

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OBREDON (hydrocodone bitartrate and guaifenesin) Oral Solution safely and effectively. See full prescribing information for OBREDON (hydrocodone bitartrate and guaifenesin) Oral Solution.

OBREDON (hydrocodone bitartrate and guaifenesin) Oral Solution CII
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

OBREDON Oral Solution is a combination product containing an opioid antitussive and expectorant indicated for:

- Symptomatic relief of cough and to loosen mucus associated with the common cold.

Important Limitations of Use:

Not indicated for pediatric patients under 18 years of age (8.4)

DOSAGE AND ADMINISTRATION

Adults and adolescents 18 years of age and older: 10 mL every 4 to 6 hours, not to exceed 6 doses (60 mL) in 24 hours. (2.1)

Measure OBREDON Oral Solution with an accurate milliliter measuring device. (5.9)

DOSAGE FORMS AND STRENGTHS

Oral Solution: Each 5 mL contains hydrocodone bitartrate, USP, 2.5 mg; and guaifenesin, USP, 200 mg. (3)

CONTRAINDICATIONS

- Patients with known hypersensitivity to hydrocodone bitartrate, guaifenesin, or any of the inactive ingredients of OBREDON Oral Solution. (4)
- Patients receiving monoamine oxidase inhibitor (MAOI) therapy or within 14 days of stopping such therapy. (4)

WARNINGS AND PRECAUTIONS

- Dose-related respiratory depression: Use with caution. (5.1)

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8 USE IN SPECIFIC POPULATIONS

- Drug Dependence: Prescribe with caution that is appropriate to the use of other opioids. (5.2)
- Head injury and increased intracranial pressure: Avoid in patients with head injury, intracranial lesions or increased intracranial pressure. (5.3)
- Activities requiring mental alertness: Avoid engaging in hazardous tasks requiring complete mental alertness such as driving or operating machinery. (5.4)
- Acute abdominal conditions: Use with caution in patients with acute abdominal conditions. (5.5)
- Coexisting conditions: Use with caution in patients with diabetes, thyroid disease, Addison's disease, prostatic hypertrophy, or urethral stricture, or asthma. (5.10)

ADVERSE REACTIONS

The most common adverse reactions of OBREDON Oral Solution include: Dizziness, headache, sedation, nausea, and decreased blood pressure (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sovereign Pharmaceuticals, LLC at tel: 1-817-284-0429; www.sovpharm.com or FDA at 1-800-FDA-1088; www.fda.gov/medwatch

DRUG INTERACTIONS

- Opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol): Avoid using with OBREDON Oral Solution; may exhibit additive CNS depression. (7.1)
- MAO inhibitors (MAOIs) or tricyclic antidepressants: Do not use. May increase the effect of either the antidepressant or hydrocodone. (7.2)
- Anticholinergic drugs: Use with caution in order to avoid paralytic ileus and excessive anticholinergic effects. (7.3)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Use with caution in patients with severe renal impairment. (8.6)
- Hepatic Impairment: Use with caution in patients with severe hepatic impairment. (8.7)

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Revised: 11/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OBREDON Oral Solution is indicated for symptomatic relief of cough and to loosen mucus associated with the common cold.

Important Limitations of Use:

Not indicated for pediatric patients under 18 years of age [see *Pediatric Use* (8.4)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended dosage

Adults and adolescents 18 years of age and older: 10 mL every 4 to 6 hours, not to exceed 6 doses (60 mL) in 24 hours.

Administer OBREDON Oral Solution by the oral route only. Measure OBREDON Oral Solution with an accurate milliliter measuring device. Do not use a household teaspoon to measure the dose [see *Dosing* (5.9)].

3 DOSAGE FORMS AND STRENGTHS

Oral Solution: Each 5 mL contains hydrocodone bitartrate, USP, 2.5 mg; and guaifenesin, USP, 200 mg [see *DESCRIPTION* (11)].

4 CONTRAINDICATIONS

OBREDON Oral Solution is contraindicated in:

- Patients with known hypersensitivity to hydrocodone bitartrate, guaifenesin, or any of the inactive ingredients of OBREDON Oral Solution.
- Patients receiving MAOI therapy or within 14 days of stopping such therapy [see *DRUG INTERACTIONS* (7.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Respiratory Depression

Hydrocodone bitartrate, one of the active ingredients in OBREDON Oral Solution, produces dose-related respiratory depression by directly acting on brain stem respiratory centers. Overdose of hydrocodone bitartrate in adults has been associated with fatal respiratory depression, and the use of hydrocodone bitartrate in children less than 6 years of age has been associated with fatal respiratory depression. Exercise caution when administering OBREDON Oral Solution because of the potential for respiratory depression. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated [see *OVERDOSAGE* (10)].

5.2 Drug Dependence

Hydrocodone can produce drug dependence of the morphine type and therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of OBREDON Oral Solution. Prescribe and administer OBREDON Oral Solution with the same degree of caution appropriate to the use of other opioid drugs [see *DRUG ABUSE AND DEPENDENCE* (9.2), (9.3)].

5.3 Head Injury and Increased Intracranial Pressure

The respiratory depression effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries. The use of OBREDON Oral Solution should be avoided in these patients.

5.4 Activities Requiring Mental Alertness

Hydrocodone bitartrate, one of the active ingredients in OBREDON Oral Solution, may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Advise patients to avoid engaging in hazardous tasks requiring mental alertness and motor coordination after ingestion of OBREDON Oral Solution. Concurrent use of OBREDON Oral Solution with alcohol or other central nervous system depressants should be avoided because additional impairment of central nervous system performance may occur.

5.5 Acute Abdominal Conditions

OBREDON Oral Solution should be used with caution in patients with acute abdominal conditions since the administration of hydrocodone may obscure the diagnosis or clinical course of patients with acute abdominal conditions. The concurrent use of other anticholinergics with hydrocodone may produce paralytic ileus [see *DRUG INTERACTIONS (7.3)*].

5.6 Co-administration with Anticholinergics

The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus. Exercise caution when using OBREDON Oral Solution in patients taking anticholinergic medications [see *DRUG INTERACTIONS (7.3)*].

5.7 Co-administration with MAOIs or Tricyclic Antidepressants

OBREDON Oral Solution should not be used in patients receiving MAOI therapy or within 14 days of stopping such therapy. The use of MAOIs or tricyclic antidepressants with hydrocodone bitartrate may increase the effect of either the antidepressant or hydrocodone [see *CONTRAINDICATIONS (4)* and *DRUG INTERACTIONS (7.2)*].

5.8 Persistent Cough

OBREDON Oral Solution should not be used in patients with a persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema, or where cough is accompanied by excessive phlegm (mucus).

5.9 Dosing

Patients should be advised to measure OBREDON Oral Solution with an accurate milliliter measuring device. Patients should be informed that a household teaspoon is not an accurate measuring device and could lead to overdosage, which can result in serious adverse reactions [see *OVERDOSAGE (10)*]. Patients should be advised to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose.

5.10 Coexisting Conditions

OBREDON Oral Solution should be used with caution in patients with diabetes, thyroid disease, Addison's disease, prostatic hypertrophy or urethral stricture, and asthma.

5.11 Renal Impairment

OBREDON Oral Solution should be used with caution in patients with severe renal impairment. [see *Renal Impairment (8.6)*].

5.12 Hepatic Impairment

OBREDON Oral Solution should be used with caution in patients with severe hepatic impairment [see *Hepatic Impairment (8.7)*].

6 ADVERSE REACTIONS

Use of hydrocodone bitartrate is associated with the following:

- Respiratory depression [see WARNINGS AND PRECAUTIONS (5.1) and OVERDOSAGE (10)]
- Drug dependence [see WARNINGS AND PRECAUTIONS (5.2) and DRUG ABUSE AND DEPENDENCE (9.3)]
- Increased intracranial pressure [see WARNINGS AND PRECAUTIONS (5.3)]
- Decreased mental alertness with impaired mental and/or physical abilities [see WARNINGS AND PRECAUTIONS (5.4)]
- Paralytic ileus [see WARNINGS AND PRECAUTIONS (5.5)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most common adverse reactions experienced by subjects taking a single dose of OBREDON Oral Solution in the clinical setting include the following: Central Nervous System: headache, dizziness, sedation (somnolence); Gastrointestinal System: nausea, diarrhea; Cardiovascular System: decreased blood pressure; Vascular System: hot flush.

7 DRUG INTERACTIONS

No specific interaction studies have been conducted with OBREDON Oral Solution.

7.1 Opioids, Antihistamines, Antipsychotics, Anti-anxiety Agents, or Other CNS Depressants (Including Alcohol)

The use of opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants concomitantly with OBREDON Oral Solution may cause an additive CNS depressant effect and should be avoided.

7.2 MAO Inhibitors or Tricyclic Antidepressants

Do not prescribe OBREDON Oral Solution if the patient is taking a prescription MAOI (i.e., certain drugs used for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping a MAOI drug. The use of MAOIs or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone [see WARNINGS AND PRECAUTIONS (5.7)].

7.3 Anticholinergic Drugs

Hydrocodone should be administered cautiously to persons receiving anticholinergic drugs in order to avoid paralytic ileus and excessive anticholinergic effects [see WARNINGS AND PRECAUTIONS (5.6)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well controlled studies of OBREDON Oral Solution in pregnant women. Reproductive toxicity studies have not been conducted with OBREDON Oral Solution; however, studies are available with an individual active ingredient or related active ingredient. Hydrocodone was teratogenic in hamsters. Codeine, an opiate related to hydrocodone, increased resorptions and decreased fetal weight in rats. Because animal reproduction studies are not always predictive of human response, OBREDON Oral Solution should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Hydrocodone:

Hydrocodone has been shown to be teratogenic in hamsters when given in a dose approximately 27 times the maximum recommended human daily dose (MRHDD) (on a mg/m² basis at a single subcutaneous dose of 102 mg/kg on gestation day 8). Reproductive toxicology studies were also conducted with codeine, an opiate related to hydrocodone. In a study in which pregnant rats were dosed throughout organogenesis, a dose of codeine approximately 40 times the MRHDD of hydrocodone (on a mg/m² basis at an oral dose of 120 mg/kg/day of codeine) increased resorptions and decreased fetal weight; however, these effects occurred in the presence of

maternal toxicity. In studies in which rabbits and mice were dosed throughout organogenesis, doses of codeine up to approximately 20 and 100 times, respectively, the MRHDD of hydrocodone (on a mg/m² basis at oral doses of 30 and 600 mg/kg/day, respectively), produced no adverse developmental effects.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

8.2 Labor and Delivery

As with all opioids, administration of OBREDON Oral Solution to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

8.3 Nursing Mothers

Caution should be exercised when OBREDON Oral Solution is administered to nursing mothers. Hydrocodone is known to be excreted in human milk. No studies have been performed to determine if guaifenesin is excreted into breastmilk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OBREDON Oral Solution, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of OBREDON Oral Solution in pediatric patients under 18 years of age has not been established. The use of hydrocodone in children less than 6 years of age is associated with fatal respiratory depression [see **WARNINGS AND PRECAUTIONS** (5.1)].

8.5 Geriatric Use

Clinical studies have not been conducted with OBREDON Oral Solution in geriatric populations. Other reported clinical experience with the individual active ingredients of OBREDON Oral Solution has not identified differences in responses between the elderly and patients younger than 65 years of age. In general, dose selection for an elderly patient should be made with caution, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

OBREDON Oral Solution should be given with caution in patients with severe impairment of renal function.

8.7 Hepatic Impairment

OBREDON Oral Solution should be given with caution in patients with severe impairment of hepatic function.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OBREDON Oral Solution is a Schedule II controlled prescription containing hydrocodone bitartrate and should be prescribed and administered with caution.

9.2 Abuse

Hydrocodone can produce drug dependence of the morphine type and therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of OBREDON Oral Solution, and it should be prescribed and administered with the same degree of caution appropriate to the use of other opioid drugs.

Abuse of guaifenesin has been linked to the formation of kidney stones composed of the major metabolite β-(2-methoxyphenoxy) lactic acid.

9.3 Dependence

Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, OBREDON Oral Solution should be prescribed and administered with caution.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued oral opioid use, although some mild degree of physical dependence may develop after a few days of opioid therapy.

10 OVERDOSAGE

No human overdosage data are available for OBREDON Oral Solution.

Hydrocodone:

Overdosage with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, dizziness, ringing in the ears, confusion, blurred vision, eye problems, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

Guaifenesin:

Overdosage with guaifenesin can cause depression of the central nervous system. While present in polypharmacy overdoses, one case of overdose with only significant levels of guaifenesin has been reported. Symptoms included slurred speech, shallow respirations, reduced heart rate with rhythm sinus bradycardia, followed by asystole.

Treatment of overdosage consists of discontinuation of OBREDON Oral Solution together with institution of appropriate therapy. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdosage or unusual sensitivity to opioids including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

11 DESCRIPTION

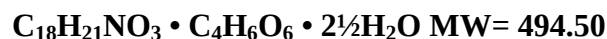
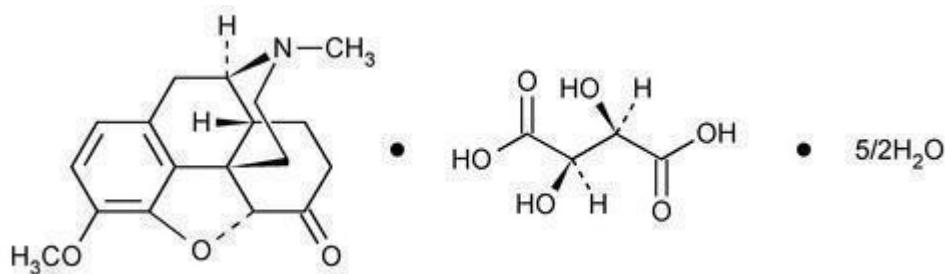
OBREDON Oral Solution contains hydrocodone bitartrate (a centrally-acting opioid antitussive) and guaifenesin (an expectorant).

Each 5 mL dose of OBREDON Oral Solution contains: hydrocodone bitartrate, USP, 2.5 mg; and guaifenesin, USP, 200 mg.

OBREDON Oral Solution also contains: artificial raspberry flavor or cherry punch flavor, citric acid, glycerin, methylparaben, potassium citrate, potassium sorbate, propylene glycol, propylparaben, purified water, and saccharin sodium.

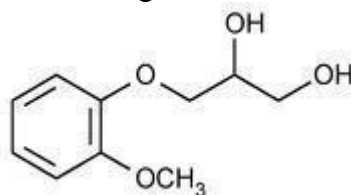
11.1 Hydrocodone Bitartrate

Hydrocodone Bitartrate is a centrally-acting opioid antitussive and analgesic. It is affected by light and occurs as fine white crystals or crystalline powder which is derived from the opium alkaloid, thebaine. Its chemical name is morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 α)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5). It is also known as 4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5); and may be represented by the following structural formula:



11.2 Guaifenesin

Guaifenesin is an expectorant and occurs as a white powder. Its chemical name is 3-(2-methoxyphenoxy)-1,2-propanediol, and may be represented by the following structural formula:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and physiological dependence.

Guaifenesin is an expectorant the action of which promotes or facilitates the removal of secretions from the respiratory tract. The precise mechanism of action of guaifenesin is not known; however, it is thought to act as an expectorant by increasing the volume and reducing the viscosity of secretions in the trachea and bronchi. In turn, this may increase the efficiency of the cough reflex and facilitate removal of the secretions.

12.3 Pharmacokinetics

Systemic exposure (in terms of peak plasma concentrations and area under plasma concentration versus time curve) of hydrocodone bitartrate and guaifenesin after single dose administration of 10 mL OBREDON Oral Solution are equivalent to respective reference solutions of 5 mL hydrocodone bitartrate (5 mg/5 mL), and 10 mL guaifenesin (200 mg/5 mL).

Hydrocodone: Following a single 10 mL oral dose of OBREDON Oral Solution administered to 36 healthy adults (19-74 years), the geometric mean $C_{\max}$ and $\text{AUC}_{0-\infty}$ for hydrocodone were 12.6 ng/mL and 80.9 ng·hr/mL, respectively. The median time to maximum concentration for hydrocodone was about 1.25 hours. Food has no significant effect on the extent of absorption of hydrocodone. The mean plasma half-life of hydrocodone is approximately 5 hours.

Guaifenesin: Following a single 10 mL oral dose of OBREDON Oral Solution administered to 57 healthy adults (19-74 years), the geometric mean $C_{\max}$ and $\text{AUC}_{0-\infty}$ for guaifenesin were 3.7 mcg/mL and 4.2 mcg·hr/mL, respectively. The median time to maximum concentration was about 20 minutes. The effect of food on guaifenesin systemic exposure is not considered to be clinically meaningful. The mean plasma half-life of guaifenesin is approximately 1 hour.

Drug interactions

When guaifenesin and hydrocodone were administered in combination, the pharmacokinetics for each component were similar to those observed when each component was administered separately.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with OBREDON Oral Solution; however, published information is available for the individual active ingredients or related active ingredients.

Hydrocodone:

Carcinogenicity studies were conducted with codeine, an opiate related to hydrocodone. In 2 year studies in F344/N rats and B6C3F1 mice, codeine showed no evidence of tumorigenicity at dietary doses up to 70 and 400 mg/kg/day, respectively (approximately 23 and 65 times, respectively, the MRHDD of hydrocodone on a mg/m² basis).

Guaifenesin:

Carcinogenicity, genotoxicity, or reproductive toxicology studies have not been conducted with guaifenesin.

14 CLINICAL STUDIES

Efficacy studies were not conducted with OBREDON Oral Solution. Efficacy of OBREDON Oral Solution is based on demonstration of bioequivalence to the individual comparator products [see *CLINICAL PHARMACOLOGY* (12.3)].

16 HOW SUPPLIED/STORAGE AND HANDLING

OBREDON Oral Solution is supplied as a clear, raspberry or cherry punch flavored liquid containing 2.5 mg hydrocodone bitartrate and 200 mg guaifenesin in each 5 mL. It is available in:

White HDPE bottles of 16 fl oz (473 mL): NDC 58716-492-16 (raspberry flavored)

White HDPE bottles of 4 fl oz (118 mL): NDC 58716-492-04 (raspberry flavored)

White HDPE bottles of 16 fl oz (473 mL): NDC 58716-505-16 (cherry punch flavored)

White HDPE bottles of 4 fl oz (118 mL): NDC 58716-505-04 (cherry punch flavored)

Store solution at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling]

Overdosage

Advise patients not to increase the dose or dosing frequency of OBREDON Oral Solution because serious adverse events such as respiratory depression may occur with overdosage [see *WARNINGS AND PRECAUTIONS* (5.1) and *OVERDOSAGE* (10)].

Dosing

Advise patients to measure OBREDON Oral Solution with an accurate milliliter measuring device. Patients should be informed that a household teaspoon is not an accurate measuring device and could lead to overdosage, especially when half a teaspoon is measured. Patients should be advised to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose [see *DOSAGE AND ADMINISTRATION* (2) and *WARNINGS AND PRECAUTIONS* (5.9)].

Concomitant Use of Alcohol and Other Central Nervous System Depressants

Advise patients to avoid the use of alcohol and other central nervous system depressants while taking OBREDON Oral Solution because additional reduction in mental alertness may occur [see WARNINGS AND PRECAUTIONS (5.4)].

Activities Requiring Mental Alertness

Advise patients to avoid engaging in hazardous tasks that require mental alertness and motor coordination such as operating machinery or driving a motor vehicle as OBREDON Oral Solution may produce marked drowsiness [see WARNINGS AND PRECAUTIONS (5.4)].

Drug Dependence

Caution patients that OBREDON Oral Solution contains hydrocodone bitartrate and can produce drug dependence [see WARNINGS AND PRECAUTIONS (5.2)].

Distributed by:

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