15 mg (Rx)[Solfoton] 94, 94A

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.

Note: Controlled substance in the U.S.

PHENOBARBITAL ELIXIR USP

Usual adult dose

See Phenobarbital Capsules .

Usual pediatric dose

See Phenobarbital Capsules .

Strength(s) usually available

U.S.¾20 mg per 5 mL (Rx) [Generic] 95, 96

Canada¾20 mg per 5 mL (Rx)[Ancalixir]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container. Protect from freezing.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.
· Keep container tightly closed.

Note: Controlled substance in the U.S. and Canada.

PHENOBARBITAL TABLETS USP

Note: Bioavailability differences between products from different manufacturers have been reported in the past 183, 184.

However, no controlled studies systematically comparing the large number of tablets commercially available from different manufacturers have been conducted. In two studies published in 1979 and 1984 comparing phenobarbital tablets from different manufacturers in male volunteers, there were no significant differences in mean peak plasma concentrations (C max) or relative area under the plasma concentration-time curve (AUC); however, statistically significant delays in reaching time of peak concentration (T max) were demonstrated among products 183, 184.

In response to the potential problem of bio-inequivalence, official dissolution standards were changed 185 , and problems have not been documented in the years following establishment of these standards 185.

The current standard excludes slow-dissolving tablets 185.

Usual adult dose

See Phenobarbital Capsules .

Usual pediatric dose

See Phenobarbital Capsules .

Strength(s) usually available

U.S.¾8 mg (Rx) [Generic]

15 mg (Rx)[Barbita] [Solfoton] [Generic]

30 mg (Rx) [Generic]

60 mg (Rx) [Generic]

100 mg (Rx) [Generic]

94, 95, 95A, 96

Canada¾15 mg (Rx) [Generic]

30 mg (Rx) [Generic]

60 mg (Rx) [Generic]

100 mg (Rx) [Generic]

109, 109A

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.

Note: Controlled substance in the U.S. and Canada.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

PHENOBARBITAL SODIUM INJECTION USP

Usual adult dose

Anticonvulsant¾Intravenous, 100 to 320 mg, repeated if necessary up to a total dose of 600 mg during a twenty-four-hour period 16, 39, 117, 119.

Status epilepticus: Intravenous (slow), 10 to 20 mg per kg of body weight, repeated if necessary 16, 39, 167.

Sedative-hypnotic¾Hypnotic¾ Intramuscular or intravenous, 100 to 325 mg 15, 55, 113.

Sedative¾ Daytime¾Intramuscular or intravenous, 30 to 120 mg a day in two or three divided doses 4, 55, 117, 119.

Preoperative¾Intramuscular, 130 to 200 mg sixty to ninety minutes before surgery 15, 55, 113, 117, 119.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients.

Usual pediatric dose

Anticonvulsant¾Initial: Intravenous, 10 to 20 mg per kg of body weight as a single loading dose 16, 55, 117.

Maintenance: Intravenous, 1 to 6 mg per kg of body weight per day 16, 55, 117, 119.

Status epilepticus: Intravenous, 15 to 20 mg per kg of body weight, administered over a period of ten to fifteen minutes 16, 55, 117, 119, 167.

Sedative-hypnotic¾Hypnotic: Dosage must be individualized.

Sedative: Preoperative¾Intramuscular or intravenous, 1 to 3 mg per kg of body weight, sixty to ninety minutes prior to surgery 4, 55, 113, 117, 119.

[Antihyperbilirubinemic] *¾Intramuscular, 5 to 10 mg per kg of body weight per day for the first few days after birth 4, 13, 113.

Strength(s) usually available

U.S.¾30 mg per mL (Rx) [Generic]

60 mg per mL (Rx) [Generic]

65 mg per mL (Rx) [Generic]

130 mg per mL (Rx)[Luminal (alcohol 10%) (propylene glycol 67.8% by volume)] [Generic]

97, 98

Canada¾30 mg per mL (Rx) [Generic] 110

120 mg per mL (Rx) [Generic] 110

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Stability:

Do not use if solution is discolored or contains a precipitate.

Note: Controlled substance in the U.S. and Canada.

PHENOBARBITAL SODIUM STERILE USP

Usual adult dose

Anticonvulsant¾Intravenous, 100 to 320 mg, repeated if necessary up to a total dose of 600 mg during a twenty-four-hour period 16, 117, 118.

Status epilepticus: Intravenous (slow), 10 to 20 mg per kg of body weight, repeated if necessary 16, 167.

Sedative-hypnotic¾Hypnotic¾ Intramuscular, intravenous, or subcutaneous, 100 to 325 mg 15, 119.

Sedative¾ Daytime¾Intramuscular, intravenous, or subcutaneous, 30 to 120 mg a day in two or three divided doses 4, 117, 119.

Preoperative¾Intramuscular, 130 to 200 mg sixty to ninety minutes before surgery 15, 117, 119.

Note: Geriatric and debilitated patients may react to usual doses of barbiturates with excitement, confusion, or mental depression. Lower doses may be required in these patients.

Usual pediatric dose

Anticonvulsant¾Initial: Intravenous, 10 to 20 mg per kg of body weight as a single loading dose 16, 117.

Maintenance: Intravenous, 1 to 6 mg per kg of body weight per day 16.

Status epilepticus: Intravenous, 15 to 20 mg per kg of body weight, administered over a period of ten to fifteen minutes 16, 167.

Sedative-hypnotic¾Hypnotic: Dosage must be individualized.

Sedative: Preoperative¾Intramuscular, 1 to 3 mg per kg of body weight 4.

[Antihyperbilirubinemic] *¾Intramuscular, 5 to 10 mg per kg of body weight per day for the first few days after birth 4, 13, 113.

Size(s) usually available:

U.S.¾120 mg (Rx) [Generic] 98

Canada¾Not commercially available.

Packaging and storage:

Prior to reconstitution, store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Preparation of dosage form:

Solutions of phenobarbital sodium for subcutaneous or intramuscular injection may be prepared by dissolving 120 mg of anhydrous phenobarbital sodium powder in 1 mL of sterile water for injection. For intravenous use, 120 mg of anhydrous phenobarbital sodium powder should be dissolved in 3 mL of sterile water for injection. When solutions are prepared, the sterile water for injection should be introduced slowly into the vial by means of a sterile syringe. Several minutes may be required for the medication to dissolve completely; solution should not be injected if it has not become clear after 5 minutes. 118

Stability:

After reconstitution, solution should be used within thirty minutes since phenobarbital hydrolyzes in solution or upon exposure to air. Solution should not be used if it does not become absolutely clear within 5 minutes after reconstitution or if a precipitate forms after the solution clears.

Note: Controlled substance in the U.S.

SECOBARBITAL

Summary of Differences

Category¾ Parenteral secobarbital also may be indicated as an anticonvulsant (in tetanus).

Pharmacology/pharmacokinetics¾ Distribution:
Distributed more rapidly than other barbiturates because it has highest lipid solubility.

Short-acting barbiturate:
Onset of action: 10 to 15 minutes.
Duration of action: 3 to 4 hours.

Protein binding:

Moderate to high.

Additional Dosing Information

See also General Dosing Information.

For parenteral dosage forms only

The rate of the intravenous injection should not exceed 50 mg per 15-second period. Faster rates of administration may cause respiratory depression or apnea, laryngospasm, or vasodilation with fall in blood pressure. 5, 58, 117

For rectal dosage forms only

To prepare a solution for rectal administration, dilute the commercially available 5% secobarbital sodium injection with lukewarm tap water to a concentration of 10 to 15 mg per mL (1 to 1.5%).

Oral Dosage Forms

SECOBARBITAL SODIUM CAPSULES USP

Usual adult dose

Sedative-hypnotic¾Hypnotic¾ Oral, 100 mg at bedtime 17, 40, 55, 99A, 117, 119.

Sedative¾ Daytime¾Oral, 30 to 50 mg three or four times a day 17, 113.

Preoperative¾Oral, 200 to 300 mg one to two hours before surgery 17, 40, 55, 99A, 117, 119.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients.

Usual pediatric dose

Sedative-hypnotic¾Sedative¾ Daytime¾Oral, 2 mg per kg of body weight or 60 mg per square meter of body surface three times a day 2, 4, 13, 168.

Preoperative¾Oral, 2 to 6 mg per kg of body weight, up to a maximum of 100 mg per dose, one to two hours before surgery 1, 17, 40, 55, 99A, 117, 119.

Strength(s) usually available

U.S.¾100 mg (Rx)[Seconal] [Generic] 99

Canada¾50 mg (Rx)[Seconal] 111

100 mg (Rx)[Novosecobarb] [Seconal] 111

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause drowsiness.

Note: Controlled substance in the U.S. and Canada.

Parenteral Dosage Forms

SECOBARBITAL SODIUM INJECTION USP

Usual adult dose

Sedative-hypnotic¾Hypnotic¾ Intramuscular, 100 to 200 mg 18, 40, 41, 55, 117, 119.

Intravenous, 50 to 250 mg 18, 40, 41, 55, 117, 119.

Sedative¾ Dentistry¾Intramuscular, 1.1 to 2.2 mg per kg of body weight ten to fifteen minutes before procedure 18, 40, 55, 117, 119.

Nerve block¾Intravenous, 100 to 150 mg 18, 40, 41, 55, 58, 117, 119.

Anticonvulsant (in tetanus)¾Intramuscular or intravenous, 5.5 mg per kg of body weight, repeated every three to four hours as needed 1, 40, 55, 58, 117, 119.

Note: Geriatric and debilitated patients may react to usual doses of barbiturates with excitement, confusion, or mental depression. Lower doses may be required in these patients.

Usual pediatric dose

Sedative-hypnotic¾Hypnotic¾ Intramuscular:
3 to 5 mg per kg of body weight or 125 mg per square meter of body surface, up to a maximum of 100 mg per dose 4, 19, 113, 168 .

Rectal, the following doses as a 1 to 1.5% solution:
Children weighing up to 40 kg: 5 mg per kg of body weight 4, 40, 58, 113.

Children weighing 40 kg and over: 4 mg per kg of body weight 4, 40, 58, 113.

Sedative¾ Preoperative:

Intramuscular, 4 to 5 mg per kg of body weight 18, 41, 55, 117.

Anticonvulsant (in tetanus)¾Intramuscular or intravenous, 3 to 5 mg per kg of body weight or 125 mg per square meter of body surface per dose 19.

Strength(s) usually available

U.S.¾50 mg per mL (Rx) [Generic] 99, 99A

Canada¾Not commercially available.

Packaging and storage:

Store between 2 and 8 °C (36 and 46 °F). Protect from light.

Preparation of dosage form:

Secobarbital sodium injection may be administered in a concentration of 50 mg per mL or it may be diluted with sterile water for injection, 0.9% sodium chloride injection, or Ringer's injection 51.

Stability:

Do not use if solution is discolored or contains a precipitate.

Note: Controlled substance in the U.S.

SECOBARBITAL AND AMOBARBITAL

Oral Dosage Forms

SECOBARBITAL SODIUM AND AMOBARBITAL SODIUM CAPSULES USP

Usual adult dose

Sedative-hypnotic¾Oral, 1 capsule at bedtime or one hour preoperatively 20, 42, 59, 101, 112, 121.

Note: Geriatric and debilitated patients may react to usual doses with excitement, confusion, or mental depression. Lower doses may be required in these patients. 121

Usual pediatric dose

Dosage has not been established 121.

Strength(s) usually available

U.S.¾50 mg of secobarbital and 50 mg of amobarbital (Rx)[Tuinal]

100 mg of secobarbital and 100 mg of amobarbital (Rx)[Tuinal]

101, 102

Canada¾50 mg of secobarbital and 50 mg of amobarbital (Rx)[Tuinal] 112

100 mg of secobarbital and 100 mg of amobarbital (Rx)[Tuinal] 112

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Auxiliary labeling:

- Avoid alcoholic beverages.
- May cause drowsiness.

Note: Controlled substance in the U.S. and Canada.

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