

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

HYCOFENIX (hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin) oral solution, CII
Initial U.S. Approval: 2015

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. See full prescribing information for complete boxed warning.

RECENT MAJOR CHANGES

Boxed Warning 1/2017
Warnings and Precautions, Risks from Concomitant use with Benzodiazepines or Other CNS Depressants (5.1) 1/2017

INDICATIONS AND USAGE

HYCOFENIX is a combination of hydrocodone, an opioid antitussive, pseudoephedrine, a nasal decongestant, and 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. (5.11)

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 Pharmaceutical 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

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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 *Use in Specific Populations (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 *Warning and Precautions (5.10)*].

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 dose-related respiratory depression by directly acting on brain stem respiratory centers. Overdose of hydrocodone bitartrate 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 overdose, 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 Renal 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 Benzodiazepines, 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 HYCOFENIX may 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/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 50 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 25 and 120 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.

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* (5.2)].

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.

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 overdose 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

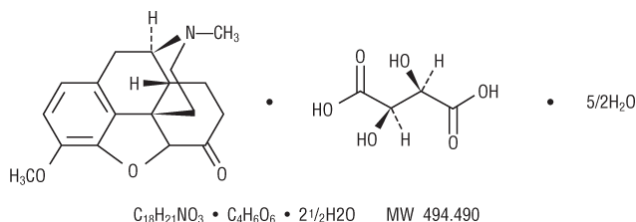
HYCOFENIX (hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin) oral solution contains hydrocodone bitartrate (a centrally-acting opioid antitussive), pseudoephedrine hydrochloride (an indirect sympathomimetic amine), and guaifenesin (an expectorant).

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.

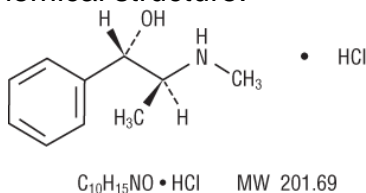
Hydrocodone Bitartrate

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-, (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:



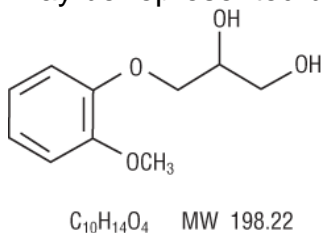
Pseudoephedrine Hydrochloride

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



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.

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-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-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-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/m² 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 24470-915-16

White HDPE bottles of 4 fl. oz. (118 mL): NDC 24470-915-04

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 child-resistant 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 (5.2)* 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 (5.11)*].

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 *Warnings and Precautions* (5.8)].



Manufactured for:

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San Antonio, TX 78230 1355

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