HYCOFENIX- hydrocodone bitartrate, pseudoephedrine hydrochloride, guaifenesin liquid
Mission Pharmacal Company

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HYCOFENIXTM safely and effectively. See full prescribing information for HYCOFENIX.

HYCOFENIX (hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin) oral solution, CII

Initial U.S. Approval: 2015

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [*see Warnings and Precautions (5.1), Drug Interactions (7.1)*]. Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol. *See full prescribing information for complete boxed warning.*

INDICATIONS AND USAGE
HYCOFENIX is a combination of hydrocodone, an opioid antitussive, pseudoephedrine, a nasal decongestant, guaifenesin, an expectorant indicated for the symptomatic relief of cough, nasal congestion, 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 4 doses (40 mL) in 24 hours (2.1)
- Measure HYCOFENIX with an accurate milliliter measuring device. (5.10)

DOSAGE FORMS AND STRENGTHS
Oral solution: Each 5 mL contains hydrocodone bitartrate, USP, 2.5 mg; pseudoephedrine hydrochloride, USP, 30 mg; and guaifenesin, USP, 200 mg. (3)

CONTRAINDICATIONS
- Patients with known hypersensitivity to hydrocodone bitartrate, pseudoephedrine hydrochloride, guaifenesin, or any of the inactive ingredients of HYCOFENIX. (4)
- Patients receiving monoamine oxidase inhibitor (MAOI) therapy or within 14 days of stopping such therapy. (4)
- Patients with narrow angle glaucoma, urinary retention, severe hypertension, or severe coronary artery disease. (4)

WARNINGS AND PRECAUTIONS
- Risks from Concomitant Use with Benzodiazepines or other CNS Depressants. (5.1)
- Dose-related respiratory depression: Use with caution. (5.2)
- Drug Dependence: Prescribe with caution that is appropriate to the use of other opioids. (5.3)
- Head injury and increased intracranial pressure: Avoid in patients with head injury, intracranial lesions or increased intracranial pressure. (5.4)
- Activities requiring mental alertness: Avoid engaging in hazardous tasks requiring complete mental alertness such as driving or operating machinery. (5.5)
- Acute abdominal conditions: Use with caution in patients with acute abdominal conditions. (5.6)
- Coexisting conditions: Use with caution in patients with diabetes, thyroid disease, Addison's disease, prostatic hypertrophy, or urethral stricture, or asthma. (5.12)

ADVERSE REACTIONS
The most common adverse reactions of HYCOFENIX include: Dizziness, headache, sedation, nausea, and decreased blood pressure (6)
To report SUSPECTED ADVERSE REACTIONS, contact Mission Pharmacal Company at 1-800-298-1087 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS
- Benzodiazepines, opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol): Avoid using with HYCOFENIX; 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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [*see Warnings and Precautions (5.1), Drug Interactions (7.1)*]. Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol.

1 INDICATIONS AND USAGE

HYCOFENIX is indicated for symptomatic relief of cough, nasal congestion, 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 4 doses (40 mL) in 24 hours.

Administer HYCOFENIX by the oral route only. Measure HYCOFENIX with an accurate milliliter measuring device. Do not use a household teaspoon to measure the dose [*see Warnings and Precautions (5.11)*].

3 DOSAGE FORMS AND STRENGTHS

Oral solution: Each 5 mL contains hydrocodone bitartrate, USP, 2.5 mg; pseudoephedrine hydrochloride, USP, 30 mg; and guaifenesin, USP, 200 mg [*see Description (11)*].

4 CONTRAINDICATIONS

HYCOFENIX is contraindicated in:

- Patients with known hypersensitivity to hydrocodone bitartrate, pseudoephedrine hydrochloride, guaifenesin, or any of the inactive ingredients of HYCOFENIX.
- Patients receiving MAOI therapy or within 14 days of stopping such therapy [*see Drug Interactions (7.2)*].
- Patients with narrow angle glaucoma, urinary retention, severe hypertension, or severe coronary artery disease.

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Benzodiazepines or other CNS Depressants

Concomitant use of opioids, including HYCOFENIX, with benzodiazepines, or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Because of these risks, avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol [*see Drug Interactions (7.1)*].

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of similar pharmacologic properties, it is reasonable to expect similar risk with concomitant use of opioid cough medications and benzodiazepines, other CNS depressants, or alcohol.

Advise both patients and caregivers about the risks of respiratory depression and sedation if HYCOFENIX is used with benzodiazepines, alcohol, or other CNS depressants [*see Patient Counseling Information (17)*].

5.2 Respiratory Depression

Hydrocodone bitartrate, one of the active ingredients in HYCOFENIX, produces doserelated 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 HYCOFENIX 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)*].

5.3 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 HYCOFENIX. Prescribe and administer HYCOFENIX with the same degree of caution appropriate to the use of other opioid drugs [*see Drug Abuse and Dependence (9.2), (9.3)*].

5.4 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 HYCOFENIX should be avoided in these patients.

5.5 Activities Requiring Mental Alertness

Hydrocodone bitartrate, one of the active ingredients in HYCOFENIX, 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 HYCOFENIX. Concurrent use of HYCOFENIX with alcohol or other central nervous system depressants should be avoided because additional impairment of central nervous system performance may occur.

5.6 Acute Abdominal Conditions

HYCOFENIX 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)*].

5.7 Co-administration with Anticholinergics

The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus. Exercise caution when using HYCOFENIX in patients taking anticholinergic medications [*see Drug Interactions (7.3)*].

5.8 Co-administration with Monoamine Oxidase Inhibitors (MAOIs) or Tricyclic Antidepressants

HYCOFENIX 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)*].

5.9 Cardiovascular and Central Nervous System Effects

The pseudoephedrine hydrochloride contained in HYCOFENIX can produce cardiovascular and central nervous system effects in some patients such as insomnia, dizziness, weakness, tremor, or arrhythmias. In addition, central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension has been reported. Therefore, HYCOFENIX should be used with caution in patients with cardiovascular disorders, and should not be used in patients with severe hypertension or coronary artery disease.

5.10 Persistent Cough

HYCOFENIX 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).

5.11 Dosing

Patients should be advised to measure HYCOFENIX 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.

5.12 Coexisting Conditions

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

5.13 Renal Impairment

HYCOFENIX should be used with caution in patients with severe renal impairment [*see Use in Specific Populations (8.6)*].

5.14 Hepatic Impairment

HYCOFENIX should be used with caution in patients with severe hepatic impairment [*see Use in Specific Populations (8.7)*].

6 ADVERSE REACTIONS

Use of hydrocodone bitartrate is associated with the following:

- Respiratory depression [*see Warnings and Precautions (5.2) and Overdosage (10)*]
- Drug dependence [*see Warnings and Precautions (5.3) and Drug Abuse and Dependence (9.3)*]
- Increased intracranial pressure [*see Warnings and Precautions (5.4)*]
- Decreased mental alertness with impaired mental and/or physical abilities [*see Warnings and Precautions (5.5)*]
- Paralytic ileus [*see Warnings and Precautions (5.6)*]

Use of pseudoephedrine, a sympathomimetic amine, may result in the following:

- Central nervous system effects such as insomnia, dizziness, weakness, tremor, or convulsions [*see Warnings and Precautions (5.9)*]
- Cardiovascular system effects such as arrhythmias, or increased blood pressure, cardiovascular collapse with accompanying hypotension [*see Warnings and Precautions (5.9)*]

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 HYCOFENIX 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 HYCOFENIX.

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

The use of benzodiazepines, opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with HYCOFENIXmay cause an additive CNS depressant effect, profound sedation, respiratory depression, coma, and death and should be avoided [*see Warnings and Precautions (5.1)*].

7.2 MAO Inhibitors or Tricyclic Antidepressants

Do not prescribe HYCOFENIX 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 an MAOI drug. The use of MAOIs or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. An increase in blood pressure of hypertensive crisis may also occur when pseudoephedrine containing preparations are used with MAOIs [*see Warnings and Precautions (5.8)*].

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 (5.7)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects
Pregnancy Category C
There are no adequate and well controlled studies of HYCOFENIX in pregnant women. Reproductive toxicity studies have not been conducted with HYCOFENIX; 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, HYCOFENIX 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 35 times the maximum recommended human daily dose (MRHDD) (on a mg/m^2 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 50 times the MRHDD of hydrocodone (on a mg/m^2 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 25 and 120 times, respectively, the MRHDD of hydrocodone (on a mg/m^2 basis at oral doses of 30 and 600 mg/kg/day, respectively), produced no adverse developmental effects.

Non-teratogenic 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 HYCOFENIX 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 HYCOFENIX is administered to nursing mothers. Hydrocodone and pseudoephedrine are 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 HYCOFENIX, 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 HYCOFENIX 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 HYCOFENIX in geriatric populations. Other reported clinical experience with the individual active ingredients of HYCOFENIX 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. The pseudoephedrine contained in HYCOFENIX is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Renal Impairment

HYCOFENIX should be given with caution in patients with severe impairment of renal function. Pseudoephedrine is primarily excreted unchanged in the urine as unchanged drug with the remainder apparently being metabolized in the liver. Therefore, pseudoephedrine may accumulate in patients with renal impairment.

8.7 Hepatic Impairment

HYCOFENIX should be given with caution in patients with severe impairment of hepatic function.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

HYCOFENIX 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 HYCOFENIX, 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, HYCOFENIX should be prescribed and administered with caution [*see Warnings and Precautions (5.2)*].

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 HYCOFENIX.

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.

Pseudoephedrine

Overdosage with sympathomimetics such as pseudoephedrine may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscle weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusion and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsion, coma, and respiratory failure.

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 HYCOFENIX 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.

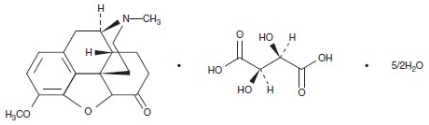
11 DESCRIPTION

HYCOFENIX (hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin) oral solution contains hydrocodone bitartrate (a centrally-acting opioid antitussive), pseudoephedrine hydrochloride (an indirect sympathomimetic amine), and guaifenesin (an expectorant). Each 5 mL dose of HYCOFENIX contains: hydrocodone bitartrate, USP, 2.5 mg; pseudoephedrine hydrochloride, USP, 30 mg; and guaifenesin, USP, 200 mg.

HYCOFENIX also contains: black raspberry flavor, citric acid, D&C Red #33, FD&C Blue #1, glycerin, methylparaben, polyethylene glycol, propylparaben, purified water, saccharin sodium, sodium citrate, and sorbitol.

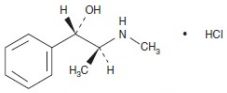
Hydrocodone Bitartrate

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-, (5α)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5). It is also known as 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5);and may be represented by the following structural formula:



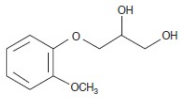
$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H_2O$ MW 494.490

Pseudoephedrine Hydrochloride
Pseudoephedrine hydrochloride is benzenemethanol, α-[1-(methylamino)ethyl]-, [S-(R*,R*)] hydrochloride and has the following chemical structure:



$C_{10}H_{15}NO \cdot HCl$ MW 201.69

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:



$C_{10}H_{14}O_4$ MW 198.22

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.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to upper respiratory allergies or common cold. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

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, pseudoephedrine hydrochloride, and guaifenesin after a single 10 mL oral dose administration of 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin are equivalent to the respective reference solutions of 5 mL hydrocodone bitartrate (5 mg/5 mL), 5 mL pseudoephedrine hydrochloride (30 mg/5 mL), and 10 mL guaifenesin (200 mg/5 mL).

Hydrocodone
Following a single 10 mL oral dose administration of 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin administered to 37 healthy adults, the geometric mean C_{max} and $AUC_{0\text{-}inf}$ for hydrocodone were 9.0 ng/mL and 61.2 ng·hr/mL, respectively. The median time to maximum concentration for hydrocodone was about 1.67 hours. Food has no significant effect on the extent of absorption of hydrocodone. The mean plasma half-life of hydrocodone is approximately 4 hours.

Pseudoephedrine
Following a single 10 mL oral dose administration of 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin administered to 37 healthy adults, the geometric mean C_{max} and $AUC_{0\text{-}inf}$ for pseudoephedrine were 0.19 mcg/mL and 1.9 mcg·hr/mL, respectively. The median time to maximum concentration for pseudoephedrine was about 2.5 hours. Food has no significant effect on the extent of absorption of pseudoephedrine. The mean plasma half-life of pseudoephedrine is approximately 6 hours.

Guaifenesin
Following a single 10 mL oral dose administration of 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin administered to 36 healthy adults, the geometric mean C_{max} and $AUC_{0\text{-}inf}$ for guaifenesin were 2.0 mcg/mL and 2.6 mcg·hr/mL, respectively. The median time to maximum concentration was about 25 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, pseudoephedrine, and hydrocodone were administered in combination, the pharmacokinetics for each component was 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 HYCOFENIX; 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 30 and 80 times, respectively, the MRHDD of hydrocodone on a mg/m2 basis).

Pseudoephedrine
Two-year feeding studies in rats and mice demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at dietary doses up to 10 and 27 mg/kg, respectively (approximately 0.3 and 0.5 times, respectively, the MRHDD of pseudoephedrine hydrochloride on a mg/m^2 basis).

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

14 CLINICAL STUDIES

Efficacy studies were not conducted with HYCOFENIX. Efficacy of HYCOFENIX is based on demonstration of bioequivalence to the individual comparator products [*see Clinical Pharmacology (12.3)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

HYCOFENIX (hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin) oral solution is supplied as a violet-colored, black raspberry flavored liquid containing 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin in each 5 mL. It is available in:
White HDPE bottles of 16 fl. oz. (473 mL): **NDC** 0178-3291-16
White HDPE bottles of 4 fl. oz. (118 mL): **NDC** 0178-3291-04
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 childresistant closure.

17 PATIENT COUNSELING INFORMATION

Overdosage
Advise patients not to increase the dose or dosing frequency of HYCOFENIX 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 HYCOFENIX 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 (5.10)*].

Interactions with Benzodiazepines and Other Central Nervous System Depressants
Inform patients and caregivers that potentially fatal additive effects may occur if HYCOFENIX is used with benzodiazepines or other CNS depressants, including alcohol. Because of this risk, patients should avoid concomitant use of HYCOFENIX with benzodiazepines or other CNS depressants, including alcohol [*see Warnings and Precautions (5.1) and Drug Interactions (7.1)*].

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 HYCOFENIX may produce marked drowsiness [*see Warnings and Precautions (5.5)*].

Drug Dependence
Caution patients that HYCOFENIX contains hydrocodone bitartrate and can produce drug dependence [*see Warnings and Precautions (5.3)*].

MAOIs
Patients should be informed that due to its pseudoephedrine component, they should not use HYCOFENIX with an MAOI or within 14 days of stopping use of an MAOI [*see Warning and Precautions (5.8)*].

Manufactured for:
MISSION PHARMACAL COMPANY
San Antonio, TX 78230 1355

1133A00 R0916

MEDICATION GUIDE
HYCOFENIX® (hye-koh-fee-niks)
(hydrocodone bitartrate, pseudoephedrine, and guaifenesin) oral solution, C-II

What is the most important information I should know about HYCOFENIX®?
- Taking HYCOFENIX with benzodiazepines, or other central nervous system depressants, including alcohol can cause severe drowsiness, breathing problems (respiratory depression), coma, and death.
- HYCOFENIX can cause you to be drowsy. Do not drive a car or operate machinery until you know how HYCOFENIX affects you. HYCOFENIX can slow your thinking and motor skills, and may affect your vision.
- Women who breastfeed should talk to their healthcare provider before taking HYCOFENIX.
- Call your healthcare provider or get emergency medical help right away if anyone taking HYCOFENIX has any of the symptoms below:
  - increased sleepiness
  - confusion
  - difficulty breathing
  - shallow breathing
  - limpness
  - your baby has difficulty breastfeeding
- Keep HYCOFENIX in a safe place away from children. Accidental use by a child is a medical emergency and can cause death. If a child accidentally takes HYCOFENIX, get emergency medical help right away.
- HYCOFENIX can cause serious side effects, including death.
- Take HYCOFENIX exactly as prescribed by your healthcare provider. If you take the wrong dose of HYCOFENIX, you could overdose and die.
- HYCOFENIX is not for children under 18 years of age.

What is HYCOFENIX?
- HYCOFENIX is a prescription medicine used to treat cough, nasal congestion and loosen mucus associated with the common cold in adults and adolescents 18 years of age and older. HYCOFENIX contains three medicines, hydrocodone, pseudoephedrine and guaifenesin. Hydrocodone is a narcotic cough suppressant. Pseudoephedrine is a nasal decongestant. Guaifenesin is an expectorant.
- HYCOFENIX is a federal controlled substance (C-II) because it contains hydrocodone that can be abused or lead to dependence. Keep HYCOFENIX in a safe place to prevent misuse and abuse. Selling or giving away HYCOFENIX may harm others, and is against the law. Tell your healthcare provider if you have abused or been dependent on alcohol, prescription medicines or street drugs.
- HYCOFENIX is not for children under 18 years of age. It is not known if HYCOFENIX is safe and effective in children.

Who should not take HYCOFENIX?
- Do not take HYCOFENIX if you are allergic to any of the ingredients in HYCOFENIX. See the end of this Medication Guide for a complete list of ingredients. You may have an increased risk of having an allergic reaction to HYCOFENIX if you are allergic to certain other opioid medicines.
- Do not take HYCOFENIX if you take a medicine for depression called a Monoamine Oxidase Inhibitor (MAOI)
  - Do not take an MAOI within 14 days after you stop taking HYCOFENIX.
  - Do not start HYCOFENIX if you stopped taking an MAOI in the last 14 days.

Before you take HYCOFENIX, tell your healthcare provider about all of your medical conditions, including if you:
- have lung or breathing problems
- have a drug dependence
- have had a head injury
- have pain in your stomach-area (abdomen)
- have a history of severe or persistent cough
- have prostate problems
- have problems with your urinary tract (urethral stricture)
- are pregnant or plan to become pregnant. It is not known if HYCOFENIX will harm your unborn baby. You and your healthcare provider should decide if you should take HYCOFENIX while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if HYCOFENIX passes into your breast milk. You and your healthcare provider should decide if you will take HYCOFENIX or breastfeed. You should not do both.
- plan to have surgery
- drink alcohol
- have kidney or liver problems
- have diabetes
- have thyroid problems, such as hypothyroidism
- have Addison's disease
- have asthma

Tell your healthcare provider about all the medicines you take, ncluding prescription and over-the-counter medicines, vitamins and herbal supplements.
Taking HYCOFENIX with certain other medicines can cause side effects or affect how well HYCOFENIX or the other medicines work. Do not start or stop other medicines without talking to you healthcare provider.
Especially tell your healthcare provider if you:
- take pain medicines such as narcotics
- take cold or allergy medicines that contain antihistamines or cough suppressants
- take medicines for mental illness (anti-psychotics, anti-anxiety)
- drink alcohol
- take medicines for depression, including monoamine oxidase inhibitors (MAOIs) and tricyclics
- take a benzodiazepine, opioid, anticholinergic, or other CNS Depressants

How should I take HYCOFENIX?
- Take HYCOFENIX exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much HYCOFENIX to take and when to take it. Do not change your dose without talking to your healthcare provider.
- HYCOFENIX should be taken using an accurate milliliter measuring device.
- Ask your pharmacist to give you a measuring device to help you measure the correct amount of HYCOFENIX. **Do not use a household teaspoon to measure your medicine. You may accidentally take too much.**
- If you take too much HYCOFENIX, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking HYCOFENIX?

- HYCOFENIX can cause you to be drowsy. Do not drive a car or operate machinery while you take HYCOFENIX until you know how it affects you.
- Avoid drinking alcohol while taking HYCOFENIX. Drinking alcohol can increase your chances of having serious side effects.

What are the possible side effects of HYCOFENIX?
HYCOFENIX may cause serious side effects, including:

- **See "What is the most important information I should know about HYCOFENIX?"**
- **Breathing problems (respiratory depression) which can lead to death.** Call your healthcare provider or get emergency treatment right away if you are sleeping more than usual, have shallow or slow breathing, or confusion.
- **Physical dependence or abuse.** Take HYCOFENIX exactly as your healthcare provider tells you to take it. Stopping HYCOFENIX suddenly could cause withdrawal symptoms.
- **Bowel problems including constipation or stomach pain.**
- Increased intracranial pressure.
- Decreased mental alertness with impaired mental and/or physical abilities.

The most common side effects of HYCOFENIX include:

- sleepiness
- confusion
- dizziness
- headache
- nausea and vomiting
- diarrhea
- difficulty urinating
- trouble breathing
- decreased blood pressure
- hot flush
- insomnia
- weakness
- tremor
- convulsions

These are not all the possible side effects of HYCOFENIX.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store HYCOFENIX?

- Store HYCOFENIX at room temperature between 20° to 25°C (68° to 77°F).
- Safely throw away medicine that is out of date or no longer needed.
- Keep HYCOFENIX oral solution and all medicines out of the reach of children.

General information about the safe and effective use of HYCOFENIX.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use HYCOFENIX for a condition for which it was not prescribed. Do not give HYCOFENIX to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about HYCOFENIX that is written for health professionals.

What are the ingredients in HYCOFENIX?
Active Ingredients: Each 5 mL dose of HYCOFENIX contains hydrocodone bitartrate, USP, 2.5 mg; pseudoephedrine hydrochloride, USP, 30 mg; and guaifenesin, USP, 200 mg.
Inactive Ingredients: black raspberry flavor, citric acid, D&C Red #33, FD&C Blue #1, glycerin, methylparaben, polyethylene glycol, propylparaben, purified water, saccharin sodium, sodium citrate, and sorbitol.

Manufactured for:
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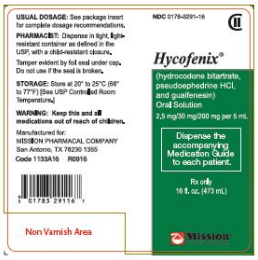
San Antonio, TX 78230 1355

For more information, go to www.hycofenix.com or call 1-800-298-1087.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Issued: January 2017



HYCOFENIX

hydrocodone bitartrate, pseudoephedrine hydrochloride, guaifenesin liquid

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0178-3291
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GUAIFENESIN (UNII: 495W7451VQ) (GUAIFENESIN - UNII:495W7451VQ)	GUAIFENESIN	200 mg in 5 mL
HYDROCODONE BITARTRATE (UNII: NO70W886KK) (HYDROCODONE - UNII:6YKS4Y3WQ7)	HYDROCODONE BITARTRATE	2.5 mg in 5 mL
PSEUDOEPHEDRINE HYDROCHLORIDE (UNII: 6V9V2RYJ8N) (PSEUDOEPHEDRINE - UNII:7CUC9DD9F)	PSEUDOEPHEDRINE HYDROCHLORIDE	30 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	
SACCHARIN SODIUM (UNII: SB8ZUX40TY)	
SODIUM CITRATE (UNII: 1Q73Q2JULR)	
SORBITOL (UNII: 506T60A25R)	
D&C RED NO. 33 (UNII: 9DBA0SBB0L)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
GLYCERIN (UNII: PDC6A3C0OX)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
POLYETHYLENE GLYCOLS (UNII: 3WQ0SDW1A)	
PROPYLPARABEN (UNII: Z8IX2SC1OH)	

Product Characteristics			
Color	PURPLE	**Score**	
Shape		**Size**	
Flavor	RASPBERRY (blue raspberry)	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0178-3291-16	473 mL in 1 BOTTLE; Type 0: Not a Combination Product	08/18/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022279	08/18/2015	

Labeler - Mission Pharmacal Company (008117095)

Establishment

Name	Address	ID/FEI	Business Operations
Mikart, Inc.		030034847	REPACK(0178-3291) , MANUFACTURE(0178-3291)