PRESCRIBING INFORMATION
INCLUDING PATIENT MEDICATION INFORMATION

N·282®
Acetylsalicylic Acid (375 mg), Codeine Phosphate (15 mg), Caffeine (15 mg*) Tablets

***equivalent to 30 mg caffeine citrate

N·292®
Acetylsalicylic acid (375 mg), Codeine Phosphate (30 mg), Caffeine (15 mg*) Tablets

***equivalent to 30 mg caffeine citrate

Analgesic
Antipyretic

PENDOPHARM, Division of Pharmascience Inc.
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Montréal, Québec
H4P 2T4

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TABLE OF CONTENT

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PART I: HEATLH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	**282** tablets Acetylsalicylic acid 375 mg Caffeine 15 mg (equivalent to 30 mg caffeine citrate) Codeine phosphate 15 mg	Corn Starch, Disodium EDTA, Ethylcellulose, FD&C Yellow No. 6 and D&C Yellow No. 10, Guar Gum, Hydrogenated Vegetable Oil, Monopotassium Citrate and Sodium Lauryl Sulfate
	292 tablets Acetylsalicylic acid 375 mg Caffeine 15 mg (equivalent to 30 mg caffeine citrate) Codeine phosphate 30 mg	Corn Starch, Disodium EDTA, Ethylcellulose, FD&C Yellow No. 6 Lake, Guar Gum, Hydrogenated Vegetable Oil, Monosodium Citrate and Sodium Lauryl Sulfate.

INDICATIONS AND CLINICAL USE

Adults

282 and 292 (Acetylsalicylic acid, Codeine Phosphate, Caffeine) are indicated for the symptomatic relief of mild to severe pain, fever and inflammation.

282 and 292 are not indicated as an as-needed (prn) analgesic.

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)

Regardless of clinical setting, codeine (including 282 and 292) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics; also, DOSAGE AND ADMINISTRATION).

The safety and efficacy of 282 and 292 has not been studied in the pediatric population. Therefore, the use of 282 and 292 is not recommended in patients over 12 and under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to the actives substances acetylsalicylic acid (ASA), codeine, caffeine 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 Product Monograph.

- Patients with gastrointestinal ulceration

- 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 mild pain that can be managed with other pain medications.

- 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.

- CYP2D6 ultra-rapid metabolizers who convert codeine into its active metabolite more rapidly and completely than other people (see WARNINGS AND PRECAUTIONS, Risk of Death in Ultra-Rapid Metabolizers of Codeine; SYMPTOMS AND TREATMENT OF OVERDOSAGE, Codeine)

- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

- Women who are breast-feeding, pregnant or during labour and delivery (see Serious Warnings and Precautions, and Warnings and Precautions).

- Pediatric patients (<18 years of age) who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome

- Patients with history of blood coagulation defects or receiving anticoagulant drugs or with severe anemia.

- Patients who had generalized urticaria, angioedema, severe rhinitis, laryngeal edema or shock precipitated by ASA or other NSAID's.

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 risks of overdose and death with immediate release opioid formulations, 282 and 292 (Acetylsalicylic acid, Codeine Phosphate, Caffeine tablets) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

282 and 292 pose risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing 282 and 292, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). 282 and 292 should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: *OVERDOSE*

Serious, life-threatening, or fatal respiratory depression may occur with use of 282 and 292. 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 282 and 292 or following a dose increase.

282 and 292 must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving 282 and 292 can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

Accidental ingestion of even one dose of 282 and 292, especially by children, can result in a fatal overdose of Codeine Phosphate (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

SERIOUS WARNINGS AND PRECAUTIONS

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of 282 and 292 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 282 and 292 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 central nervous system (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 282 and 292 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

Patients should be instructed not to give 282 and 292 (Acetylsalicylic acid, Codeine Phosphate, Caffeine) tablets to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. 282 and 292 should be stored securely to avoid theft or misuse.

282 and 292 should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking 282 and 292 as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of Codeine Phosphate can occur at particularly high doses. A Codeine Phosphate dose reduction or change in opioid may be required.

Patients should be counselled to discontinue codeine products and to seek urgent medical help at the earliest sign of codeine toxicity including symptoms such as confusion, shallow breathing, or extreme sleepiness which may be life threatening.

Excessive and prolonged therapy has been associated with nephropathy.

ASA is one of the most frequent causes of accidental poisoning in toddlers and infants. ASA containing preparations should therefore be kept well out of the reach of all children.

Salicylates should be administered with caution to patients with asthma and other allergic conditions, with bleeding tendencies, or with hypoprothrombinemia or in patients prone to dyspepsia or known to have a lesion of the gastric mucosa. It should not be administered to patients with hemophilia or other hemorrhagic disorders or to those with intolerance to ASA (especially ASA-sensitive asthmatics). Caution is necessary when renal or hepatic function is impaired.

Salicylates can produce changes in the thyroid function tests.

ASA may precipitate or worsen attacks of gout.

Do not take this medicine for 5 to 7 days before any surgery, including dental surgery, unless otherwise directed by your physician or dentist.

Usage of this medication may cause drowsiness, dizziness or light-headedness, or false sense of well-being. If it occurs, lying down for a while may help reduce dizziness or light-headedness. Getting up slowly may also help lessen these two side effects.

Abuse and Misuse

Like all opioids, 282 and 292 are a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, 282 and 292 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.

Opioids, such as 282 and 292, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

282 and 292 is intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Cardiovascular

Codeine Phosphate administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of 282 and 292.

The use of 282 and 292 in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of 282 and 292 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.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur 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 analgesic 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).

Use in Drug and Alcohol Addiction

282 and 292 are opioids 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 pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to 282 or 292; extreme caution and awareness is warranted to mitigate the risk.

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

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

Use of 282 and 292 is contraindicated in pregnant women (see CONTRAINDICATIONS).

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol)
282 and 292 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.

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 other CNS depressant drugs with opioid analgesics (see DRUG INTERACTIONS). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when 282 and 292 is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advised 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).

282 and 292 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).
Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics.

Should pain suddenly subside, these effects may rapidly become manifest.

Head Injury
The respiratory depressant effects of Codeine Phosphate, 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, Codeine Phosphate may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, Codeine Phosphate must be used with extreme caution and only if it is judged essential (see CONTRAINDICATIONS).

Risk of Death in Ultra-Rapid Metabolizers of Codeine
Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labelled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing (see also Labour, Delivery and Nursing Women in Special Populations). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. When physicians prescribe codeine-containing drugs, they should choose the lowest effective dose for the shortest period of time and inform their patients about these risks and the signs of morphine overdose (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

Serotonin Syndrome
282 and 292 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 serotoninergic 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. 282 and 292 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).

Peri-Operative Considerations

282 and 292 are not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with 282 and 292 for at least 24 hours before the operation and 282 and 292 should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if 282 and 292 is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief.

The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Codeine Phosphate and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

282 and 292 should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Psychomotor Impairment

Respiratory Depression

282 and 292 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 Codeine Phosphate with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

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. Codeine Phosphate 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 282 and 292, 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 282 and 292 and following dose increases.

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.

To reduce the risk of respiratory depression, proper dosing and titration of 282 and 292 are essential. Overestimating the 282 and 292 dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and DOSAGE AND ADMINISTRATION).

Codeine

Respiratory depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children with obstructive sleep apnea who are

treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine-containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome (see CONTRAINDICATIONS).

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 pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with 282 and 292, as in these patients, even usual therapeutic doses of 282 and 292 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 282 and 292 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
Codeine Phosphate 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. Studies in humans have not been conducted. 282 and 292 crosses the placental barrier and is contraindicated in pregnant women.

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

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.

Labour, Delivery and Nursing Women
Since opioids can cross the placental barrier and are excreted in breast milk, 282 and 292 are contraindicated in nursing women and during labour and delivery. 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 282 and 292 are used in this population.

Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. However, some women are ultra-rapid metabolisers of codeine (see CONTRAINDICATIONS, Ultra-Rapid Metabolisers of Codeine; and WARNINGS AND PRECAUTIONS, Risk of Death in Ultra-Rapid Metabolizers of Codeine). These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breast-fed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death in nursing infants.

Since there is a risk of infant exposure to codeine and morphine through breast milk, 282 and 292 is contraindicated in breast-feeding. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about any use of codeine during breast-feeding.

ASA does not appear to have any teratogenic effects.

Chronic, high-dose salicylate therapy late in pregnancy may result in increased risk of maternal or fetal hemorrhage (see WARNINGS).

High doses (3 g daily) of ASA during pregnancy may lengthen the gestation and parturition time. This effect has also been described with NSAIDs which inhibit prostaglandin synthesis. They may also prolong and complicate labor and delivery. Studies in animals have shown that ASA and caffeine causes birth defects. ASA and opioid analgesics cross the placenta.

Pediatrics (< 18 years of age)
Regardless of clinical setting, codeine (including 282 and 292) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see INDICATIONS, and DOSAGE AND ADMINISTRATION). The safety and efficacy of 282 and 292 have not been studied in the pediatric population. Therefore, use of 282 and 292 is not recommended in patients under 18 years of age.

Use of ASA may be associated with the development of Reye's syndrome in children and teenagers with acute febrile illnesses, especially influenza and varicella. Although a direct causal relationship has not been established, salicylates should not be administered to, or used by, children or teenagers who have chicken pox or manifest flu symptoms before a physician or pharmacist is consulted about Reye's syndrome, a rare and serious illness.

Pediatric patients are especially susceptible to overdose of caffeine and its adverse Central Nervous System (CNS) effects.

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).

The elderly may be more susceptible to the toxic effects of salicylates, possibly because of decreased renal function. Inhibiting production of renal prostaglandins by ASA and other NSAIDs can result in an acute reduction in renal blood flow with subsequent deterioration of renal function.

Certain prostaglandins may act as renal vasodilators if renal blood flow is reduced. Individuals at risk are those with pre-existing renal dysfunction, heart failure, and liver cirrhosis and ascites. The first two conditions occur more commonly in the elderly and may also depend on renal prostaglandins to act as vasodilators.

Opioids may increase the risk of adverse effects especially respiratory depression.

Patients with Hepatic Impairment
Caution is necessary when hepatic function is impaired (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY sections).

Patients with Renal Impairment
Caution is necessary when hepatic function is impaired (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY sections).

ADVERSE REACTIONS

Adverse effects of 282 and 292 (Acetylsalicylic acid, Codeine Phosphate, Caffeine) tablets are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most frequently observed adverse effects of 282 and 292 are:

Gastrointestinal:
Dyspepsia, heartburn, nausea, vomiting, constipation, diarrhea, abdominal pain, gastrointestinal ulceration and bleeding.

Ear and Labyrinth:
Tinnitus, hearing loss, dizziness.

Hematologic:
Anemia, leukopenia, thrombocytopenia, hypoprothrombinemia, purpura.

Dermatologic and hypersensitivity:
Urticaria, angioedema, pruritus, various skin eruptions, asthma and anaphylaxis.

Hepatic:
Reversible hepatotoxicity particularly in patients with juvenile rheumatoid arthritis and systernic lupus erythematosus.

Miscellaneous:
Mental confusion, headache, drowsiness, sweating and thirst, palpitation, excessive diuresis.

CNS Depression:

Coma, cardiovascular collapse, respiratory failure, vertigo, muscle tremor, sensory disturbances, nervousness, insomnia.

The potential for habituation may occur.

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.

Sedation

Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced, and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting

Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation

Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

DRUG INTERACTIONS

Overview

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants
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. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment). 282 and 292 should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Salicylates increase the effects of oral anticoagulant. Caution is necessary when salicylates and anticoagulants are prescribed concurrently. Also, salicylates may depress the concentration of prothrombin in the plasma.

Salicylates may potentiate sulfonylurea hypoglycemic agents. Large doses of salicylates may have a hypoglycemic action, and thus, affect the insulin requirements of diabetics.

Although salicylates in large doses are uricosuric agents, smaller amounts may depress uric acid clearance and thus decrease the uricosuric effects of probenecid, sulfinpyrazone and phenylbutazone.

Sodium excretion produced by spironolactone may be decreased in the presence of salicylates.

Salicylates also retard the renal elimination of methotrexate

Salicylates may potentiate ototoxic agents (vancomycin, others). Concurrent or sequential administration of these medications with salicylate should be avoided because hearing loss may occur and may progress to deafness even after discontinuation of the medication: although these effects may be reversible, but usually are permanent.

Salicylates decrease the clearance of zidovudine, leading to potentiation of zidovudine toxicity: concurrent use of ASA and zidovudine should be avoided.
Care should be observed in the use of codeine although tolerance and addiction to its use are rare.

Coadministration of codeine phosphate 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).

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

282 and 292 should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

282 and 292 must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving 282 and 292 can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS)

282 and 292 should not be used in children less than 18 years old. Regardless of clinical setting, codeine (including 282 and 292) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see INDICATIONS AND CLINICAL USE).

282 and 292 initial dosing should be reduced in patients with hepatic or renal impairment.

For acute pain, it is recommended that 282 and 292 be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

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 282 and 292 is 12 and 6 tablets respectively, which is 180 mg codeine (27 morphine milligram equivalent). Each patient should be assessed for their risk prior to prescribing 282 and 292, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of 282 and 292 (see DOSAGE AND ADMINISTRATION, Adjustment or reduction of Dosage)

Dosing Considerations

282 and 292 (Acetylsalicylic acid (375 mg), Codeine Phosphate, Caffeine tablets) should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see WARNINGS AND PRECAUTIONS, Peri-operative Considerations).

282 and 292 are not indicated for rectal administration.

282 and 292 may be taken with or without food with a glass of water.

Recommended Dose and Dosage Adjustment

282 and 292 should be prescribed at the lowest effective dose for the shortest period of time. Dosing should be as needed every 4 to 6 hours and not on scheduled intervals.

282
ADULT: One (1) or two (2) tablets with a large glass of water (250 mL) every 4 to 6 hours, as required.

292
ADULT: One (1) tablet with a large glass of water (250 mL) every 4 to 6 hours, as required.

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. 282 and 292 should be initiated at a low dose and slowly titrated to effect (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Dose Titration
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage
Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including 282 and 292. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, 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.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see WARNINGS AND PRECAUTIONS). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Disposal

282 and 292 should be kept in a safe place, out of the sight and reach of children before, during and after use. 282 and 292 should not be used in front of children, since they may copy these actions.

282 and 292 should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired 282 and 292 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.

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.

OVERDOSAGE

Symptoms

In mild overdosage, these may include rapid and deep breathing, severe drowsiness, nausea, vomiting (leading to alkalosis), stomach pain, diarrhea, headache, hyperpnea, vertigo, tinnitus, flushing, sweating, thirst and tachycardia. High blood levels of ASA lead to acidosis. Severe cases may show fever, hemorrhage, bloody urine, excitement, confusion, hallucinations, severe nervousness, convulsions or coma, and respiratory failure.

Codeine and related narcotic analgesics depress respiration by an action on the brain stem respiratory centers.

Other symptoms of overdose may include euphoria, dysphoria, and visual disturbances.

Treatment

Treatment is essentially symptomatic and supportive. Administer water, activated charcoal and ipecac syrup unless the patient is comatose, and remove by gastric lavage or emesis. Patients with mild intoxication should be encouraged to drink plenty of fluids. In patients with more severe intoxication forced alkaline diuresis may be required. Plasma electrolytes, especially potassium, and the acid-base balance should be monitored regularly. In the presence of cardiac or renal impairment or in very severe intoxication, hemodialysis or hemoperfusion may need to be considered.

Respiratory depression may require artificial intubation measures aimed at supporting respiration and the administration of a narcotic antagonist, e.g., naloxone.

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

ACTION AND CLINICAL PHARMACOLOGY

Central Nervous System
Codeine Phosphate produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

Codeine Phosphate depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Codeine Phosphate causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of codeine overdose.

Gastrointestinal Tract and Other Smooth Muscle
Codeine Phosphate causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System
Codeine Phosphate may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Endocrine System
Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System
In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Special Populations and Conditions

Pediatrics
Individuals under 18 years of age should not take 282 and 292 tablets /other formulations.

Geriatrics
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 another drug therapy.

Hepatic Impairment
Caution is necessary when hepatic function is impaired.

Renal Impairment
Caution is necessary when renal function is impaired.

STORAGE AND STABILITY

Store between 15°C - 30°C. Protect from light and moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Available in bottles of 500 tablets. Each **282** tablet is round, biconvex, orange-yellow, with a "ø" on one side and plain on other side and contains the following medicinal ingredients:

Acetylsalicylic add	375 mg
Caffeine	15 mg (equivalent to 30 mg caffeine citrate)
Codeine phosphate	15 mg

Non-medicinal ingredients (in alphabetical order): Corn Starch, Disodium EDTA, Ethylcellulose, FD&C Yellow No. 6 and D&C Yellow No. 10, Guar Gum, Hydrogenated Vegetable oil, Monopotassium Citrate, Sodium Lauryl Sulfate.

Available in bottles of 50 and 500 tablets. Each **292** tablet is round, biconvex, orange, with an ellipse separated by a score line in the center on one side and "292" on the other side and contains the following medicinal ingredients:

Acetylsalicylic add	375 mg
Caffeine	15 mg (equivalent to 30 mg caffeine citrate)
Codeine phosphate	30 mg

Non-medicinal ingredients (in alphabetical order): Corn Starch, Disodium EDTA, Ethylcellulose, FD&C Yellow No. 6 Lake, Guar Gum, Hydrogenated Vegetable Oil, Monosodium Citrate and Sodium Lauryl Sulfate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

The components of 282 (Acetylsalicylic Acid (375 mg), Codeine Phosphate (15 mg), Caffeine (15 mg*)) and 292 (Acetylsalicylic acid (375 mg), Codeine Phosphate (30 mg), Caffeine (15 mg*)) tablets have the following formula:

Drug Substance: **Acetylsalicylic Acid**

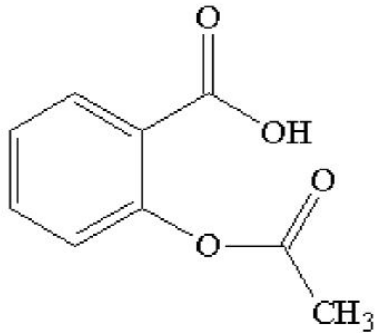
Proper name: Acetylsalicylic acid (ASA)

Chemical name: Benzoic acid, 2-(acetylocy)-

Molecular formula: $C_9H_8O_4$,

Molecular mass: 180.16 g/Mol

Structural formula:



Physicochemical Properties

Description: ASA is an odourless white, needle-like crystalline or powdery substance. When exposed to moisture, ASA hydrolyzes into salicylic and acetic acids, and gives off a vinegary-odour.

Solubility: It is highly lipid soluble and slightly soluble in water.

Drug Substance: **Codeine Phosphate**

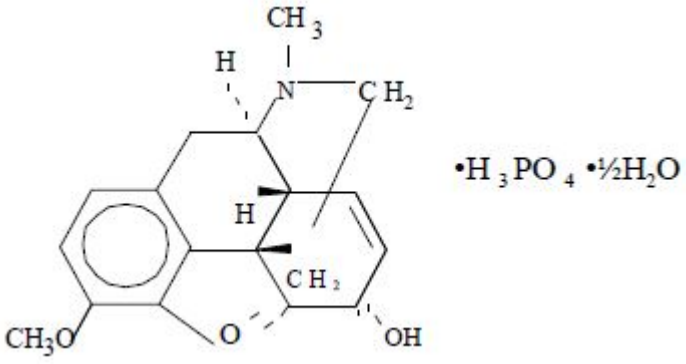
Proper name: Codeine Phosphate

Chemical name: 7, 8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate

Molecular formula: $C_{18}H_{21}NO_3 \bullet H_3PO_4 \bullet ½H_2O$,

Molecular mass: 406.4 g/Mol

Structural formula:



Physicochemical Properties

Description: Hemihydrate, fine, white, needle-shaped crystals; a crystalline powder; odourless, affected by light.

Solubility: Freely soluble in water, very soluble in hot water, slightly soluble in alcohol, more soluble in boiling alcohol.

Drug Substance: **Caffeine**

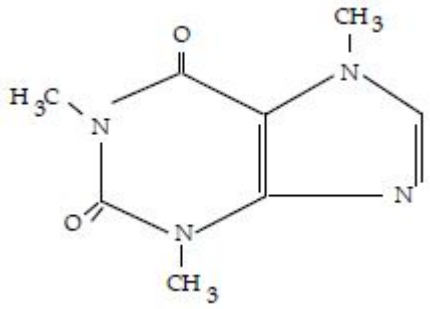
Proper name: Caffeine

Chemical name: 3,7-dihydro-1,3,7-trimethyl-1H-purine-2, -6-dione; 1,3,7-trimethylxanthine; 1,3,7-trimethyl-2,6-dioxopurine

Molecular formula: $C_8H_{10}N_4O_2$,

Molecular mass: 194.19 g/Mol

Structural formula:



Physicochemical Properties

Description: White powder or white, glistening needles, usually matted; odorless and has a bitter taste.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

282 and 292
(Acetylsalicylic acid, Codeine Phosphate, Caffeine tablets)

Read this carefully before you start taking 282 or 292 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 282 and 292.

Serious Warnings and Precautions

- **Even if you take 282 and 292 as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**

- **When you take 282 and 292, it must be swallowed whole. Do not cut, break, crush, chew, dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.**

- **You may get life-threatening breathing problems while taking 282 and 292. 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 282 and 292. They could die from taking it. If a person has not been prescribed 282 and 292, taking even one dose can cause a fatal overdose. This is especially true for children.**

- **If you took 282 and 292 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 282 and 292 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 are 282 and 292 used for?
282 and 292 are used to manage your pain in adults.

How does 282 and 292 works?
282 and 292 consist of codeine, acetylsalicylic acid (ASA), and caffeine.

Codeine is a painkiller belonging to the class of drugs known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain. ASA reduces pain, fever and inflammation. Caffeine is a mild stimulant which may enhance pain-relieving effects.

What are the ingredients in 282 and 292?
282 tablets
Medicinal ingredients:

Acetylsalicylic add	375 mg
Caffeine	15 mg (equivalent to 30 mg caffeine citrate)
Codeine phosphate	15 mg

Non-medicinal ingredients (in alphabetical order): Corn Starch, Disodium EDTA, Ethylcellulose, FD&C Yellow No. 6 and D&C Yellow No. 10, Guar Gum, Hydrogenated Vegetable Oil, Monopotassium Citrate and Sodium Lauryl Sulfate.

292 tablets
Medicinal ingredients

Acetylsalicylic add	375 mg
Caffeine	15 mg (equivalent to 30 mg caffeine citrate)
Codeine phosphate	30 mg

Non-medicinal ingredients (in alphabetical order): Corn Starch, Disodium EDTA, Ethylcellulose, FD&C Yellow No. 6 Lake, Guar Gum, Hydrogenated Vegetable Oil, Monosodium Citrate and Sodium Lauryl Sulfate.

282 and 292 comes in the following dosage forms:
Tablets

Do not use 282 and 292 if:
- your doctor did not prescribe it for you
- you are allergic to Acetylsalicylic acid, Codeine Phosphate, Caffeine or any of the other ingredients in 282 and 292
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart 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 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 allergic to any other non-steroidal anti-inflammatory drugs (NSAIDs) or other pain relievers/fever reducers
- you have an ulcer or a history of ulcers
- you are prone to bleeding

- you are going to have, or recently had, a planned surgery
- have been told by your doctor that you break down codeine rapidly. This can lead to codeine overdose even at the usual adult dose.
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding. The use of codeine-containing products while breast-feeding may harm your baby. If you breastfeed and take 282 and 292, seek immediate medical care for your baby if they are overly drowsy, sedated, have difficulty breast-feeding, have breathing difficulties, and are floppy (have decreased muscle tone). This is very serious for the baby and can lead to death. Tell the baby's doctor that you are breastfeeding and took 282 and 292.
- you are less than 18 years old and are having (or have recently had) your tonsils or adenoids removed because of frequent interruption of breathing during sleep
- you are less than 12 years old

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take 282 and 292. 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 low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- suffer from migraines
- are pregnant or planning to become pregnant
- are planning to become pregnant
- Suffer from migraines

Other warnings you should know about:

Some people metabolize codeine at a much faster rate than the general population, which may lead to accidental overdose, if this should happen to you, seek help immediately (see Overdose, for symptoms of overdose and what to do if it happens). If you know that you metabolize codeine rapidly, tell your doctor BEFORE starting this medication.

282 and 292 are 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

Opioid dependence and addiction

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.

Pregnancy, nursing, labour and delivery

If contraindicated, add: Do not use 282 and 292 while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. 282 and 292 can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking 282 and 292, 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 taking282 and 292. 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 282 and 292. 282 and 292 can cause:

- drowsiness
- dizziness or
- light-headedness

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

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 282 and 292.

Serotonin Syndrome
282 and 292 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 282 and 292 with certain anti-depressants 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.

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 282 and 292:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking 282 or 292. 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 282 or 292
- other 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 282 and 292 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 for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take 282 and 292:
Swallow whole. Do not cut, break, crush, chew or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.

Usual Adult Starting Dose:
Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take 282 and 292 for up to 7 days. If you need to take 282 and 292 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.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take 282 and 292 for up to 7 days. If you need to take 282 and 292 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.

Usual Adult Dose:
One (1) or two (2) tablets with a large glass of water (250 mL) every 4 to 6 hours, as required.

Review your pain regularly with your doctor to determine if you still need 282 or 292. Be sure to use 282 and 292 only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking 282 and 292, tell your doctor immediately.

Stopping your Medication
If you have been taking 282 or 292 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 282 and 292. 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 opioid treatment, your body will become less used to opioids. 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 282 and 292.

Refilling your Prescription for 282 and 292
A new written prescription is required from your doctor each time you need more 282 and 292. Therefore, it is important that you contact your doctor before your current supply runs out.

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 for your pain management.

Overdose:

If you think you have taken too much 282 or 292, 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 miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using 282 and 292?
These are not all the possible side effects you may feel when taking 282 or 292. 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
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using 282 or 292.

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.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html#a1) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

- Keep unused or expired 282 and 292 in a secure place to prevent theft, misuse or accidental exposure.
- Store between 15°C - 30°C. Protect from light and moisture
- **Keep 282 and 292 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 282 and 292, get emergency help right away.**

Disposal:

282 and 292 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 282 and 292:

- Talk to your healthcare professional
- Find the full product monograph 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.pendopharm.ca, or by calling 1-888-550-6060.

This leaflet was prepared by Pendopharm, Division of Pharmascience Inc.

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