

PRESCRIBING INFORMATION
INCLUDING PATIENT MEDICATION INFORMATION

NTUSSIONEX[®]

Controlled-Release Hydrocodone Resin Complex and Phenyltoloxamine Resin Complex

5 mg / 5 mL Hydrocodone
10 mg / 5 mL Phenyltoloxamine

Oral Suspension

Antitussive - Antihistamine

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N[®]TUSSIONEX[®]

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Suspension: 5 mg hydrocodone bitartrate and 10 mg phenyltoloxamine citrate, per 5 mL	alcohol 95%, D&C yellow No. 10, FD&C yellow No. 6, glycerin, methylparaben, peach flavour, pineapple flavour, propylene glycol, propylparaben, sorbitol solution 70%, washed hydrogen cycle resin, water, xanthan gum.

INDICATIONS AND CLINICAL USE

Adults

TUSSIONEX is indicated for the treatment of exhausting or non-productive cough; associated with cold or with upper respiratory allergic condition that does not respond to non-narcotic antitussives.

Geriatrics (> 65 years of age)

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Geriatrics**).

Pediatrics (< 18 years of age)

TUSSIONEX is not indicated for use in patients younger than 18 years of age because of the risk of opioid toxicity due to the variable and unpredictable metabolism of hydrocodone to hydromorphone and because the benefits of symptomatic treatment of cough associated with allergies or the common cold do not outweigh the risks for use of hydrocodone in these patients (see also **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS**, **Neurologic**, **Respiratory**, **Special Populations**, **Pediatrics**; and **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

- Children younger than 6 years of age.
- Patients who are hypersensitive to the active substances hydrocodone or phenyltoloxamine or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Prescribing Information.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Patients with marked hypertension.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with controlled release opioid formulations, TUSSIONEX (hydrocodone and phenyltoloxamine) should only be used in patients for whom alternative non-opioid treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate cough management (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

TUSSIONEX poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing TUSSIONEX, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). TUSSIONEX should be stored securely to avoid theft or misuse.

SERIOUS WARNINGS AND PRECAUTIONS

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of TUSSIONEX. Infants exposed *in-utero* or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of TUSSIONEX or following a dose increase. Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

Accidental exposure to TUSSIONEX, especially by children, can result in a fatal overdose of hydrocodone (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of TUSSIONEX during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol

The co-ingestion of alcohol with TUSSIONEX should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- Reserve concomitant prescribing of TUSSIONEX and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

General

Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of the cough is identified, that modification of the cough does not increase the risk of clinical or physiological complications, and that appropriate therapy for the primary disease is provided.

Accidental ingestion, especially by children, can result in a fatal overdose of hydrocodone bitartrate (see DOSAGE AND ADMINISTRATION, disposal, for instructions on proper disposal).

Patients should be instructed not to give TUSSIONEX to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. TUSSIONEX should be stored securely to avoid theft or misuse.

Patients should be cautioned not to consume alcohol while taking TUSSIONEX as it may increase the chance of experiencing serious adverse events, including death.

Administer with caution to patients hypersensitive to sympathomimetic preparations, patients with hyperthyroidism, hypertension, diabetes mellitus, thyrotoxicosis, glaucoma, cardiac disease and peripheral vascular disease and in patients receiving methyldopa or beta adrenergic blockers.

TUSSIONEX suspension must not be diluted with fluids or mixed with other drugs because this alters the resin-binding and changes the absorption rate, possibly increasing the toxicity.

Abuse and Misuse

Like all opioids, TUSSIONEX is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, TUSSIONEX should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Use in Drug and Alcohol Addiction

TUSSIONEX is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of cough requiring opioids. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to TUSSIONEX; extreme caution and awareness is warranted to mitigate the risk.

Cardiovascular

Hydrocodone administration may result in hypotension and dizziness.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of TUSSIONEX and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Continuous dosage over extended periods of time may cause a hydrocodone bitartrate dependent state.

Patients on prolonged therapy could experience withdrawal symptoms following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**).

Endocrine

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Gastrointestinal Effects

Hydrocodone and other morphine-like opioids have been shown to decrease bowel motility.

Patients with chronic constipation should be given the drug only after weighing the potential therapeutic benefit against the hazards involved. Hydrocodone may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

TUSSIONEX is not recommended to be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the risks. If **TUSSIONEX** was used during pregnancy, special attention to NOWS is warranted.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Hydrocodone should be used with caution and in a reduced dosage during concomitant

administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the 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 when TUSSIONEX is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

TUSSIONEX should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Sedation, and DRUG INTERACTIONS**).

Head Injury: The respiratory depressant effects of hydrocodone, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, hydrocodone may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, hydrocodone must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS**).

Use in Patients with Convulsive or Seizure Disorders: The hydrocodone in TUSSIONEX may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Therefore, TUSSIONEX should not be used in these patients (see **CONTRAINDICATIONS**).

Serotonin syndrome: TUSSIONEX could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. TUSSIONEX should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic

antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

Psychomotor Impairment

TUSSIONEX may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of hydrocodone with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. TUSSIONEX should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see **CONTRAINDICATIONS**).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of TUSSIONEX, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with TUSSIONEX and following dose increases.

Hydrocodone, including TUSSIONEX, is not recommended for use in any patient in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, lung infections, multiple trauma or extensive surgical procedures

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Hydrocodone, including TUSSIONEX, is not indicated for patients under 18 years of age. Hydrocodone is contraindicated in patients below the age of 6 years. In young children, the respiratory centre is especially susceptible to the depressant action of narcotic cough suppressants. The use of hydrocodone bitartrate in children less than 6 years of age has been associated with fatal respiratory depression. A 5 year old child treated for cough died after a few hours of exposure to hydrocodone bitartrate; the child was a CYP2D6 poor metabolizer and was concomitantly exposed to clarithromycin, a CYP3A4 inhibitor and valproic acid, a broad-spectrum inhibitor of the uridine diphosphate glucuronosyltransferases (UGTs), resulting in blood hydrocodone levels associated with fatality. Such a scenario of hydrocodone overdose can be equally plausible in CYP2D6 intermediate, extensive, and ultrarapid metabolizers, especially in the presence of other drug interactions and physical vulnerabilities for children up to 18 years of age and adults. Exercise caution when administering TUSSIONEX because of the potential for respiratory depression. If respiratory depression occurs, discontinue and use naloxone hydrochloride when indicated to antagonize the effect and other supportive measures as necessary.

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with TUSSIONEX, as in these patients, even usual therapeutic doses of TUSSIONEX may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of TUSSIONEX is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS, Post-Marketing Experience**).

Special Populations

Special Risk Groups: Hydrocodone should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women: Studies in humans have not been conducted. **TUSSIONEX** crosses the placental barrier and is not recommended to be administered to pregnant women unless, in the judgement of the physician, potential benefits outweigh the risks.

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome, ADVERSE REACTIONS, Post-marketing Experience**).

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, **TUSSIONEX** is not recommended to be used in nursing women and during labour and delivery unless, in the judgement of the physician, the potential benefits outweigh the risks. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if TUSSIONEX is used in this population. Babies of nursing mothers using opioids may become physically dependent.

Pediatrics (< 18 years of age): TUSSIONEX is not indicated for use in patients younger than 18 years of age because of the risk of opioid toxicity due to the variable and unpredictable metabolism of hydrocodone to hydromorphone and because the benefits of symptomatic treatment of cough associated with allergies or the common cold do not outweigh the risks for

use of hydrocodone in these patients (see **INDICATIONS AND CLINICAL USE** and **DOSAGE AND ADMINISTRATION**).

TUSSIONEX is contraindicated in children younger than 6 years of age. In young children, the respiratory centre is especially susceptible to the depressant action of narcotic cough suppressants.

Geriatrics (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

ADVERSE REACTIONS

These can include mild constipation, nausea, facial pruritus, and drowsiness that typically disappear with adjustment of dose or discontinuance of treatment.

Post-Marketing Experience

Other adverse reactions reported with the use of cough and cold medications include: convulsions, hallucinations, allergic reaction, breathing difficulties, rapid heart rate, reflex bradycardia and urinary retention.

Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

DRUG INTERACTIONS

Do not use with a monoamine oxidase inhibitor (MAOI) or for 2 weeks after stopping the MAOI drug (see **CONTRAINDICATIONS**).

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants (including alcohol): Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death and should be avoided (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor**

Impairment). TUSSIONEX should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Serotonergic Agents: Coadministration of hydrocodone with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS, Neurologic**).

Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

Patients should be cautioned not to operate vehicles or hazardous machinery until their response to the drug has been determined.

DOSAGE AND ADMINISTRATION

Increasing Risk with Higher Doses

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. The maximum recommended daily dose of TUSSIONEX is 10 mL of suspension (10 mg morphine milligram equivalent). Each patient should be assessed for their risk prior to prescribing TUSSIONEX, as the likelihood of experiencing serious adverse events can depend upon the type of opioid and duration of treatment, as well as the patient's own level of tolerance. In addition, the coughing should be assessed routinely to confirm the most appropriate dose and the need for further use of TUSSIONEX.

Dosing Considerations

TUSSIONEX should not be diluted with fluids or mixed with other drugs. Shake well before using.

Recommended Dose and Dosage Adjustment

Adults:

5 mL (1 teaspoonful) of suspension every 8 to 12 hours. Maximum daily dose is 10 mL of suspension. May be adjusted to individual requirements. Do not use for longer than 7 days.

Pediatrics (<18 years of age):

TUSSIONEX is not indicated for use in patients younger than 18 years of age because of the risk of opioid toxicity due to the variable and unpredictable metabolism of hydrocodone to hydromorphone and because the benefits of symptomatic treatment of cough associated with allergies or the common cold do not outweigh the risks for use of hydrocodone in these patients. TUSSIONEX is contraindicated in children younger than 6 years of age.

Geriatrics:

Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. TUSSIONEX should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Adjustment or Reduction of Dosage:

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including **TUSSIONEX**. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, goosebumps, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

Disposal

TUSSIONEX should be kept in a safe place, out of the sight and reach of children before, during and after use. TUSSIONEX should not be used in front of children, since they may copy these actions.

TUSSIONEX should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired TUSSIONEX should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms: Symptoms are similar to those of codeine overdose. Narcosis is usually present, sometimes associated with convulsions. Tachycardia, bradycardia, pupillary constriction, nausea and vomiting and respiratory depression can occur. The resinated formulation mitigates the immediate absorption of large quantities of hydrocodone; however, the absorption period may be prolonged.

Treatment: If respiration is severely depressed, administer the narcotic antagonist, naloxone. Adults: 0.4 mg to 2.0 mg by intravenous, intramuscular or subcutaneous routes and repeated at 2 to 3 minute intervals if necessary. Children: 0.01 mg/kg by intravenous, intramuscular or subcutaneous routes. Dosage may be repeated also at 2 to 3 minute intervals if necessary. Since the duration of action of hydrocodone in this formulation may exceed that of naloxone, the

patient should be kept under surveillance and repeated doses of naloxone should be administered as needed. Failure to obtain significant improvement after 2 to 3 doses suggests that causes other than narcotic overdosage may be responsible for the patient's condition.

If naloxone is unsuccessful, institute intubation and respiratory support and conduct gastric lavage in the unconscious patient.

Convulsions, sometimes seen in children, can be controlled by intravenous administration of benzodiazepines (e.g., diazepam).

STORAGE AND STABILITY

Store between 15 – 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:

Each 5 mL of yellow-coloured suspension contains: hydrocodone resin complex as bitartrate equivalent to 5 mg of hydrocodone, and phenyltoloxamine resin complex as citrate equivalent to 10mg of phenyltoloxamine.

Non-Medicinal Ingredients:

Alcohol 95%, D&C yellow No. 10, FD&C yellow No. 6, glycerin, methylparaben, peach flavour, pineapple flavour, propylene glycol, propylparaben, sorbitol solution 70%, washed hydrogen cycle resin, water, xanthan gum.

Packaging:

The suspension is available in bottles of 500 mL.

ACTION AND CLINICAL PHARMACOLOGY

Hydrocodone is a semi-synthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. As an antitussive, hydrocodone is approximately three times as potent as codeine on a weight for weight basis. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to inhibit coughing by interfering with the central modulation of afferent signals, thereby decreasing sensitivity of the cough centre to incoming stimuli.¹ In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. Hydrocodone can produce miosis, euphoria, physical and psychological dependence.

Phenyltoloxamine acts as competitive inhibitor of histamine². As with other antihistamines, it is possible that its sedative and tranquillizing characteristics may contribute to its antitussive

action.³ In addition, phenyltoloxamine in a similar manner to other antihistamines has been shown to potentiate the effects of hydrocodone.⁴

Both of the above active ingredients are complexed to an inert cation exchange resin. It has been shown that the resin itself does not impart any additional toxicity into the final product, and the drug-resin complex produces a higher LD₅₀ in mice and rats for the drug substances than when they are administered in their free or common salt form.⁵ The time required to cause death in rats following a certain lethal dose of drug as an ion-exchange resin complex was longer than when the drug was administered as a soluble salt. These two factors combine to make these resin complexes less toxic and, hence, safer to administer orally than the soluble salt form of the drug.

The benefits derived from the sustained release action resulting from this complexing and the apparent potentiation of the narcotic antitussive effect by phenyltoloxamine constitute the basis of action of this preparation.

In a study of 44 pulmonary tuberculosis patients, hydrocodone was found to be highly effective as a cough suppressant in diminishing the intensity and frequency of the cough. However, when the tracheobronchial secretions reach the irritable level, patients had no difficulty expelling sputum.⁶

Cass and Frederik studied the long-term (from 3 to 29 months) effectiveness of TUSSIONEX in the control of chronic cough due to asthma, bronchitis, tuberculosis, and emphysema⁷. Cough was suppressed without an increase in sputum. TUSSIONEX retained its effectiveness over the course of the study. The antitussive medication was limited to two doses daily. In only one instance was it necessary to stop the medicine because of drowsiness. There was no evidence of addiction.

TUSSIONEX has been found to provide excellent antitussive results lasting from eight to twelve hours^{3,4,8}. Townsend carried out a clinical study on 356 patients with cough associated with measles, upper respiratory infection, and bronchitis, and with so-called allergic cough, and nocturnal cough with emesis. One group of patients received an aqueous solution of hydrocodone 5 mg/mL plus phenyltoloxamine 10 mg/5 mL. The second group received a resinated complex of the same drugs in equivalent dosage concentrations. Eighty-four percent of the patients receiving the resinated formulation experienced cough suppression for 10 hours or more. For those receiving the aqueous solution, a 4-hour cough suppression was maximal and was attained in only 36% of these patients.³

It has been found that antihistamines may potentiate the antitussive effects of hydrocodone. In a laboratory study using mongrel dogs, Chan and Hays compared the relative cough-suppressant effectiveness of (a) codeine (2.2 mg/kg), (b) hydrocodone (3.7 mg/kg), (c) hydrocodone (0.37 mg/kg) as a resin complex, and (d) hydrocodone (0.37 mg/kg) plus phenyltoloxamine (2.2 mg/kg) both as resin complexes.⁴

The antitussive effects of both the codeine and hydrocodone solutions disappeared after 5 and 6 hours respectively. By 10 hours into the experiment, the resinated hydrocodone formulation had

also lost its effect, but the hydrocodone/phenyltoloxamine resin complex was still providing cough suppression even after 13 hours.

In a subsequent clinical study, these investigators noted that while TUSSIONEX effectively suppressed the hacking non-productive cough for 8 to 12 hours, the less frequent productive cough still appeared and performed its physiological role.

In another double-blind clinical study, Cass compared the relative clinical effectiveness of four antitussive preparations.

Each dose of the four preparations contained the following:

	mg/dose
1. Hydrocodone (as an ion exchange resin)	1.66
Phenyltoloxamine	5
Chlorpheniramine	3
Ephedrine	25
Guaiacol Carbonate	20
2. Hydrocodone	5
Homatropine methylbromide	1.5
Pyrilamine maleate	12.5
Ammonium chloride	60
Phenylephrine hydrochloride	10
Sodium citrate	85
3. Hydrocodone (as an ion exchange resin)	5
Phenyltoloxamine (as an ion exchange resin)	10
4. Codeine (as an ion exchange resin)	10
Phenyltoloxamine (as a controlled-release resin)	5
Chlorpheniramine (as a controlled-release resin)	3
Ephedrine (as a controlled-release resin)	25
Guaiacol Carbonate	20

The hydrocodone/phenyltoloxamine resin complex provided consistently superior results, compared to the other preparations, measured as the percent of maximal cough suppression achieved.⁹

Cass and Frederik (1958) in one double-blind study and one single blind study involving 127 chronic cough patients verified the 12-hour duration of cough relief provided by the TUSSIONEX formulation. Control of cough was again 2 to 3 times longer than for the same active ingredients in aqueous salt form.

PART II: SCIENTIFIC INFORMATION

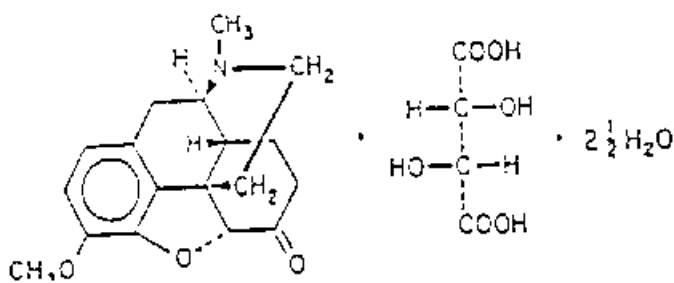
PHARMACEUTICAL INFORMATION

Drug Substance

1. Proper Name: Hydrocodone Bitartrate

Chemical Name: 4,5 α Epoxy - 3 methoxy -17- methylmorphinan -6- one tartrate.

Structural Formula:



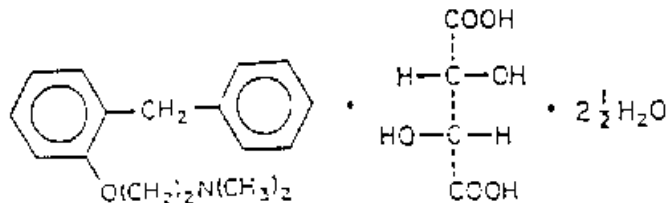
Molecular Weight: 494.5

Description: a white crystalline powder, soluble in water, melting point of 186°C to 190°C.

2. Proper Name: Phenyltoloxamine Citrate

Chemical Name: N,N - Dimethyl -2- (α - phenyl -0- tolyloxy) ethylamine.

Structural Formula:



Molecular Weight: 492.47

Description: a white crystalline powder, soluble in water, pH of 1% solution in water is 3.2 to 4.2, melting point 138°C to 140°C.

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3. Townsend EH. Prolonged cough suppression. New England Journal of Medicine 1958; 258:63-67.
4. Chan YT, Hays EE. A resin complex for prolonged antitussive effects. The American Journal of the Medical Sciences 1957; 234:207-212.
5. Becker BA, Swift JG. Effective reduction of the acute toxicity of certain pharmacological agents by use of synthetic ion exchange resins. Toxicology and Applied Pharmacology 1959; 1:42-54.
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8. Cass LJ, Frederik WS. The clinical evaluation of sustained released antitussives. Annals of Internal Medicine 1958; 49:151-160.
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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^NTUSSIONEX[®]

Controlled-Release Hydrocodone Resin Complex and Phenyltoloxamine Resin Complex

Read this carefully before you start taking **TUSSIONEX** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TUSSIONEX**.

Serious Warnings and Precautions

- **Even if you take **TUSSIONEX** as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life-threatening breathing problems while taking **TUSSIONEX**. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your **TUSSIONEX**. They could die from taking it. If a person has not been prescribed **TUSSIONEX**, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took **TUSSIONEX** while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
 - **has changes in their breathing (such as weak, difficult or fast breathing)**
 - **is unusually difficult to comfort**
 - **has tremors (shakiness)**
 - **has increased stools, sneezing, yawning, vomiting, or fever****Seek immediate medical help for your baby.**
- **Taking **TUSSIONEX** with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is TUSSIONEX used for?

TUSSIONEX is used for the temporary relief, in adults, of coughs, runny nose, and stuffy nose associated with:

- allergies, or
- the common cold

TUSSIONEX is not for use in patients younger than 18 years of age.

How does TUSSIONEX work?

TUSSIONEX contains two ingredients, hydrocodone bitartrate and phenyltoloxamine citrate.

Hydrocodone belongs to the family of cough medicines. It acts on the brain to suppress cough. Phenyltoloxamine belongs to the family of antihistamines. It relieves allergy symptoms.

What are the ingredients in TUSSIONEX?

Medicinal ingredients: hydrocodone bitartrate and phenyltoloxamine citrate

Non-medicinal ingredients: alcohol 95%, D&C yellow No. 10, FD&C yellow No. 6, glycerin, methylparaben, peach flavour, pineapple flavour, propylene glycol, propylparaben, sorbitol solution 70%, washed hydrogen cycle resin, water, xanthan gum.

TUSSIONEX comes in the following dosage forms:

Suspension, 5 mg hydrocodone bitartrate and 10 mg phenyltoloxamine citrate, per 5 mL

Do not use TUSSIONEX if:

- your doctor did not prescribe it for you
- you are allergic to hydrocodone, phenyltoloxamine, or any of the other ingredients in TUSSIONEX
- you have severe asthma, trouble breathing, or other breathing problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you have a brain tumor
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery
- you have uncontrolled high blood pressure
- you are under 6 years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TUSSIONEX. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- suffer from migraines
- have diabetes
- have glaucoma
- are planning to become pregnant

Other warnings you should know about:

Some people metabolize hydrocodone at a much faster rate than the general population. This may lead to accidental overdose. Stop taking TUSSIONEX and seek immediate medical help if you start feeling confused, have shallow breathing, or extreme sleepiness. If you know that you metabolize hydrocodone at a much faster rate, tell your doctor BEFORE starting this medication.

Stop taking TUSSIONEX and consult with your healthcare professional if:

- you get a high fever, rash or persistent headache along with the cough.
- your symptoms or cough worsen or continue for more than 7 days.

These could be signs of a serious condition.

Opioid dependence and addiction:

As with all opioids, taking TUSSIONEX may cause you to become dependent on it. Do not take more than the dose prescribed to you by your doctor. There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Breathing Problems:

TUSSIONEX is not recommended for anyone who has or is at risk for breathing problems such as:

- lung infections, or respiratory conditions
- neuromuscular disorders
- severe heart problems
- recent multiple traumas or extensive surgical procedures

Pregnancy, nursing, labour and delivery:

Opioids can be transferred to your baby through breast milk, or while still in the womb. TUSSIONEX can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your doctor will determine if the benefits of using TUSSIONEX outweigh the risks to your unborn baby or nursing infant.

If you are pregnant and are taking TUSSIONEX, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking TUSSIONEX. This may help avoid serious harm to your unborn baby.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to TUSSIONEX. TUSSIONEX can cause:

- drowsiness
- dizziness or
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

Serotonin Syndrome: TUSSIONEX can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take TUSSIONEX with certain antidepressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones.

You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off TUSSIONEX.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Tell your healthcare professional about all the medicines you take, including any drugs,

vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TUSSIONEX:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking TUSSIONEX. It can lead to:
 - drowsiness
 - unusually slow or weak breathing
 - serious side effects or
 - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by TUSSIONEX
- opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take TUSSIONEX with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used to prevent vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medication (such as beta blockers)
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort
- warfarin (such as coumadin) and other anticoagulants (used to prevent or treat blood clots)
- anti-retroviral drugs (used to treat viral infections)
- anti-fungal drugs (used to treat fungal infections)
- antibiotic drugs (used to treat bacterial infections)
- grapefruit juice

How to take TUSSIONEX:

- TUSSIONEX suspension should not be diluted with fluids or mixed with other drugs. Shake well before using.
- Your doctor will prescribe the lowest dose that works to control your symptoms.
- It is recommended that you only take TUSSIONEX for up to 7 days. If you need to take TUSSIONEX for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.
- TUSSIONEX may be taken with or without food.

Usual Dose:

Adults: 5 mL (1 teaspoonful) of suspension every 8 to 12 hours. Maximum daily dose is 10 mL of suspension. May be adjusted to individual requirements. Do not use TUSSIONEX for more than 7 days.

Review your symptoms regularly with your doctor to determine if you still need TUSSIONEX. Be sure to use TUSSIONEX only for the condition for which it was prescribed.

If you develop any side effect as a result of taking TUSSIONEX, tell your doctor immediately.

Stopping your Medication

If you have been taking TUSSIONEX for more than a few days, you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking TUSSIONEX. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your TUSSIONEX treatment, your body will become less used to TUSSIONEX. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking TUSSIONEX.

Refilling your Prescription for TUSSIONEX:

A new written prescription is required from your doctor each time you need more TUSSIONEX.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor.

Overdose:

If you think you have taken too much TUSSIONEX, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:

If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take two doses at the same time

What are possible side effects from using TUSSIONEX?

These are not all the possible side effects you may feel when taking TUSSIONEX. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Mild mental stimulation
- Convulsions
- Urinary retention
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using TUSSIONEX.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin			✓
Respiratory Depression: slow, shallow or weak breathing			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
Fast, Slow or Irregular Heartbeat: heart palpitations.		✓	
Low Blood Pressure: dizziness, fainting, light-headedness	✓		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

<p>Reporting Side Effects</p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> • Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or • Calling toll-free at 1-866-234-2345. <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>

Storage:

- **Keep unused or expired TUSSIONEX in a secure place to prevent theft, misuse or accidental exposure.**
- **Keep TUSSIONEX under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes TUSSIONEX, get emergency help right away.**
- Store at room temperature (15° - 30°C).

Disposal:

TUSSIONEX should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about TUSSIONEX:

- Talk to your healthcare professional
- Find the full prescribing information that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.sanofi.ca, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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