Prescribing Information

Including Patient Medication Information

ⓃMERSYNDOL® with codeine

Acetaminophen, codeine phosphate and doxylamine succinate tablets

325 mg, 8 mg and 5 mg

Tablet

Analgesic, Antihistamine

sanofi-aventis Canada Inc.
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Recent Major Label Changes

7 WARNINGS AND PRECAUTIONS, General	2025-02
7 WARNINGS AND PRECAUTIONS, General	2025-09

Table of Contents

Certain sections (as indicated in section 2.1 of the PM Guidance) or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1 Indications

MERSYNDOL with codeine is indicated in patients older than 18 years of age for relief of headaches, cold symptoms, muscular aches and pains.

2 Contraindications

- Hypersensitivity to acetaminophen, doxylamine, codeine or other opioids, or to any of the non-medicinal ingredients (see 6 Dosage Forms, Strengths, Composition, and Packaging).
- Concomitant treatment with Monoamine inhibitors (MAOIs) or treatment within 14 days of stopping MAOIs (see 9 Drug Interactions)
- Pre-existing respiratory depression or insufficiency, acute asthma attacks or other chronic lung diseases.
- During last trimester of pregnancy, in the event of impending childbirth, in case of premature birth or breastfeeding (see **Error! Reference source not found. Error! Reference source not found.**, Special Populations, Pregnant Women and Breast-feeding)
- Risk of blocked intestines
- Head injury
- Seizures
- Glucose-6-phosphate-dehydrogenase deficiency
- Patients for whom it is known they are CYP2D6 ultra-rapid metabolisers
- Children (aged below 18 years) who undergo tonsillectomy and/or adenoidectomy to treat obstructive sleep apnea due to an increased risk of developing serious and life-threatening adverse reactions.
- Severe hepatocellular insufficiency
- Children below 12 years of age

4 Dosage and Administration

4.2 Recommended Dose and Dosage Adjustment

Adults (18years and older): 1 - 2 tablets every 4 to 6 hours as required. Do not exceed 12 tablets in a 24-hour period.

5 Overdose

Symptoms of overdosage

Acetaminophen:

Elderly persons, small children, patients with liver disorders, chronic alcohol consumption or chronic malnutrition, as well as patients concomitantly treated with enzyme-inducing drugs are at an increased risk of intoxication, including fatal outcome.

Nausea, vomiting, anorexia, pallor, sweating, abdominal pain, generally appear during the first 24 hours of overdosage with acetaminophen. This initial period is frequently followed by an asymptomatic phase after which hepatic damage may become evident.

Increased levels of hepatic transaminases, lactate dehydrogenase and bilirubin with a reduction in prothrombin level can appear 12 to 48 hours after acute overdosage.

Overdosage with acetaminophen may cause hepatic cytolysis which can lead to hepatocellular insufficiency, jaundice, gastrointestinal bleeding, metabolic acidosis, hypoglycemia, encephalopathy, myocardial damage, disseminated intravascular coagulation, cardiomyopathy, coma and death. It can also lead to pancreatitis, acute renal failure and pancytopenia.

Factors contributing to an accurate evaluation of toxicity include: the amount of drug ingested and more significantly, the serum acetaminophen concentration measured optimally, after 4 hours of ingestion. When serum determinations of acetaminophen are above 990 μmol/L at 4 hours, above 460 μmol/L at 8 hours or above 260 μmol/L at 12 hours following the estimated time of ingestion, the patient is at risk of liver damage and antidotal therapy should be instituted immediately.

An additional reliable indicator of possible hepatic injury is the serum half-life. The normal half-life of acetaminophen in a healthy adult is approximately 2 hours. If the serum half-life exceeds 4 hours, it can be assumed that hepatic necrosis will occur; if the half-life exceeds 12 hours hepatic coma is a likely possibility.

Codeine phosphate:

Symptoms: May result in euphoria, dysphoria, visual disturbances, hypotension and coma or death from respiratory depression.

The ingestion of very high doses can cause initial excitation, anxiety, insomnia followed by drowsiness in certain cases, areflexia progressing to stupor or coma, headache, miosis, alterations in blood pressure, arrhythmias, dry mouth, hypersensitivity reactions, cold clammy skin, bradycardia, tachycardia, convulsions, gastrointestinal disorders, nausea, vomiting and respiratory depression.

Severe intoxication can lead to apnoea, circulatory collapse, cardiac arrest and death.

In an evaluation of codeine intoxication in children, symptoms ranked by decreasing order of frequency included: sedation, rash, miosis, vomiting, itching, ataxia and swelling of the skin. Respiratory failure may occur. Blood concentrations of codeine ranged from 1.4 to 5.6 μg/mL in 8 adults whose deaths were attributed primarily to codeine overdosage.

Doxylamine succinate:

Symptoms: Dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion, restlessness or tachycardia.

Reactions associated with doxylamine succinate overdosage may vary from central nervous system depression to stimulation. Stimulation is particularly likely in children; insomnia, nervousness, euphoria, irritability, tremors, nightmares, hallucinations and convulsions can occur. Atropine-like signs and symptoms; dry mouth; mydrasis; fixed, dilated pupils; flushing; and gastrointestinal symptoms may also occur.

Severe rhabdomyolysis after doxylamine succinate overdose has been reported in humans.

Treatment of overdosage

Related to acetaminophen

Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention.

Treatment involves gastric aspiration and lavage, preferably within 4 hours of ingestion.

Determinations of the plasma concentration of acetaminophen are recommended. Plasma concentration of acetaminophen should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Where acetaminophen intoxication is suspected, intravenous administration of SH group donators such as N-acetylcysteine within the first 10 hours after ingestion is indicated. Although N-acetylcysteine is most effective if initiated within this period, it can still offer some degree of protection if given as late as 48 hours after ingestion; in this case, it is taken for longer.

Further measures will depend on the severity, nature and course of clinical symptoms of acetaminophen intoxication and should follow standard intensive care protocols.

Related to Codeine

In general, treatment should be symptomatic: re-establish adequate respiratory exchange by ensuring a clear airway and using mechanical ventilation.

The opioid antagonist naloxone hydrochloride is an antidote to respiratory depression and must be administered intravenously.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-Medicinal Ingredients

oral	White, flat-faced, bevelled-edged tablet with stylized “S” embossed on one side. The tablet is round and contains: 325 mg acetaminophen; 8 mg codeine phosphate; 5 mg doxylamine succinate.	Croscarmellose sodium, magnesium stearate, microcrystalline cellulose, pregelatinized starch, povidone and silicon dioxide.

Bisulfites-, gluten-, lactose-, parabens- and tartrazine- free.

Available in HDPE bottles of 100 tablets.

7 Warnings and Precautions

General

Both doxylamine and codeine may cause drowsiness in some patients. MERSYNDOL with codeine may cause drowsiness, disturbances of visuomotor coordination and visual acuity, impairing the mental and/or physical ability required for the performance of potentially dangerous tasks, such as driving vehicles or using machines. Patients should be cautioned not to operate vehicles or hazardous machinery until their response to the drug has been determined. Avoid alcohol.

Related to codeine phosphate

Extensive use of analgesics to relieve headaches or migraines, especially at high doses, may induce headaches that must not be treated with increased doses of the drug. In such cases the analgesic should not continue to be taken without medical advice.

Codeine is metabolized by the liver enzyme CYP2D6 into morphine, its active metabolite. In ultra-rapid opiate/codeine metabolisers, there is an increased risk of developing opioid toxicity even at low doses. Prevalence of CYP2D6 ultra-rapid metabolisers differs according to racial and ethnic group and has been estimated at 1.2% to 2% in Asians, 1% to 6.5% in Caucasians, 3,4% to 6.5% in African Americans, and 29% in African/Ethiopians. Symptoms of opioid toxicity include nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression.

If a patient has a deficiency or is completely lacking the CYP2D6 enzyme an adequate therapeutic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency.

Opioid-Induced Hyperalgesia or Allodynia
Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain (hyperalgesia), or an increase in sensitivity to pain (allodynia). This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect. Symptoms of OIH include increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). The pain experienced may be at the same location of the underlying pain or can be more generalized or widespread in nature. These symptoms may suggest the occurrence of OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.
If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of

the current opioid analgesic, or opioid rotation (safety switching the patient to a different opioid moiety).

Concomitant use of opioids, including codeine, with benzodiazepines may result in sedation, respiratory depression, coma, and death (see 9 Drug Interactions). Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate. If a decision is made to prescribe codeine concomitantly with benzodiazepines, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of sedation and respiratory depression.

Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma, and death (see 9 Drug Interactions). Concomitant use with alcohol is not recommended.

Concomitant use of opioids including codeine, with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death. Concomitant use with gabapentinoids is not recommended.

MERSYNDOL with codeine should only be used after careful risk-benefit assessment in case of:

- Opioid dependence
- Chronic constipation
- Conditions with elevated intracranial pressure and head trauma. Codeine can increase the pressure of cerebrospinal fluid and may increase the respiratory depressant effect. Like other narcotics, it causes adverse reactions that can obscure the clinical course of patients with head injury.
- Impaired consciousness
- Compromised respiratory function (due to emphysema, kyphoscoliosis, severe obesity) and chronic obstructive airway disease

Patients who have had a cholecystectomy should be treated with caution. The contraction of the sphincter of Oddi can cause symptoms resembling those of myocardial infarction or intensify the symptoms in patients with pancreatitis.

Use with caution in patients with convulsive disorders.

Monitoring after prolonged use should include blood count, liver function and renal function.

MERSYNDOL with codeine must be administered with caution in certain patients, such as those who present with impaired cardiac, hepatic or renal function, hypotension, and in cases of benign prostatic hyperplasia, urethral stenosis, adrenal insufficiency (Addison's disease), hypothyroidism, multiple sclerosis, chronic ulcerative colitis, gallbladder conditions and diseases that present with reduced respiratory capacity such as emphysema, kyphoscoliosis and severe obesity.

Elderly people may be more sensitive to the effects of this medicinal product, especially respiratory depression; they are also more prone to suffering hypertrophy, prostatic obstruction and age-related kidney impairment and they have a higher likelihood of undesirable effects due to opioid-induced urinary retention.

<u>Related to acetaminophen</u>

To avoid the risk of overdose, check that acetaminophen is absent from the composition of other medicinal products taken concomitantly.

MERSYNDOL with codeine should be used with caution and upon medical advice in patients with the following pre-disposing factors:

- Mild to moderate hepatocellular insufficiency
- Severe renal insufficiency and sepsis
- Chronic alcohol use including recent cessation of alcohol intake
- Malnutrition and other sources of low glutathione reserves
- Glucose-6-phosphate-dehydrogenase deficiency
- Gilbert's syndrome

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness pre-disposing factors (see above) who were treated with acetaminophen at therapeutic dose for a prolonged period or combination of acetaminophen and flucloxacillin. Symptoms of HAGMA may include serious breathing difficulties with deep rapid breathing, drowsiness, nausea and vomiting. Prompt discontinuation of acetaminophen and close monitoring is recommended if symptoms of HAGMA appear. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Related to Codeine and Doxylamine

MERSYNDOL with codeine must be administered with caution in patients with:

- -Benign prostatic hyperplasia

Related to Doxylamine:

MERSYNDOL with codeine must be administered with caution in patients with:

- -Urinary retention
- -Susceptibility to angle closure glaucoma

Related to System Organ Class:

Gastrointestinal

Codeine phosphate may cause constipation.

Hematologic

Agranulocytosis may occur with acetaminophen (see 8 Adverse Reactions).

Hepatic/Biliary/Pancreatic

Hepatotoxicity may occur with acetaminophen even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction (see 8 Adverse Reactions and 9 Drug Interactions).

Immune

Allergic reactions are rare with acetaminophen but have occurred. Patients with salicylate induced urticaria or angioedema can suffer cross reactivity with acetaminophen.

Monitoring and Laboratory Tests

Intake of acetaminophen may affect the laboratory determination of uric acid by phosphotungstic acid and of blood glucose by glucose oxidase-peroxidase.

Psychiatric

Products containing codeine should not be given for prolonged periods. Codeine may be habit-forming.

Codeine has a primary potential for dependence. Tolerance, psychological and physical dependence to codeine develop with prolonged use in high doses, with withdrawal symptoms after sudden discontinuation of the drug. Cross-tolerance with other opioids exists. Rapid relapses can be expected in patients with pre-existing opiate dependence (including those in remission).

Administration must be discontinued gradually after prolonged treatments.

There have been reports of drug abuse with codeine, including cases in children and adolescents. Caution is particularly recommended for use in children, adolescents, young adults, and in patients with a history of drug and/or alcohol abuse.

Renal

Papillary renal failure may occur with acetaminophen (see 8 Adverse Reactions).

Respiratory

In patients with asthma or pulmonary emphysema, indiscriminate use may precipitate respiratory insufficiency resulting from increased viscosity of bronchial secretions and suppression of the cough reflex (see **Error! Reference source not found. Error! Reference source not found.**).

<u>Use of Codeine in children population and risk of Respiratory Depression</u>
Codeine is not recommended for use in children in whom respiratory function might be compromised. Codeine is not recommended in children 12 to 18 years of age with risk factors that may increase their sensitivity to the respiratory depressant effects of codeine. Risk factors include conditions associated with hypoventilation, such as obstructive sleep apnea, obesity, and pulmonary disease.

Use with caution in sedated or debilitated patients, in patients who have undergone thoracotomies or laparotomies, since suppression of the cough reflex may lead to retention of secretions postoperatively in these patients.

Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Skin

Severe cutaneous adverse reactions (SCARs): Life-threatening cutaneous reactions Stevens-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN) have been reported with the use of acetaminophen. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should stop immediately MERSYNDOL with codeine treatment and seek medical advice.

7.1 Special Populations

7.1.1 Pregnancy

No data are available on the use of MERSYNDOL with codeine during pregnancy. Safe use in pregnancy has not been established in human studies; therefore, this medication should not be used during pregnancy unless, in the opinion of the prescribing doctor, the potential benefits outweigh the potential risks.

There have been no observations of an increase in the frequency of malformations or other direct or indirect harmful effects on the foetus in pregnant women and women of child-bearing age who have taken acetaminophen and doxylamine.

There is inadequate evidence of safety of codeine in pregnancy. Since codeine phosphate crosses the placental barrier, its use in pregnancy is not recommended.

Codeine may cause respiratory depression and withdrawal syndrome in neonates born to mothers who use codeine during the third trimester of pregnancy. As a precautionary measure, use of MERSYNDOL with codeine should be avoided during the third trimester of pregnancy, in case of premature birth and during labor (see **Error! Reference source not found. Error! Reference source not found.**).

7.1.2 Breastfeeding

MERSYNDOL with codeine is contraindicated during breastfeeding (see **Error! Reference source not found. Error! Reference source not found.**). Acetaminophen, doxylamine and codeine are excreted into human breast milk. Codeine is partially metabolized by cytochrome P450 2D6 (CYP2D6) into morphine, which is excreted into breast milk. If nursing mothers are CYP2D6 ultra-rapid metabolisers, higher levels of morphine may be present in their breast milk. This may result in symptoms of opioid toxicity in both mother and the breast-fed infant. Life-threatening adverse events or neonatal death may occur even at therapeutic doses (see **Error! Reference source not found. Error! Reference source not found.**, General).

8 Adverse Reactions

8.5 Post-Market Adverse Reactions

Acetaminophen:

The incidence of gastrointestinal upset is less than after salicylate administration.

Hepatic toxicity has been associated with acetaminophen. Non-fatal hepatic damage is usually reversible. Cytolytic hepatitis, which may lead to acute hepatic failure have been reported.

The chronic ingestion of alcohol may be implicated in the increasing potential for hepatic toxicity. In patients with compromised liver function, acetaminophen could exacerbate liver insufficiency.

There have been reports of kidney damage. Papillary renal failure has been reported following large amount of acetaminophen. There have been no authenticated reports of renal papillary necrosis with therapeutic doses of acetaminophen alone. Renal insufficiency may occur as an effect secondary to liver failure.

Changes in blood picture (very rare thrombocytopenia, neutropenia, leucopenia and, in isolated cases, pancytopenia) may occur. There have been reports agranulocytosis, thrombocytopenic purpura, methemoglobinemia and hemolytic anemia in particular in patients with underlying glucose 6-phosphate dehydrogenase deficiency.

Rarely, asthmatic attacks and bronchospasm have been reported.

Skin rashes and fixed dermatitis with pruritus (erythema, urticaria) have been reported. Toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), acute generalized exanthematous pustulosis, fixed drug eruption have been rarely reported (see **Error! Reference source not found. Error! Reference source not found.**).

Hypersensitivity such as anaphylactic shock, angioedema, difficulty in breathing and drop in blood pressure have also been reported.

Kounis syndrome (allergic angina/allergic myocardial infarction) has been reported.

High anion gap metabolic acidosis due to pyroglutamic acidosis, in patients with pre-disposing factors have been reported (frequency not known) (see 7 WARNINGS AND PRECAUTIONS, General section).

Codeine phosphate:

Adverse reactions due to codeine phosphate may include:

- Ear and labyrinth disorders: tinnitus
- Eye disorders: miosis; visuomotor coordination and visual acuity may be adversely affected in a dose-dependent manner at higher doses or in particularly sensitive patients
- Gastrointestinal disorders: nausea, vomiting, constipation, dry mouth
- General disorders: fatigue
- Immune disorders: hypersensitivity
- Nervous system disorders: seizure, headache, dizziness, sedation
- Psychiatric disorders: confusional state, dysphoria, euphoria, drowsiness. Long-term use also entails the risk of drug dependence.
- Renal and urinary disorders: urinary retention
- Vascular disorders: hypotension
- Respiratory depression

Infrequent adverse effects include palpitation, and, rarely, hyperhidrosis and agitation have been reported. Pruritus has also been reported.

Very rare occurrence of pancreatitis has been observed.

Codeine, consumed in higher doses and over a prolonged period, may cause addiction.

Doxylamine succinate:

Adverse reactions due to doxylamine may include:

- Nervous system disorders: paradoxical stimulation, psychomotor impairment
- Eye disorders: blurred vision
- Respiratory, thoracic and mediastinal disorders: thickened respiratory tract secretions
- Gastrointestinal disorders

Drowsiness, vertigo, nervousness, epigastric pain, headache, palpitation, diarrhea, disorientation, irritability, convulsions, urinary retention, or insomnia have been reported.

Other infrequently observed side effects with MERSYNDOL with codeine are anorexia, depression, dizziness, dry mouth and sweating.

Related to Codeine and Doxylamine succinate

- Somnolence

9 Drug Interactions

9.4 Drug-Drug Interactions

Since the depressant effects of antihistamines and codeine are additive to those of other drugs affecting the CNS, patients should be cautioned against drinking alcoholic beverages or taking tranquilizers, hypnotics, sedatives, psychotherapeutic agents, narcotic analgesics, antitussives, antihypertensives, antihistamines or other drugs with CNS depressant effects.

Tricyclic antidepressants: Codeine-induced respiratory depression can be potentiated by tricyclic antidepressants (imipramine, amitriptyline).

Mono Amine Oxidase Inhibitors (MAOI): Concomitant administration of MAOI (e.g. tranylcypromine) can potentiate the central nervous effects and other side effects of unpredictable severity. MERSYNDOL with codeine should not be used within two weeks after the discontinuation of MAOI treatment.

Antiperistaltic antidiarrheal drugs: Concomitant use of codeine with antiperistaltic antidiarrheal drugs can increase the risk of severe constipation and CNS depression.

Morphinic agonists-antagonists: Concomitant use of codeine with a partial agonist (e.g. buprenorphine) or antagonist (e.g. naltrexone) can precipitate or delay codeine effects.

The concomitant use of benzodiazepines and opioids increases the risk of sedation, respiratory depression, coma, and death, because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see **Error! Reference source not found. Error! Reference source not found.**).

The concomitant use of opioids with gabapentinoids (gabapentin and pregabalin) increases the risk of respiratory depression, hypotension, profound sedation, coma or death because of additive CNS depressant effect (see 7 WARNINGS AND PRECAUTIONS).

The concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. Concomitant use with alcohol is not recommended (see **Error! Reference source not found. Error! Reference source not found.**).

The risk of acetaminophen toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes, such as certain antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), rifampicin and alcohol. The induced metabolism results in an elevated production of the hepatotoxic oxidative metabolite of acetaminophen. Hepatotoxicity will occur if this metabolite exceeds the normal glutathione binding capacity.

Co-administration of flucloxacillin with acetaminophen may lead to high anion gap metabolic acidosis due to pyroglutamic acidosis, particularly with patients with risk factors (see 7 WARNINGS AND PRECAUTIONS, General section).

Acetaminophen may increase the risk of bleeding in patients taking warfarin and other antivitamin K. Patients taking acetaminophen and antivitamin k should be monitored for appropriate coagulation and bleeding complications.

Acetaminophen may considerably slow down the excretion of chloramphenicol, entailing the risk of increased toxicity.

When used concurrently with zidovudine, an increased tendency for neutropenia may develop. Combination of MERSYNDOL with codeine and zidovudine should be avoided.

Concurrent intake of drugs which delay gastric emptying may slow down the uptake of acetaminophen, thereby retarding its onset of action. Conversely, drugs which accelerate gastric emptying, such as metoclopramide or domperidone, may accelerate the uptake of acetaminophen and its onset of action.

Chelating resin can decrease the intestinal absorption of acetaminophen and potentially decrease its efficacy if taken simultaneously. In general, there must be an interval of more than 2 hours between taking the resin and taking acetaminophen, if possible.

Codeine is metabolized by the liver enzyme CYP2D6 to its active metabolite morphine. Medicines that inhibit CYP2D6 activity may reduce the analgesic effect of codeine. Patients taking codeine and moderate to strong CYP2D6 inhibitors (such as quinidine, fluoxetine, paroxetine, bupropion, cinacalcet, methadone) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

Medicines that induce CYP3A4 activity may reduce the analgesic effect of codeine. Patients taking codeine and CYP3A4 inducers (such as rifampin) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

10 Clinical Pharmacology

10.1 Mechanism of Action

Acetaminophen

Acetaminophen, also known as paracetamol, is the major metabolite of phenacetin and acetanilid.

Acetaminophen is an effective and fast-acting analgesic which acts centrally to relieve mild to moderate pain.

Acetaminophen is an analgesic and antipyretic agent, similar in potency and efficacy to salicylates.

Like the salicylates, acetaminophen reduces fever by a direct effect on the heat-regulating centers to increase dissipation of body heat.

Unlike the salicylates, acetaminophen does not have uricosuric activity and does not affect acid base balance in normal therapeutic doses. Acetaminophen does not interfere with hemostasis and does not inhibit platelet aggregation.

Allergic reactions are rare with acetaminophen but have occurred. Patients with salicylate induced urticaria or angioedema can suffer cross reactivity with acetaminophen (see **Error! Reference source not found. Error! Reference source not found.**).

Codeine phosphate:

Codeine phosphate is an effective oral analgesic which provides relief from mild to moderate pain. Codeine alters processing affecting both the perception and emotional responses to pain. Codeine also exerts antitussive action by directly depressing the cough centre.

The abuse potential of codeine is lower than that of other opiates.

Doxylamine succinate

Doxylamine belongs to the ethanolamine class of antihistamines with sedative properties. Its sedative effect is useful in reducing the restlessness and allaying the anxiety which can perpetuate or increase pain.

It has antinauseant and antiemetic activity. Its anticholinergic effects tend to lessen rhinorrhea.

10.3 Pharmacokinetics

Absorption

Acetaminophen

Acetaminophen is rapidly and completely absorbed from the gastrointestinal tract. Food intake delays acetaminophen absorption.

Codeine phosphate:

Codeine is well absorbed from the gastrointestinal tract after oral administration.

Metabolism:

Acetaminophen

Small amounts of acetaminophen are normally converted to a highly reactive metabolite by hepatic microsomal enzymes. At therapeutic doses, the small amounts of the active metabolite so formed are rapidly inactivated by hepatic glutathione and removed by renal excretion.

However, where hepatic glutathione has been rapidly depleted by a large dose of acetaminophen, covalent binding of the metabolite to liver-cell macromolecules occurs and is presumed to be responsible for the hepatic cell necrosis.

Prompt administration of acetylcysteine is indicated to prevent acetaminophen induced hepatic necrosis in the treatment of overdosage (see **Error! Reference source not found. Error! Reference source not found.**).

Codeine phosphate:

Codeine is mainly metabolized by glucuronidation to codeine-6-glucuronide. Minor routes of metabolism include O-demethylation leading to morphine, N-demethylation to norcodeine and both O- and N-demethylation to normorphine. Morphine and norcodeine are further transformed to glucuronide conjugates. The O-demethylation of codeine in morphine is catalyzed by the cytochrome P450 isozyme 2D6 (CYP2D6) which shows genetic polymorphism that may affect the efficacy and toxicity of codeine. Genetic polymorphism in CYP2D6 leads to ultrarapid, extensive and poor metaboliser phenotypes.

Elimination

Acetaminophen

Approximately 85%-90% of the administered dose is recovered from the urine in 24 hours. Less than 5% is excreted unchanged, the balance being conjugated principally to the glucuronide or sulfate.

Peak plasma concentrations of the free and conjugated drug are achieved 1/2 to 2 hour after oral administration. The elimination half-life varies from 1 to 4 hours.

Codeine phosphate:

Unchanged codeine and its metabolites are mainly excreted by urinary route within 48 hours (84.4±15.9%).

Doxylamine succinate

Doxylamine has a half-life of approximately 9 hours.

Special populations and conditions

- **Hepatic Insufficiency**

  MERSYNDOL with codeine should be used with caution in mild to moderate hepatocellular insufficiency or severe renal dysfunction.

- **Renal Insufficiency**

  MERSYNDOL with codeine should be used with caution in mild to moderate hepatocellular insufficiency or severe renal dysfunction.

11 Storage, Stability, and Disposal

Store between 15°C and 30°C.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MERSYNDOL® with codeine

Acetaminophen, codeine phosphate, doxylamine succinate

This patient medication information is written for the person who will be taking **MERSYNDOL® with codeine**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **MERSYNDOL® with codeine**, talk to a healthcare professional.

What MERSYNDOL® with codeine is used for:

For temporary relief of: headaches, muscular aches and pains, cold symptoms: sneezing, runny nose, itchy, watery eyes, itchy nose and throat.

This preparation contains codeine and should not be administered to children except on the advice of a physician, dentist, or nurse practitioner.

How MERSYNDOL® with codeine works:

MERSYNDOL® with codeine contains 3 medicinal ingredients. The analgesic effects of acetaminophen are combined with codeine phosphate, which relieves mild to moderate pain by acting on your brain and spinal cord. Doxylamine succinate relieves symptoms of allergy and the common cold by blocking natural substances (i.e. histamines) your body makes.

The ingredients in MERSYNDOL® with codeine are:

Medicinal ingredients: acetaminophen 325 mg (analgesic); codeine phosphate 8 mg (analgesic), doxylamine succinate 5 mg (antihistamine).

Non-medicinal ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, pregelatinized starch, povidone and silicon dioxide.

MERSYNDOL® with codeine comes in the following dosage forms:

Tablet of acetaminophen 325 mg, codeine phosphate 8 mg and doxylamine succinate 5 mg

Do not use MERSYNDOL® with codeine if you:

- are allergic to acetaminophen, doxylamine, codeine, or other opioids, or to any of the non-medicinal ingredients (see Inactive Ingredients section)
- have difficulty breathing, acute asthma attacks or other chronic lung disease
- have suffered head injury
- are at risk of blocked intestines or constipation
- suffer from seizures

- are in your last trimester of pregnancy, in case of risk of premature birth, or are breastfeeding. Codeine may cause serious harm to a breastfed baby.
- have severe liver dysfunction
- are taking other drugs containing **acetaminophen, codeine and doxylamine succinate.** If you are not sure whether a drug contains these ingredients, ask a doctor or pharmacist.
- **do not use** in children under 18 years old.
- are taking monoamine inhibitors (MAOIs) or within 14 days of stopping MAOIs
- have conditions with elevated intracranial pressure and head trauma
- have compromised respiratory function and chronic obstructive airway disease.

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

- have chronic alcoholism, or you are taking 3 or more alcoholic beverages per day
- suffered from alcoholism, drug abuse or dependence
- have a liver disease or serious kidney disease
- have a liver disease called Gilbert's syndrome
- have a heart disease, hypertension, a thyroid disease or a disease called Addison's disease
- have chronic constipation
- are or have been dependent to other medications called opioids
- have had a surgery to remove the gallbladder
- have recently had surgery under general anaesthesia
- are taking Warfarin-containing blood thinning drugs
- are taking other medications that can make you sleepy or less alert, for example: narcotic analgesics, benzodiazepines or sedating antihistamines, or you are currently taking anti-depressants, other prescription drugs or natural health products
- are taking gabapentin or pregabalin which are medications to treat epilepsy or pain due to nerve problems (neuropathic pain)
- have glaucoma
- have difficulty in urination due to enlargement of the prostate gland
- have glucose-6-phosphate-dehydrogenase deficiency
- are pregnant
- are planning to breastfeed
- have low levels of glutathione as this may result in the build up of acid in your body
- have sepsis (when bacteria and their toxins circulate in the blood leading to organ damage)
- suffer from malnutrition
- are also taking flucloxacillin (an antibiotic)

Other warnings you should know about:

Liver warning: severe or possibly fatal liver damage may occur if you take:

- more than the recommended dose in 24 hours
- with other drugs containing acetaminophen
- while drinking three (3) or more alcoholic drinks every day

Symptoms of liver damage may include:

- yellow skin or eyes
- dark urine
- sweating
- nausea
- vomiting
- stomach pain
- unusual tiredness
- loss of appetite

Allergy alert: Acetaminophen may cause serious skin reactions. Symptoms may include:

- skin reddening
- blisters
- rash

Pain:

- if you have pain that gets worse after you take this medicine, do not take more without first talking to your doctor.
- if you feel more sensitive to pain, or if you have new pain after taking this medicine

If any of the above noted symptoms occur, stop use and seek medical help right away.

Elderly persons, small children, patients with liver disorders, chronic alcohol consumption, as well as patients concomitantly treated with other medicines are at an increased risk of intoxication, including fatal outcome.

Blood and fluid abnormality: A serious condition that can make blood more acidic (called metabolic acidosis which is a blood and fluid abnormality) can happen in patients:

- with liver disease
- with severe illnesses, such as severe kidney disease or sepsis (when bacteria and their toxins circulate in the blood leading to organ damage)
- suffering for malnutrition or chronic alcoholism
- with glucose-6-phosphate-dehydrogenase deficiency
- with a liver disease called Gilbert's syndrome

Metabolic acidosis has been reported in patients in these situations when acetaminophen is used at regular doses for a prolonged period or when acetaminophen is taken together with flucloxacillin (an antibiotic).

Symptoms of metabolic acidosis may include:

- serious breathing difficulties with deep rapid breathing
- drowsiness
- feeling sick (nausea)
- being sick (vomiting)

Contact your doctor immediately if you develop any of these symptoms during treatment with MERSYNDOL® with codeine.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may also interact with MERSYNDOL® with codeine:

- Drugs affecting the nervous system such as tranquilizers, hypnotics, psychotherapeutic agents, narcotic analgesics, antitussives, antihypertensives, antihistamines or any other drug which affects the nervous system
- Imipramine
- Amitriptyline
- Mono Amine Oxidase Inhibitors (e.g. tranylcypromine)
- Drugs used to treat diarrhea
- Morphinic agonists-antagonists (e.g. buprenorphine, naltrexone)
- Benzodiazepines
- Opioids
- Phenobarbital
- Phenytoin
- Carbamazepine
- Topiramate
- Rifampicin
- Flucloxacillin
- Warfarin
- Antivitamin K
- Chloramphenicol
- Zidovudine
- Metoclopramide
- Domperidone
- Chelating Resins
- Drugs which inhibit the metabolism of Codeine, which include Quinidine, Fluoxetine, Paroxetine, Bupropion, Cinacalcet and Methadone
- Rifampin
- Gabapentinoids (gabapentin and pregabalin)

How to take MERSYNDOL® with codeine:

Usual dose:

Do not take more than directed (see liver warnings).

Adults (18years and older): 1 or 2 tablets every 4-6 hours as required. To be used only on the advice of a physician. Do not exceed 12 tablets in 24 hours unless advised by a doctor.

Overdose:

If you think you, or a person you are caring for, have taken too much MERSYNDOL® with codeine, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are

no signs or symptoms.

Possible side effects from using MERSYNDOL® with codeine:

These are not all the possible side effects you may have when taking MERSYNDOL® with codeine. If you experience any side effects not listed here, tell your healthcare professional.

When using this product:

- drowsiness may occur
- alcohol, sedatives and tranquilizers may increase drowsiness
- do not drive or engage in activities requiring alertness
- avoid alcoholic drinks
- excitability may occur, especially in children
- addiction may occur following prolonged use and at high doses

Stop use and ask a doctor if:

- your symptoms worsen or last for more than five days
- you feel sedated or drowsy, confused, have shallow breathing or severe constipation

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15°C and 30°C.

Keep out of reach and sight of children.

If you want more information about MERSYNDOL® with codeine:

- Talk to your healthcare professional
- Find the full prescribing information that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website:

(https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sanofi.com/en/canada, or by calling 1-800-265-7927.

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