PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N] APO-METHADONE

Methadone Hydrochloride Tablets

1 mg, 5 mg, 10 mg and 25 mg

Apotex Standard

Opioid Analgesic

APOTEX INC
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[N]APO-METHADONE®

Methadone Hydrochloride Tablets,
Apotex Standard

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablets 1, 5, 10 and 25 mg	D&C Yellow No.10 aluminium (10 mg), FD&C Blue No. 1 (1 and 10 mg), FD&C Yellow No.6 (5 mg), lactose, magnesium stearate, mannitol, microcrystalline cellulose and tromethamine

INDICATIONS AND CLINICAL USE

Adults

APO-METHADONE (Methadone Hydrochloride Tablets) is indicated for the relief of severe pain. In general, APO-METHADONE, as an analgesic, should not be used in opioid naive patients.

Geriatrics (> 65 years of age)

The safety and efficacy of methadone hydrochloride tablets in patients 65 years and older have not been established. 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)

The safety and efficacy of methadone hydrochloride tablets have not been studied in the pediatric population. Therefore, the use of APO-METHADONE is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance methadone hydrochloride 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.
- 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 anytype).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).

- Patients with mild, intermittent or short duration pain that can be managed with other pain medications.
- The management of acute pain.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant or during labour and delivery (see **SERIOUS WARNINGS AND PRECAUTIONS** and **WARNINGS AND PRECAUTIONS**).
- Patients with diarrhea which is associated with pseudomembranous colitis caused by cephalosporins, lincomycins (possibly including topical clindamycin), or penicillins, or to patients having diarrhea caused by poisoning, until toxic material has been eliminated from the gastrointestinal tract.
- Patients naive to opioids.

WARNINGS AND PRECAUTIONS

Warning: MAY BE HABIT FORMING

SERIOUS WARNINGS AND PRECAUTIONS

APO-METHADONE (methadone hydrochloride tablets) is for oral administration only. This preparation must not be injected. It is recommended that APO-METHADONE tablets, if dispensed, be packaged in child resistant containers and kept out of the reach and sight of children and pets to prevent accidental ingestion.

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, APO-METHADONE 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

APO-METHADONE poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing APO-METHADONE, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). Appropriate security measures should be taken to safeguard stocks of methadone against diversion. APO-METHADONE 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 APO-METHADONE. 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 APO-METHADONE or following a dose increase.

APO-METHADONE must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving APO-METHADONE tablets can cause rapid release and absorption of a potentially fatal dose of methadone hydrochloride leading to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects are typically delayed. This characteristic can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

QT interval prolongation

Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Accidental Exposure

Accidental ingestion of even one dose of APO-METHADONE, especially by children, can result in a fatal overdose of methadone hydrochloride (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of APO-METHADONE 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 APO-METHADONE should be avoided as it may result in dangerous additive effects due to increased plasma levels of methadone hydrochloride, which can result in overdose, 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 APO-METHADONE 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

Methadone hydrochloride, a synthetic opioid, is a controlled substance listed in Schedule I to the Controlled Drugs and Substances Act (CDSA).

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

APO-METHADONE 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 APO-METHADONE as it may increase the chance of experiencing serious adverse events, including death.

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

Abuse and Misuse

Like all opioids, APO-METHADONE is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, APO-METHADONE 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 APO-METHADONE, 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.

APO-METHADONE 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.

Methadone is a μ-agonist opioid with an abuse liability similar to that of morphine and is a **controlled substance listed in Schedule I to the Controlled Drugs and Substances Act (CDSA)**. Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.

Carcinogenesis and Mutagenesis
See **TOXICOLOGY** section.

Cardiovascular
Methadone 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 APO-METHADONE.

Cardiac Conduction Effects: Laboratory studies, both *in vivo* and *in vitro*, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (>200 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia). Careful monitoring is recommended when using methadone in patients with a history of cardiac conduction abnormalities, those taking medications affecting cardiac conduction, and in other cases where history or physical exam suggest an increased risk of dysrhythmia. QT prolongation has also been reported in patients with no prior cardiac history who have received high doses of methadone. Patients developing QT prolongation while on methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities, and drugs which might act as inhibitors of methadone metabolism. For use of methadone to treat pain, the risk of QT prolongation and development of dysrhythmias should be weighed against the benefit of adequate pain management and the availability of alternative therapies.

Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone has beenconsidered to outweigh the risk of QT prolongation that has been reported with high doses of methadone.

The use of methadone in patients already known to have prolonged QT interval has not been systemically studied.

In using methadone an individualized benefit to risk assessment should be carried out and should include evaluation of patient presentation and complete medical history. For patients judged to beat risk, careful monitoring of cardiovascular status, including QT prolongation and dysrhythmias and those described previously should be performed.

If a patient taking APO-METHADONE experiences symptoms suggestive of an arrhythmia (such as palpitations, dizziness, light-headedness, or syncope), that patient should seek immediate medical attention.

Methadone, like other opioids, may produce orthostatic hypotension in ambulatory patients.

The use of APO-METHADONE 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 APO-METHADONE 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 (see **DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**). 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 **DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**).

Incomplete Cross-Tolerance Between Methadone and Other Opioids: Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is a particular concern for patients tolerant to other μ-opioid agonists when converting to methadone, making determination of dosing during opioid conversion complex. Deaths have been reported during conversion from chronic, high dose treatment with other opioid agonists. Therefore, it is critical to understand the pharmacokinetics of methadone when converting patients from other opioids (see **WARNINGS AND PRECAUTIONS, Respiratory; and DOSAGE AND ADMINISTRATION**). A high degree of "opioid tolerance" does not eliminate the possibility ofmethadone toxicity.

Use in Drug and Alcohol Addiction
APO-METHADONE is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia.

Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to APO-METHADONE unless used under extreme caution and awareness.

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 maybe 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

Methadone hydrochloride and other morphine-like opioids have been shown to decrease bowel motility. The administration of methadone hydrochloride or other narcotics 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 APO-METHADONE for analgesia is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): APO-METHADONE 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 analgesicsalone. 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 APO-METHADONE is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for riskof 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**).

APO-METHADONE 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.

Serotonin toxicity / Serotonin syndrome: Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with methadone, including methadone hydrochloride tablets particularly during combined use with other serotonergic drugs (see **DRUG INTERACTIONS**).

Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with APO-METHADONE and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **DRUG INTERACTIONS**). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Head Injury: The respiratory depressant effects of methadone hydrochloride, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Also, methadone hydrochloride may produce confusion, miosis, vomiting and other side effects which obscure theclinical course of patients with head injury. In such patients, methadone hydrochloride must be used with extreme caution and only if it is deemed essential (see **CONTRAINDICATIONS**).

Psychomotor Impairment
APO-METHADONE 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 methadone hydrochloride with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory

Respiratory Depression: 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. Methadone hydrochloride should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see **CONTRAINDICATIONS**).

There is significant risk of respiratory depression if the patient is switched abruptly from other opioids to methadone. Conversion to methadone should be undertaken with caution.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of APO-METHADONE, 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 APO-METHADONE 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 APO-METHADONE are essential (see **DOSAGE AND ADMINISTRATION**). Overestimating the APO-METHADONE 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**).

Sleep Apnea: Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes(including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids(see **DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**; **WARNINGS AND PRECAUTIONS, Dependence/Tolerance**).

Use in Patients with Chronic Pulmonary Disease: APO-METHADONE should be administered with extreme caution to patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve (such as asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma), hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with APO-METHADONE, as in these patients, even usual therapeutic doses of APO-METHADONE may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. These patients should be monitored and use of alternative non-opioid analgesics should be considered, if possible, and APO-METHADONE should be employed only under careful medical supervision at the lowest effective dose. The use of APO-METHADONE 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-Market Adverse Drug Reactions**).

Special Populations

Special Risk Groups: Methadone given on a fixed-dose schedule may have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known potential risks of cardiac conduction abnormalities, respiratory depression, altered mental states and postural hypotension.

APO-METHADONE (methadone hydrochloride tablets) should be given with caution and the initial dose should be reduced in certain patients, such as the elderly or debilitated; those with severe impairment of hepatic or renal function, hypothyroidism, Addison'sdisease, myxedema, toxic psychosis, prostatic hypertrophy, or urethral stricture; patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease; and in patients with comorbid conditions or concomitant medications which may predispose to dysrhythmia. The usual precautions appropriate to the use of parenteral opioids should be observed and the possibility of respiratory depression should always be kept in mind.

Pregnant Women: No controlled studies of methadone use in pregnant women have been conducted. APO-METHADONE crosses the placental barrier and is contraindicated in pregnant women.

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

Studies show methadone exposure to be associated with an increased risk of very pre-term birth (< 32 weeks of gestation), being small for gestational age (< 10^{th} percentile), admission to the neonatal unit, and diagnosis of a major congenital anomaly.

Several studies have suggested that infants prenatally exposed to methadone present decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. Moreover it has been suggested that prenatally exposed infants are at a higher risk of presenting neurodevelopmental and neuropsychological impairments, as well as visual (see section below, **Neonate Growth and Development**).

Additional information on the potential risks of methadone with pre-natal opioid exposure may be derived from animal data (see Part II of Product Monograph, **TOXICOLOGY, Teratogenicity**).

Labour, Delivery and Nursing Women: Since methadone has a long duration of action, can crossthe placental barrier and is secreted in saliva, breast milk, amniotic fluid and

umbilical cord plasma, APO-METHADONE is contraindicated for obstetric analgesia, during labour, delivery and in nursing mothers. As with all opioids, administration of methadone to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses areused. Naloxone, a drug that counters the effects of opiates, should be readily available if APO-METHADONE is used in this population. Cases of death have been reported in association with methadone in children less than one year of age exposed through breast milk.

Women being treated with methadone, who are already breast feeding, should be counselled to wean breast-feeding gradually in order to prevent neonatal abstinence syndrome. Methadone-treated mothers considering nursing an opioid-naïve infant should be counselled of the presence of methadone in breast milk.

Neonate Growth and Development: Exposure to opioids *in utero* can result in the development of life-threatening, Neonatal Opioid Withdrawal Syndrome (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome**).

There are conflicting reports on whether the risk of sudden infant death syndrome (SIDS) is increased in infants born to women treated with methadone during pregnancy.

Prenatal opioid exposure, including to methadone, is suggested to have an effect on the visual system and on brain development.

Lower performance on tests of cognitive function and neurodevelopmental abnormalities have been found in some, although not all, studies and children have been shown to demonstrate mild, but persistent deficits in performance on psychometric and behavioral tests. It is unclear whether these differences in performance are caused by the direct effects of in-utero exposure to methadone or indirectly by genetic and environmental risk factors, or are a consequence of pre-term birth.

Ophthalmic Abnormalities: Infants prenatally exposed to methadone are at risk of a range of visual problems, the underlying causes of which are not clear. Ophthalmic abnormalities included reduced acuity, nystagmus, delayed visual maturation, strabismus, refractive errors, and cerebral visual impairment. Those infants with NOWS severe enough to receive pharmaceutical treatment may be at particular risk of developing nystagmus. Delayed visual development has also been reported. Exposure to opioids including methadone, during pregnancy may result in permanently reduced vision and nystagmus.

Pediatrics (< 18 years of age): The safety and efficacy of methadone hydrochloride tablets have not been studied in the pediatric population. Therefore, use of APO-METHADONE is not recommended in patients under 18 years of age.

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 titrating 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**).

Patients with Hepatic Impairment: The use of methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized in the liver and patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Patients with Renal Impairment: The use of methadone has not been extensively evaluated in patients with renal insufficiency.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of APO-METHADONE are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class.

The major hazards of methadone are respiratory, central nervous system depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest and death have occurred.

The most frequently observed adverse effects of APO-METHADONE include light-headedness, dizziness,sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses of methadone are advisable.

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 ofthe 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.

Other adverse reactions that have been reported in patients receiving methadone include the following:

Body as a Whole: asthenia (weakness), edema, headache.

Cardiovascular: Arrhythmias, bigeminal rhythms, bradycardia, extrasystoles, tachycardia, Torsade de Pointes, ventricular fibrillation, ventricular tachycardia. ECG abnormalities, prolonged QT interval, T-wave inversion, cardiomyopathy, flushing, heart failure, hypotension, palpitations,phlebitis, syncope

Digestive: Abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis

Metabolic and Nutritional: Hypokalemia, hypomagnesemia, weight gain

Nervous: Agitation, confusion, seizures, disorientation, dysphoria, euphoria, insomnia

Ocular: Visual disturbances

Respiratory: Pulmonary edema

Special senses: Visual disturbances

Urogenital: Antidiuretic effect, amenorrhea, urinary retention or hesitancy, reduced libido and/orpotency

Abnormal Hematologic and Clinical Chemistry Findings: Reversible thrombocytopenia hasbeen described in patients with chronic hepatitis.

Post-marketing Experience

Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadalaxis, 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.

Nervous System Disorders: Serotonin toxicity/Serotonin syndrome

DRUG INTERACTIONS

Overview

Interactions with Central Nervous System (CNS) Depressants (including benzodiazepines and alcohol): Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. 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**). APO-METHADONE should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-drug Interactions

Anti-retroviral agents:

*Nevirapine***:** Based on the known metabolism of methadone, nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Opioid withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Methadone maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

*Efavirenz***:** Coadministration of efavirenz in HIV-infected methadone-maintenance patients has resulted in decreased methadone plasma concentrations associated with signs of opioid withdrawal, and necessitating increases in methadone dose.
Ritonavir and Ritonavir/lopinavir: Reduced plasma methadone levels have been observed after administration of ritanovir alone or ritanovir/lopinavir combination. Withdrawal symptoms were however, inconsistently observed. Caution is warranted when administering methadone to patients receiving ritonavir-containing regimens in addition to other drugs known to decrease methadone plasma levels.

Zidovudine: Experimental evidence suggests that methadone increases the area under the concentration-time curve (AUC) of zidovudine with possible toxic effects.

*Didanosine and Stavudine***:** Experimental evidence suggests that methadone decreased the AUC and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.

Cytochrome P450 inhibitors: Since the metabolism of methadone is mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone. The expected clinical results would be increased or prolonged opioid effects. Thus patients coadministered with inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), while receiving methadone should be carefully monitored and dosage adjustment made if warranted. Some selective serotonin reuptake inhibitors (SSRI's) (i.e. sertraline,

fluvoxamine) upon coadministration may increase methadone plasma levels and result in increased opiate effects or toxicity.

Specifically, repeat dose administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 4 days) increased the C_{max} and AUC of pharmacologically active R-methadone by 31% (90% CI: 22%, 40%) and 47% (90% CI: 38%, 57%), respectively, in subjects receiving a methadone maintenance dose (30 to 100 mg QD). Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.

Cytochrome P450 inducers: The following drug interactions were reported following coadministration of methadone with inducers of cytochrome P450 enzymes.

*Rifampin***:** In patients well-stabilized on methadone, concomitant administration of rifampin resulted in marked reduction in serum methadone levels and concurrent appearance of withdrawal symptoms.

*Phenytoin***:** In a pharmacokinetic study with patients on methadone maintenance therapy, phenytoin administration (250 mg b.i.d. initially for 1 day followed by 300 mg QD for 3 to 4 days) resulted in ~50% reduction in methadone exposure and concurrently withdrawal symptoms occurred. Upon discontinuation of phenytoin, the incidence of withdrawal symptoms decreased and the methadone exposure increased and was comparable to pre-phenytoin dose scenario.

Phenobarbital, carbamazepine: Administration of methadone along with other CYP3A4 inducersmay result in withdrawal symptoms (see also **DRUG INTERACTIONS, Drug-Herb Interactions** below).

Potentially Arrhythmogenic Agents: Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers. Caution should also be exercised when prescribing concomitant drugs capable of inducing electrolyte disturbances that may prolong the QT interval (hypomagnesemia, hypokalemia). These include diuretics, laxatives, and in rare cases, mineralocorticoid hormones.

Monoamine Oxidase (MAO) Inhibitors: Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Since the safety of methadone in this regard has not been established, the use of methadone in patients who have received MAO inhibitors during the previous 14-day period is contraindicated. However, if the use of methadone is necessary in suchpatients, a sensitivity test should be performed in which repeated small incremental doses are administered over the course of several hours while the patient's condition and vital signs are undercareful observation.

Opioid antagonist, mixed agonist/antagonist, and partial agonists drugs: Agonist/ antagonistanalgesics (i.e., pentazocine, nalbuphine, butorphanol, or buprenorphine) when

administered concomitantly with a pure opioid agonist, such as methadone hydrochloride may reduce the analgesic effect of methadone hydrochloride and/or may precipitate withdrawal symptoms, the latter being a particular risk to patients on prolonged methadone therapy.

Protease inhibitors: *Agenerase:* Coadministration of methadone with Agenerase resulted in a decrease in the C_{max} and AUC of the active methadone enantiomer (R-enantiomer) of 25% and 13% respectively, while the C_{max}, AUC and C_{min} of the inactive methadone enantiomer (S- enantiomer) were decreased by 48%, 40% and 23% respective. When methadone is coadministered with Agenerase, patients should be monitored for methadone underdosing, in particular if low-dose ritonavir is also given. As compared to a non-matched historical control group, coadministration of methadone and Agenerase resulted in a 30%, 27% and 25% decrease in serum Agenerase AUC, C_{max} and C_{min} respectively. No recommendations can be made regardingadjustment of Agenerase dose when Agenerase is coadministered with methadone.

Viracept: When coadministered with Viracept, changes are reported for total plasma methadone; changes for the individual R-enantiomer and S-enantiomer were similar. Dosage of methadone may need to be increased.

Non–nucleoside reverse transcriptase inhibitors: *Rescriptor:* Dosage of methadone may need to be decreased when coadministered with Rescriptor.

Desipramine: Blood levels of desipramine have increased with concurrent methadone therapy.

Serotonergic Drugs: Some selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline,fluvoxamine) may increase methadone plasma levels upon co-administration with APO-METHADONE and result in increased opioid effects and/or toxicity.

Coadministration of APO-METHADONE with serotonergic drugs such as a Selective Serotonin Re-uptake Inhibitor, a Serotonin Norepinephrine Re-uptake Inhibitor or other serotonergic drug, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS, Neurologic**). If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue APO-METHADONE if serotonin syndrome is suspected.

Drug-Herb Interactions

Administration of methadone along with other CYP3A4 inducers such as St. John's Wort may result in withdrawal symptoms.

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

For the management of chronic non-cancer, non-palliative pain, consider the benefits and the risks of higher doses as they are associated with an increased risk of adverse events and overdose. The level of pain should be assessed regularly to evaluate the need for further use of APO-METHADONE.

Patients prescribed methadone should be carefully monitored and provided appropriate supportive psychological and social services.

APO-METHADONE should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids).

APO-METHADONE tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving APO-METHADONE can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

Dosing Considerations

Dosing is to be determined by the physician. **Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration**.**APO-METHADONE** is not indicated for injection or rectal administration. After interruption of chronic dosing, if methadone treatment is to be continued, starting doses should be low and patients should be titrated slowly to effect in order to avoid severe toxicity and respiratory depression.

Recommended Dose and Dosage Adjustment

Adults (over 18 years): Dosage should be carefully titrated and adjusted according to the severity of the pain and response of the patient. The usual adult oral dose is 2.5 to 10 mg every 4 hours during the first 3 to 5 days, followed by a fixed dose every 8 to 12 hours depending on the patient'srequirements. In geriatric patients the dosage schedule could be given on a once daily basis.

Pediatrics (< 18 years of age): The safety and efficacy of methadone hydrochloride tablets has not been studied in the pediatric population. Therefore, the use of APO-METHADONE is not recommended in patients under 18 years of age (see **INDICATIONS, Pediatrics (< 18 years of age)**).

Geriatrics (> 65 years of age): 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. APO-METHADONE should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Patients with Hepatic Impairment:
Dosage adjustments should be based on the patient's clinical response (see **WARNINGS AND PRECAUTIONS, Patients with Hepatic Impairment**).

Patients with Renal Impairment:
Dosage adjustments should be based on the patient's clinical response (see **WARNINGS AND PRECAUTIONS, Patients with Renal Impairment**).

Patients Not Receiving Opioids at the Time of Initiation of Methadone Hydrochloride Treatment:

APO-METHADONE should not be used in opioid naive patients.

Switching Patients from an Alternate Opioid Product
When switching from an alternate opioid product to methadone, there is significant risk of respiratory depression if the patient is switched abruptly (see **WARNINGS and PRECAUTIONS, Incomplete Cross-Tolerance Between Methadone and Other Opioids**). Conversion to methadone should be undertaken with caution.

Dose Titration:
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of dosesscaled 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 APO-METHADONE. 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 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 treatedwith opioid analgesics and who undergo gradual withdrawal of the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualized 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.

Use with Non-Opioid Medications:
If a non-opioid analgesic is being provided, it may be continued. APO-METHADONE can be safely used concomitantly with usual doses of other non-opioid analgesics.

Disposal

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

APO-METHADONE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired APO-METHADONE 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

For management of a suspected drug overdose, contact your regional poison control centre.

Signs and Symptoms: Serious overdosage of methadone hydrochloride is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin and, sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Other important adverse events reported with methadone overdose include toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy, sudden sensorial hearing loss, rhabdomyolysis progressing to renal failure and serotonin syndrome.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation.If a non-tolerant person, especially a child, takes a large dose of methadone, effective narcotic antagonists are available to counteract the potentially lethal respiratory depression. **The physician must remember, however, that methadone is a long-acting depressant (thirty-six to forty- eight hours), whereas the antagonists act for much shorter periods (one to three hours).** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and may need to be treated repeatedly with the narcotic antagonist as needed. If the diagnosis is correctand respiratory depression is due only to overdosage of methadone, the use of respiratory stimulants is not indicated.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or cardiovascular depression. In an individual physically dependant on opioids, the administration of the usual dose of an opioid antagonist may precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. If antagonists must be used to treat serious respiratory depression in the physically dependant patient, the antagonist should be administered with extreme care and by titration with smaller than

usual doses of the antagonist.

Intravenously administered naloxone or nalmefene may be used to reverse signs of intoxication. Because of the relatively short half-life of naloxone as compared with methadone, repeated injections may be required until the status of the patient remains satisfactory. Naloxone may also be administered by continuous intravenous infusion.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

Note: In an individual physically dependent on opioids, the administration of the usual doseof opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. The use of an opioid antagonist in such a person should be avoided if possible. If it must be used to treat serious respiratory depression in the physically dependent patient,the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist (10 to 20% of the usual recommended initial dose of the antagonist).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Methadone hydrochloride is a μ-agonist synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involve the central nervoussystem and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation and detoxification or maintenance in opiate addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset isslower, the course is more prolonged, and the symptoms are less severe.

Pharmacodynamics

When administered orally, methadone is approximately one-half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect. The steady-state elimination half-life of methadone isapproximately 25 hours. Large inter-individual variability in elimination half-life may necessitate 2 to 9 days for steady-state serum levels.

The pharmacokinetic parameters of methadone following the administration of a single methadone hydrochloride tablet 10 mg dose, under fasting conditions, to twenty-four (24) healthy male and female subjects are presented in the table below.

Mean (CV%) Methadone Pharmacokinetic Parameters after Administration of a Single 10 mg dose of methadone hydrochloride tablet to Healthy Subjects (n=24)

Parameter	**Unit**	**Methadone hydrochloride tablet dose**
		1 x 10 mg tablet
C_{max}	(ng/mL)	38.12 (28.3)
T_{max} [a]	(h)	2.50 (1.67 – 5.07)

AUC_{0-72}	(ng.h/mL)	1042.77 (31.0)
AUC_{0-inf}	(ng.h/mL)	1429.78 (45.2)
$T_{1/2}$	(h)	36.71 (32.6)

[a] median (range)

Acutely, methadone has similar effects to other opioids; however, its pharmacological properties are significantly different from other opioid agonists in that it is extremely long-acting (36 to 48 hours) in humans.

After interruption of chronic dosing, if methadone treatment is to be continued, starting doses should be low and patients should be titrated slowly to effect in order to avoid severe toxicity and respiratory depression.

Central Nervous System: Methadone hydrochloride 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.

Methadone hydrochloride 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.

Methadone hydrochloride 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).

Gastrointestinal Tract and Other Smooth Muscle: Methadone hydrochloride 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: Methadone hydrochloride 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: The pharmacokinetics of methadone hydrochloride tablets have not been evaluated in the pediatricpopulation. Individuals under 18 years of age should not take APO-METHADONE.

Geriatrics: The pharmacokinetics of methadone hydrochloride tablets have not been evaluated in the geriatric population. 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.

Hepatic Impairment: The use of methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized in the liver and patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Renal Impairment: The use of methadone has not been extensively evaluated in patients with renal insufficiency.

STORAGE AND STABILITY

Dispense in tight containers, protect from light, store at 15°C - 30°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-METHADONE is available is in the following dosage forms: tablet.

APO-METHADONE Tablets

1 mg Blue, round, flat face, beveled-edge tablet. Engraved “APO” over “1” on one side, plain with bisect on the other side.

5 mg Peach, round, flat face, beveled-edge tablet. Engraved “APO” over “5” on one side, plain with bisect on the other side.

10 mg Pale green, round, flat face, beveled edge tablet. Engraved “APO” over “10” on one side, plain with bisect on the other side.

25 mg White, capsule shaped, biconvex tablet. Engraved “APO 25” on one side, plain with bisect on the other side.

Composition:

The tablet formulation cannot be dissolved in water.

Each tablet of APO-METHADONE (methadone hydrochloride) contains: D&C Yellow

No.10 aluminium (10 mg), FD&C Blue No. 1 (1 and 10 mg), FD&C Yellow No.6 (5 mg), Lactose, magnesium stearate, mannitol, microcrystalline cellulose and tromethamine.

This tromethamine-based APO-METHADONE tablet formulation was studied *in vitro* in different solution media to observe the solubility of its methadone content. The new formulation showed a methadone solubility reduced by 70% to 100% in an aqueous solution. Methadone solubility in alcoholic solutions (ethanol or isopropyl alcohol) or in simulated gastric fluid was not affected by tromethamine. However, its solubility in water after evaporation of such an alcoholic solution was reduced by close to 100%.

Packaging:

APO-METHADONE Tablets

Available in HDPE bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

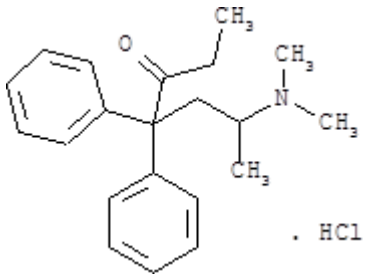
Drug Substance

Proper name: Methadone Hydrochloride

Chemical name: 6-Dimethylamino-4,4-diphenyl-3-heptanone hydrochloride

Molecular formula and molecular mass: $C_{21}H_{27}NO \bullet HCl$ 345.91 g/mol

Structural formula:



Physicochemical Properties:

Description:	White or almost white powder
Solubility:	Soluble in water, freely soluble in ethanol (96 %). Insoluble in *n*-hexane, toluene, diethyl ether, chloroform, ethyl acetate, and acetone
pKa and pH:	8.25 (water, 20°C) and 4.5 to 6.5 (1% w/w, water)
Partition co-efficient:	Log P = 2.1 (octanol/water, pH 7.4)
Melting point:	235°C (DSC)

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, two-treatment, two-period, single oral dose, cross-over, comparative bioavailability study of APO-METHADONE 10 mg tablets (Apotex Inc.) and METADOL® 10 mg tablets (Paladin Labs Inc.) was conducted in healthy, adult, male and female subjects under fasting conditions. A summary of the comparative bioavailability data from 20 subjects included in the statistical analysis is presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Methadone (1 x 10 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72h}[3] (ng·h/mL)	940.62 962.49 (22.3)	927.80 950.43 (22.2)	101.4	97.4 - 105.5
C_{max} (ng/mL)	33.91 34.76 (24.4)	33.77 34.47 (20.8)	100.4	94.1 - 107.2
T_{max}[4] (h)	2.69 (1.33 - 8.00)	2.67 (1.37 - 6.00)		

[1] APO-METHADONE (methadone hydrochloride) tablets, 10 mg (Apotex Inc.)
[2] METADOL® (methadone hydrochloride) tablets, 10 mg (Paladin Labs Inc., Canada)
[3] n=18 subjects
[4] Expressed as median (range) only
Due to the long elimination half-life of methadone, AUC_I and $T_{1/2}$ could not be accurately calculated from the data obtained in this study.

APO-METHADONE 1 mg tablets have satisfied the criteria for a Biopharmaceutics Classification System (BCS)-based biowaiver in comparison to METADOL® 1 mg tablets (methadone, as methadone hydrochloride), Paladin Labs Inc.

DETAILED PHARMACOLOGY

Pharmacodynamics:
Many of the actions of methadone, in various animal species, are characteristic of those seen with other opioid agonists which exert their activity primarily at the mu receptor. The analgesic effect and other morphine-like properties of methadone are exhibited chiefly by the l-form.

The effect of methadone in common laboratory animal paradigms is qualitatively the same as that of morphine, e.g., the Straub reaction in mice, purposeless excitement in cats, and effects on behaviour and reflex activity in decorticate, decerebrate and spinal dogs and cats.

Methadone hasan effect similar to that of morphine on circulation and respiration and on

smooth muscle. In ratsor dogs chronically injected, tolerance to the analgesic effect of methadone develops at nearly the same rate as for morphine. However, dogs rendered only moderately tolerant to methadone are even more tolerant to other opioids than they are to methadone itself.

The heightened activity and increased lability found for methadone in the rat may be related to the persistence of pharmacologically active concentrations of the drug. Exposure to the prenatal period produces a significant delay in postnatal brain growth associated with a reduction in brain DNA content measured at 21 days of age. Studies of plasma drug concentrations indicate a plasma half-life in the rat of only a few hours, but studies using titrated methadone indicate that following prenatal administration, methadone accumulates and persists in neonatal brain and liver for long periods and may alter the maturation of the cholinergic-adrenergic or catecholamine systems.

Gravid rats administered a 5, 10, or 15 mg/kg regimen of methadone on the last two weeks of gestation showed blood levels of methadone which were dose-related, corresponding to the levels found in human subjects receiving daily maintenance doses of approximately 30, 60 and 100 mg,respectively.

Methadone, like morphine, blocks ovulation in the rat but only at doses approaching toxicity.

TOXICOLOGY

In animals methadone is three to ten times more toxic than morphine, according to the species, and two to three times more toxic than meperidine.

In comparative acute toxicity studies in rats, methadone on a weight-for weight basis is about 10 times more toxic than morphine orally, about 6 times more toxic subcutaneously, and about 25 times more toxic intravenously. The l-isomer of methadone, which accounts for nearly all the analgesic activity of the racemic mixture, is little if any more toxic than dl-methadone.

The following Table summarizes the acute toxicity data for dl-methadone obtained in rats and mice:

LD_{50} values (mg/kg)

Route	Mouse	Rat
s.c.	27	48
i.p.	31	33
i.v.	18	-

A single dog injected subcutaneously with 50 mg/kg of dl-methadone suffered violent convulsions, and died 4 hours after injection.

Rats administered a daily dose of 4 mg/kg methadone hydrochloride subcutaneously for ten weeks showed retarded growth. At autopsy, the only gross change noted was a slight increase in liver weight to body weight ratio. Considerable local subcutaneous irritation was observed at the injection sites.

Young adult mongrel female dogs (n=8) injected twice daily on weekdays, and once daily

on weekends, with a dose of 2 mg/kg of methadone for up to 16 weeks, exhibited the following extreme side effects: general depression, narcosis, and sedation. Tolerance to these effects were shown to develop much more slowly with methadone than with morphine. Other long-term effects were bradycardia to which no tolerance developed, vomiting, and reduction in voltages of P and R waves on the electrocardiogram. Signs observed after withdrawal of methadone included increase in resting respiratory rate, tachycardia, loss of appetite, and pronounced muscular tremors,with twitching and rigidity.

Methadone has been found to be teratogenic in the hamster. However, reproduction studies in rats and rabbits revealed no evidence of teratogenicity or embryotoxicity.

Administration of a 5, 10, 15 or 20 mg/kg regimen of methadone to gravid rats on the last two weeks of gestation showed a dose-related increase in resorptions and still births, but no teratogenicity. The two intermediate dose levels produced body weights that were reduced at birth but similar to controls by weaning.

Behavioral teratology studies have suggested that dose levels producing a relatively high maternal and offspring mortality may yield survivors that are more resistant to the toxic effects of the drug and thus not show effects seen among the lower dose-level groups.

Teratogenicity:
Methadone does not appear to be teratogenic in the rat or rabbit models. However, following large doses, methadone produced teratogenic effects in the guinea pig, hamster and mouse.

One published study found that in hamster fetuses, subcutaneous methadone doses of 31 mg/kg or greater (estimated exposure was approximately 2 times a human daily oral dose of 120 mg/day on a mg/m^2 basis, or equivalent to a human daily intravenous dose of 120 mg/day) on day 8 of gestation produced exencephaly and neurological effects. Some of the reported effects were observed at doses that were maternally toxic. In another study, a single subcutaneous dose of 22 to 24 mg/kg methadone (estimated exposure was approximately equivalent to a human daily oral dose of 120 mg/day on a mg/m^2 basis; or half a human daily intravenous dose of 120 mg/day) on day 9 of gestation in mice also produced exencephaly in 11% of the embryos. However, no effectswere reported in rats and rabbits at oral doses up to 40 mg/kg (estimated exposure was approximately 3 and 6 times, respectively, a human daily oral dose of 120 mg/day on a mg/m^2 basis; or 1.5 and 3 times a human daily intravenous dose of 120 mg/day) during days 6 to 15 and 6 to18, respectively.

Abnormal fetal nonstress tests (NSTs) have been reported to occur more frequently when the testis performed 1 to 2 hours after a maintenance dose of methadone in late pregnancy compared to controls. Published animal studies suggest that perinatal exposure to opioids including methadone may alter neuronal development and behaviour in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociception responses and sensitivity to other drugs. Additional animal data demonstrates evidencefor neurochemical changes in the brains of methadone-treated offspring, including the cholinergic,dopaminergic noradrenergic and serotonergic systems.

Carcinogenicity and Genotoxicity:
Data from published reports of carcinogenicity studies indicate that there was a significant

increase in pituitary adenomas in female B6C2F1 mice consuming 15 mg/kg/day methadone for two years.This dose was approximately 0.6 times a human daily oral dose of 120 mg/day, on a body surface area basis. However, this finding was not seen in mice consuming 60 mg/kg/day (approximately 2.5 times a human daily oral dose of 120 mg/day). Furthermore, in a two-year study of dietary administration of methadone to Fischer 344 rats, there was no clear evidence for treatment related increase in the incidence of neoplasms, at doses as high as 28 mg/kg/day in males and 88 mg/kg/day in females (approximately 2.3 times and 7.1 times, respectively, a human daily oral dose of 120 mg/day) based on body surface area comparison.

In published reports, methadone tested negative in tests for chromosome breakage and disjunction and sex-linked recessive lethal gene mutations in germ cells of Drosophila using feeding and injection procedures. Methadone treatment of male mice increased sex chromosome and autosome univalent chromosomes and translocations in multivalent chromosomes. Methadone tested positive in the E. coli DNA repair system and Neurospora crassa and mouse lymphoma forward mutation assays.

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[N] APO-METHADONE
Methadone Hydrochloride Tablets

Read this carefully before you start taking **APO-METHADONE** 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 **APO-METHADONE**.

Serious Warnings and Precautions

- **Even if you take APO-METHADONE as prescribed you are at risk for opioid addiction, abuse,and misuse that can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your prescriber (e.g., doctor).**
- **Life-threatening breathing problems can happen while taking APO-METHADONE, especially if not taken as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **Never give anyone your APO-METHADONE. They could die from taking it. If a person has not been prescribed APO-METHADONE, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took APO-METHADONE 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 APO-METHADONE with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

What is APO-METHADONE used for?

APO-METHADONE is used for the long-term management of pain, when:
- the pain is severe enough to require daily, around-the-clock painkillers
- the doctor determines that other treatment options are not able to effectively treat your pain

APO-METHADONE is NOT used ("as needed") to treat pain that you only have once in a while.

How does APO-METHADONE work?
APO-METHADONE contains methadone hydrochloride which is a pain medication belonging to the classof medicines known as opioids which include codeine, fentanyl, morphine and oxycodone. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in APO-METHADONE*?*

Medicinal ingredient: methadone hydrochloride

Non-medicinal ingredients:
- APO-METHADONE tablets contain D&C Yellow No.10 aluminium (10 mg), FD&C Blue No. 1 (1 and 10 mg), FD&C Yellow No.6 (5 mg), lactose, magnesium stearate, mannitol, microcrystalline cellulose and tromethamine

APO-METHADONE comes in the following dosage forms:
APO-METHADONE tablets: 1 mg, 5mg, 10 mg and 25 mg

Do not use APO-METHADONE if:

- your doctor did not prescribe it for you
- you are allergic to methadone hydrochloride or other opioid analgesics or to any of the other ingredients of APO-METHADONE **(see What are the ingredients in APO-METHADONE?)**
- have never used an opioid analgesic before
- your pain can be controlled by the occasional use of painkillers including those available without a prescription
- you have severe asthma, trouble breathing, or any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have a severe diarrhea caused by antibiotics
- you have a head injury or other risks for seizures
- you suffer from alcoholism
- are going to have, or recently had, a planned surgery
- you have taken a certain type of antidepressant (MAO inhibitors) within the last 14 days.
- you are pregnant or plan to become pregnant, breastfeeding, or in labour

Do not use APO-METHADONE tablets if:

- You have rare inherited diseases, which affect how your body uses the sugar lactose(because lactose is an ingredient in APO-METHADONE).
- **To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-METHADONE. Talk about any health conditions or problems you may have, including if you:**
- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- suffer from migraines
- have, or had in the past abdominal pain, thyroid gland problems, prostate problems, unusual narrowing of the urethra, adrenal gland problems such as Addison's disease, seizure, convulsions, hallucinations, or severe mental problems.

Other warnings you should know about:

Opioid dependence and addiction:

There is a risk of abuse or addiction with all opioids. Some patients, particularly those who have abused drugs in the past, may have a higher risk of abusing or developing an addiction while taking opioids, such as APO-METHADONE. Patients who have taken APO-METHADONE for a period of time may develop physical dependence, and should not abruptly stop taking it. See "**Stopping your Medication**:" section of this leaflet.

There are important differences between physical dependence and addiction, and each is a reason for close medical supervision and honest questions with your doctor. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pediatrics (less than 18 years of age): The safety and efficacy of APO-METHADONE has not been studied in the pediatric population. Therefore, the use of APO-METHADONE is not recommended in patients under18 years of age.

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

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to APO-METHADONE. APO-METHADONE 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 APO-METHADONE.

Serotonin toxicity (also known as Serotonin syndrome): APO-METHADONE 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 toxicity if you take APO-METHADONE with certain anti-depressants or migraine medications.

Serotonin toxicity symptoms include:

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

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.

Sleep Apnea: Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your doctor if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

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 APO-METHADONE:

- alcohol, including prescription and non-prescription medications containing alcohol.
  Do not drink alcohol while taking APO-METHADONE. This can lead to drowsiness, depressed breathing, unusually slow or weak breathing, serious side effects or a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by APO-METHADONE
- other opioid analgesics (for pain)
- general anesthetics (used during surgery)
- drugs used to help you sleep or to reduce anxiety
- antidepressants (for depression and mood disorders). **Do not** take APO-METHADONE with MAO inhibitors or if you have taken MAOi's in the last 14 days before treatment with APO-METHADONE.
- drugs used to treat serious mental or emotional disorders such as schizophrenia
- drugs used for the treatment of epilepsy (e.g. phenytoin, carbamazepine);
- antihistamines (for allergies) or cold medicines
- anti-emetics (for prevention of vomiting)

- diuretics
- drugs used to treat muscle spasms and back pain
- warfarin and other coumarin anticoagulants (for prevention/treatment of blood clots)
- anti-retroviral, anti-fungal and antibiotic drugs
- drugs that use a system called CYP3A4 in the body (e.g. erythromycin, sertraline)
- any non-prescription, (over the counter) medication including laxatives
- any herbal remedies including the herbal remedy St. John's Wort (primarily used for thetreatment of depressive moods)

How to take APO-METHADONE:
For APO-METHADONE tablets: Swallow whole. Do not break, chew, dissolve or crush.

Do not use APO-METHADONE for injection or rectal administration.

Usual Adult Starting Dose:
Dosage is individualized. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor. Taking higher doses can lead to more side effects and a greater chance of overdose.

The usual adult oral dose is 2.5 mg to 10 mg every 4 hours during the first 3 to 5 days, followed a fixed dose every 8 to 12 hours depending on your requirements.

In patients 65 years old and older, APO-METHADONE could be given once a day.

Your dose of APO-METHADONE will be clearly labeled on the medication bottle. Be sure to follow the directions on the label exactly; this is very important. Do not increase or decrease your dose without consulting your doctor. If your dosage is changed by your doctor, be sure to write it down at the time your doctor calls or sees you, and follow the new directions exactly.

Review your pain regularly with your doctor to determine if you still need APO-METHADONE. Be sure to use APO-METHADONE only for the condition for which it was prescribed.

Should your pain increase or any other complaint develop as a result of taking APO-METHADONE, tell your doctor immediately.

Stopping your Medication:
You should not stop taking APO-METHADONE all at once if you have been taking it for more than a few days.

Your doctor will monitor and guide you on how to slowly stop taking APO-METHADONE. 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 with sleeping
- an unusual increase in sweating

- heart palpitations
- an unexplained fever
- weakness
- vomiting
- 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 APO-METHADONE.

Refilling Prescriptions for APO-METHADONE:
A new written prescription is required from your doctor each time you need more APO-METHADONE. 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, or a person you are caring for, have taken too much APO-METHADONE, contact a 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:
It is important that you do not miss any doses. However, if you do 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 APO-METHADONE?
These are not all the possible side effects you may feel when taking APO-METHADONE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Drowsiness, insomnia
- Dizziness, fainting
- Lightheadedness
- Nausea, vomiting, poor appetite, dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sleepiness
- Sweating, facial flushing
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility.

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

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, seizures.			√
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 toxicity (also knownas Serotonin syndrome): a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38°C), or rigid muscles.			√

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) 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 APO-METHADONE in a secure place to prevent theft, misuse or accidental exposure.**
- Store at 15°C - 30°C. Keep tightly closed. Protect from light.
- **Keep APO-METHADONE 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 accidently takes APO-METHADONE, get emergency help right away.**

Disposal:
APO-METHADONE 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 APO-METHADONE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this patient 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). Find the Patient Medication Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

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