PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N] ODAN-METHADONE

Methadone Hydrochloride Oral Concentrate, USP
Cherry Flavored
10 mg / mL

Methadone Hydrochloride Oral Concentrate, USP
Dye-Free, Sugar-Free, Unflavored
10 mg / mL

Treatment of Opioid Dependence

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Table of Contents

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Warning: MAY BE HABIT FORMING

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedical Ingredients
Oral	Liquid Concentrate, 10 mg / mL	Odan-Methadone Oral Concentrate contains: Natural and artificial cherry flavor, citric acid anhydrous, FD&C Red No. 40, D&C Red No. 33, methylparaben, poloxamer 407, propylene glycol, propylparaben, purified water, sodium citrate dihydrate, sucrose. Odan-Methadone Sugar-Free Oral Concentrate contains: citric acid anhydrous, purified water, sodium benzoate.

INDICATIONS AND CLINICAL USE

Adults
Odan-Methadone is indicated for substitution treatment in opioid drug dependence in adults.

Odan-Methadone is not indicated as an as-needed (prn) analgesic.

Patients prescribed Odan-Methadone should be carefully monitored within a framework of medical, social and psychological support as part of a comprehensive opioid dependence treatment program.

Geriatrics (> 65 years of age)
The safety and effectiveness of methadone hydrochloride in patients 65 years of age or 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 has not been studied in the pediatric population. Therefore the use of Odan-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 any type).
- Odan-Methadone should not be given to patients with diarrhea associated with pseudomembranous colitis or caused by poisoning, until toxic material has been eliminated from the gastrointestinal tract
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

WARNINGS AND PRECAUTIONS

FOR ORAL USE ONLY

SERIOUS WARNINGS AND PRECAUTIONS

<u>Addiction, Abuse, and Misuse</u>
Odan-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 Odan-Methadone, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). Odan-Methadone should be stored securely to avoid theft or misuse.

<u>Life-threatening Respiratory Depression : OVERDOSE</u>
Serious, life-threatening, or fatal respiratory depression may occur with use of Odan-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 Odan-Methadone or following a dose increase. Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Deaths have been reported during initiation of methadone treatment for opioid dependence. In some cases, drug interactions with other drugs, both licit and illicit, have been suspected. However, in other cases, deaths appear to have occurred due to the respiratory or cardiac effects of methadone and too-rapid titration without appreciation for the accumulation of methadone over time. It is critical to understand the pharmacokinetics of methadone and to exercise vigilance during treatment initiation and dose titration (see DOSAGE AND ADMINISTRATION). Patients must also be strongly cautioned against self-medicating with central nervous system (CNS) depressants during initiation of methadone treatment.

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.

<u>QT interval prolongation</u>
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.

<u>Accidental Exposure</u>
Accidental ingestion of even one dose of Odan-Methadone, especially by children, can result in a fatal overdose of methadone hydrochloride (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

<u>Neonatal Opioid Withdrawal Syndrome</u>
Prolonged maternal use of Odan-Methadone during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

<u>Interaction with Alcohol</u>
The co-ingestion of alcohol with Odan-Methadone should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

<u>Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants</u>
Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, <u>Neurologic</u> and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of Odan-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

Odan-Methadone and Odan-Methadone Sugar-Free are for oral administration only. The preparation must not be injected. Odan-Methadone and Odan-Methadone Sugar-Free, if dispensed, should be packaged in child-resistant containers and kept out of reach of children to prevent accidental ingestion.

Methadone Hydrochloride, a synthetic opioid, is a controlled substance (Classification N) under the *Controlled Drugs and Substances Act* (CDSA).

Patients should be instructed not to give Odan-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. Odan-Methadone should be stored securely to avoid theft or misuse.

Odan-Methadone should only be prescribed by persons knowledgeable in the continuous administration of potent opioids 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 Odan-Methadone as it may increase the chance of experiencing serious adverse events, including death.

Abuse and Misuse

Like all opioids, Odan-Methadone is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Odan-Methadone should be prescribed and handled with caution. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

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

Odan-Methadone is sought by people with addiction to opioids and is subject to diversion. This should be considered when prescribing Odan-Methadone in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Prescribe and dispense Odan-Methadone with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the patient's home.

Methadone is a μ-agonist opioid with an abuse liability similar to that of morphine and other opioid agonists and is a Schedule I controlled substance. Methadone, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion.

Use in Drug and Alcohol Addiction:

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

Carcinogenesis and Mutagenesis
See **TOXICOLOGY** section.

Cardiovascular
This information is intended to alert the prescriber to comprehensively evaluate the risks and benefits of methadone treatment. The intent is not to deter the appropriate use of methadone in patients with a history of cardiac disease.

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). Although most cases involve patients being treated for pain with large, multiple daily doses of methadone, cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In most of the cases seen at typical maintenance doses, concomitant medications and/or clinical conditions such as hypokalemia were noted as contributing factors. However, the evidence strongly suggests that methadone possesses the potential for adverse cardiac conduction effects in some patients.

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.

The potential risks of methadone, including the risk of life-threatening arrhythmias, should be weighed against the risks of discontinuing methadone treatment. In the patient being treated for opioid dependence with methadone maintenance therapy, these risks include a very high likelihood of relapse to illicit drug use following methadone discontinuation.

The use of methadone in patients already known to have a prolonged QT interval has not been systematically studied. The potential risks of methadone should be weighed against the substantial morbidity and mortality associated with untreated opioid addiction.

When treating patients with 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 be at risk, careful monitoring of cardiovascular status, including evaluation of QT prolongation and dysrhythmias should be performed.

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 Odan-Methadone.

Patients who are ambulatory should be cautioned that Odan-Methadone, like other opioids, may produce orthostatic hypotension.

The use of Odan-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 Odan-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. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**).

Endocrine

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

Incomplete Cross-tolerance between Methadone and other Opioids
Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-

tolerance is of particular concern for patients tolerant to other μ-opioid agonists who are being converted to methadone, thus making determination of dosing during opioid conversion complex. Deaths have been reported during conversion from chronic, high-dose treatment with other opioid agonists. A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise.

Patients Experiencing Anxiety

Since methadone as used by tolerant patients at a constant maintenance dosage does not act as a tranquilizer, patients will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dose of Odan-Methadone. The action of methadone in maintenance treatment is limited to the control of narcotic withdrawal symptoms and is ineffective for relief of general anxiety.

Patients Experiencing Acute Pain

Patients in methadone maintenance treatment for opioid dependence who experience physical trauma, postoperative pain or other acute pain cannot be expected to derive analgesia from their existing dose of Odan-Methadone. Such patients should be administered analgesics, including opioids, in doses that would otherwise be indicated for non-methadone-treated patients with similar painful conditions. Due to the opioid tolerance induced by methadone, when opioids are required for management of acute pain in methadone patients, somewhat higher and/or more frequent doses will often be required than would be the case for non-tolerant patients.

Gastrointestinal Effects

Methadone and other morphine-like opioids have been shown to decrease bowel motility. Methadone may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

Neonatal Opioid Withdrawal Syndrome (NOWS)

Special care is required for the infant born to a mother who has been dependent on methadone and/or other opioids. Newborn infants who have been exposed to opioids in uteri within four weeks of delivery are potentially dependent and must be closely observed for withdrawal symptoms for at least two weeks. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Sign of neonatal opioid withdrawal syndrome include: irritability, hyperactivity and abnormal sleep pattern, increased respiratory rate, excessive or high pitched crying, tremor, vomiting, diarrhea, sneezing, yawning, fever and failure to gain weight. The onset and severity of the syndrome can vary, along with the duration which may range from a few days to weeks or even months. This variability is due to the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

The contribution of maternal methadone dose to the development of NOWS is not clear at present, as there are conflicting results. Some studies support an association, while others do not. In addition, there is currently no consensus on the appropriate management of infant withdrawal.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Odan-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. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored. Odan-Methadone should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (see **DRUG INTERACTIONS**).

Deaths have been reported when methadone has been abused in conjunction with benzodiazepines. Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Odan-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 risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

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

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

Serotonin Toxicity/Serotonin Syndrome: Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with methadone, and may be observed when using Odan-Methadone, particularly during combined use with other serotonergic drugs (see **DRUG INTERACTIONS**).

Serotonin toxicity is characterised 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 Odan-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.

Monoamine Oxidase Inhibitors (MAOIs)

Severe and unpredictable reactions have been reported with concomitant use of MAOIs and opioid analgesics. Therefore, the use of methadone is not recommended in patients taking MAOIs (or within 14 days of such therapy). If the use of Odan-Methadone is necessary in such patients, a sensitivity test should be performed in which incremental doses of Odan-Methadone are administered over the course of several hours while the patient's condition and vital signs are under careful observation (see also **DRUG INTERACTIONS, Monoamine Oxidase Inhibitors**).

Psychomotor Impairment

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

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Odan-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 Odan-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.

Methadone's peak respiratory depressant effects are typically delayed following intake. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

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

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) (see **ADVERSE REACTIONS**). 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**).

Sexual Function/Reproduction

Fertility – Reproductive function in human males may be decreased by methadone treatment. Reductions in ejaculate volume and seminal vesicle and prostate secretions have been reported in methadone-treated individuals. In addition, reductions in serum testosterone levels and sperm motility, and abnormalities in sperm morphology have been reported.

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

Published animal studies provide additional data indicating that methadone treatment of males can alter reproductive function. Methadone produces a significant regression of sex accessory organs and testes of male mice and rats. Additional data have been published indicating that methadone treatment of male rats increases death rate of embryos and neonates.

Special Populations

Special Risk Groups: Odan-Methadone should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients

with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Acute Abdominal Conditions
The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Pregnant Women
Although methadone crosses the placental barrier, reproduction studies in humans have not been conducted.

It is the physician's responsibility to ensure that female patients are fully informed concerning the possible risks to a pregnant woman or her unborn child from both the use of methadone, and stopping the use of methadone. Care of pregnant patients should be under the supervision of a physician experienced in the management of this patient population in opioid addiction.

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

Animal reproduction studies have revealed no evidence of harm to the fetus due to methadone.

Gestation
Methadone has been detected in amniotic fluid and cord plasma at concentrations proportional to maternal plasma and in newborn urine at lower concentrations than corresponding maternal urine. Methadone and its primary metabolite have been detected in samples of meconium.

A retrospective series of 101 pregnant, opioid-dependent women who underwent in-patient opioid detoxification with methadone did not demonstrate any increased risk of miscarriage in the second trimester or premature delivery in the third trimester.

Abnormal fetal non-stress tests (NSTs) have been reported to occur more frequently when the test is performed 1 to 2 hours after a maintenance dose of methadone in late pregnancy compared to controls. Fetuses of methadone maintained mothers show decreased fetal heart rate and motor activity.

Several studies have suggested that infants born to opioid-abusing women treated with methadone during all or part of pregnancy have been found to have decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. This growth deficit does not appear to persist into later childhood.

Additional information on the potential risks of methadone may be derived from animal data (see Part II of Product Monograph, **TOXICOLOGY**).

Perinatal
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. With increasing maternal methadone dose, there may be a corresponding increase in infants' risk of being born pre-term, being symmetrically smaller, spending longer periods in hospital and the need for treatment for Neonatal Abstinence Syndrome.

Neonatal Growth and Development

There are conflicting reports on whether SIDS (Sudden Infant Death Syndrome) occurs with an increased incidence in infants born to women treated with methadone during pregnancy.

Studies show opioid exposure *in utero* has an effect on the development of the brain and visual system. 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, whether they are caused indirectly by genetic and environmental risk factors, or are a consequence of pre-term birth.

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 evidence for neurochemical changes in the brains of methadone-treated offspring, including the cholinergic, dopaminergic noradrenergic and serotonergic systems. Published animal data have reported increased neonatal mortality and significant differences in behavioral tests in the offspring of male rats that were treated with methadone prior to mating. Mechanistic studies in this rat model suggest that the developmental effects of "paternal" methadone on the progeny may be due to decreased testosterone production; decreased testosterone levels reported in men on methadone maintenance therapy.

Ophthalmic Abnormalities

Infants born to drug-misusing mothers prescribed methadone in pregnancy 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 Neonatal Abstinence Syndrome severe enough to receive pharmaceutical treatment may be at particular risk of developing nystagmus. Delayed visual development has also been reported. Exposure to opioid including methadone, during pregnancy may result in permanently reduced vision and nystagmus.

Labour, Delivery and Nursing Women

As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. Naloxone, a drug that counters the effects of opioids, should be readily available if Odan-Methadone is used in this population. Odan-Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn. Narcotics with mixed agonist/antagonist properties should not be used for pain

control during labor in patients chronically treated with Odan-Methadone as they may precipitate acute withdrawal.

Methadone is secreted into human milk. Caution should be exercised when Odan-Methadone is administered to a nursing woman. There have been rare cases of sedation, respiratory depression, and death in infants exposed to methadone through breast milk.

The evaluation of the risks and benefits of breastfeeding while on methadone maintenance therapy should be done jointly by the physician and the patient. Patients who express a desire to breastfeed should clearly understand why they should not use illicit substances or any other drug not prescribed by their health professional while breastfeeding and how the use of additional drugs can pose additional risks to the breastfeeding infant beyond those associated with Odan-Methadone .

Mothers using Odan-Methadone should receive specific information about how to identify respiratory depression and sedation in their babies. They should know when to contact a health professional or seek immediate medical care.

At maternal oral doses of 10 to 80 mg/day, methadone concentrations from 50 to 570 mcg/L in milk have been reported, which, in the majority of samples, were lower than maternal serum drug concentrations at steady state. Peak methadone levels in milk occur approximately 4 to 5 hours after an oral dose. Based on an average milk consumption of 150 mL/kg/day, an infant would consume approximately 17.4 mcg/kg/day, which is approximately 2 to 3% of the oral maternal dose. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone.

Women being treated with Odan-Methadone for any indication who are already breastfeeding should be counseled to wean breastfeeding gradually in order to prevent the development of withdrawal symptoms in the infant.

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

Ingestion by a child, whether accidental or deliberate, is a medical emergency that may result in death. Patients with take-home doses should be instructed to keep Odan-Methadone in a secure place out of the reach and sight of children and to discard unused Odan-Methadone in such a way that individuals other than the patient for whom it was originally prescribed will not come in contact with the drug.

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

Patients with Hepatic Impairment:
Methadone is metabolized in the liver and therefore patients with liver impairment may be at risk of accumulating methadone after multiple dosing. The use of methadone hydrochloride has not been extensively evaluated in patients with hepatic insufficiency (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Caution should be used as methadone may precipitate porto-systemic encephalopathy in patients with severe liver damage.

As with other opioids, methadone may cause troublesome constipation, which is particularly dangerous in patients with severe hepatic impairment, and measures to avoid constipation should be initiated early.

Patients with Renal Impairment:
The use of methadone hydrochloride has not been extensively evaluated in patients with renal insufficiency (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Urine acidification has been shown to increase renal elimination of methadone.

Gender
The use of methadone hydrochloride has not been evaluated for gender specificity.

Monitoring and Laboratory Tests
Pregnancy Tests
Methadone may interfere with urine testing for pregnancy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Adverse effects of Odan-Methadone are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

Heroin Withdrawal
During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following signs and symptoms associated with acute withdrawal from heroin or other opioids: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, gooseflesh, fever, chilliness alternating with flushing, restlessness, irritability, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration
The initial Odan-Methadone dose should be carefully titrated to the individual. Too rapid titration for the patient's sensitivity is more likely to produce adverse effects.

The major hazards of methadone are respiratory depression, QT interval prolongation and systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred. Patients may be particularly vulnerable during the stabilization period (see WARNINGS AND PRECAUTIONS).

Maintenance on a Stabilized Dose
During prolonged administration of methadone hydrochloride, as in a methadone maintenance treatment program, there is usually a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, constipation and sweating.

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.

Adverse Drug Reactions

Cardiac disorders (see **WARNINGS AND PRECAUTIONS, Cardiovascular**): arrhythmias, bigeminal rhythms, bradycardia, cardiomyopathy, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, syncope, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia

Eye disorders: visual disturbances

Gastrointestinal disorders: abdominal pain, constipation, dry mouth, glossitis, nausea, vomiting

General disorders and administration site conditions: asthenia (weakness), edema

Hepatobiliary disorders: biliary colic

Investigations: ECG abnormal, Electrocardiogram QT prolonged, T-wave inversion

Metabolic and Nutritional disorders: anorexia, hypokalemia, hypomagnesemia, weight gain

Nervous system disorders: dizziness, headache, lightheadedness, sedation, sleep-disordered breathing, seizures

Psychiatric disorders: hallucinations, agitation, confusion, disorientation, dysphoria, euphoria, insomnia

Renal and urinary disorders: antidiuretic effect, urinary retention or hesitancy

Reproductive system and breast disorders: amenorrhea, reduced libido and/or potency

Respiratory, thoracic and mediastinal disorders: pulmonary edema, respiratory depression (see **WARNINGS AND PRECAUTIONS, Respiratory Depression**)

Skin and subcutaneous tissue disorders: pruritis, urticaria, other skin rashes, and rarely, hemorrhagic urticaria

Abnormal Hematologic and Clinical Chemistry Findings
Reversible thrombocytopenia has been described in patients with chronic hepatitis.

Post-marketing Experience
The following adverse reactions have been identified during post-approval use of methadone hydrochloride.

Endocrine Disorders: Androgen deficiency

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

Nervous System Disorders: Serotonin syndrome

Pregnancy, puerperium and perinatal conditions: Neonatal opioid withdrawal syndrome (NOWS)

General Disorders and Administration Site Conditions: drug ineffective

Isolated reports have been received for drug ineffectiveness following a switch between different methadone products. The current data are insufficient to support an estimate of the incidence or to establish causation. Patients presenting with symptoms of withdrawal following formulation change should be clinically monitored and dose titrated as needed.

DRUG INTERACTIONS

Serious Drug Interactions

- **CNS depressants**
- **MAOIs**
- **Serotonergic Drugs (including SSRIs)**
- **Potentially Arrhythmogenic Agents**

(See **Drug-Drug Interactions**).

Overview: Effects of CYP inhibitors and inducers

In vitro results suggest that methadone undergoes hepatic N-demethylation by cytochrome P450 enzymes, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Co-administration of methadone with inducers of these enzymes may result in a more rapid metabolism and potential for decreased effects of methadone, whereas administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Although anti-retroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, and lopinavir + ritonavir combination are known to inhibit CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity.

Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy (see also **Drug-Herb Interactions, St. John's Wort**).

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**). Odan-Methadone should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects

Monoamine Oxidase Inhibitors (MAOIs)

Severe and unpredictable reactions have been reported with concomitant use of MAOIs and opioid analgesics. Since the safety of methadone in this regard has not been established, the use of methadone in patients who have received MAOIs during the previous 14-day period is not recommended. However, if the use of Odan-Methadone is necessary in such patients, a sensitivity test should be performed in which incremental doses of Odan-Methadone are administered over the course of several hours while the patient's condition and vital signs are under careful observation (see also **WARNINGS AND PRECAUTIONS, Monoamine Oxidase Inhibitors**).

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

Co-administration of methadone with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS, Serotonin Syndrome**).

Potentially Arrhythmogenic Agents: Methadone and QT interval prolongation
In patients taking drugs affecting cardiac conduction, or drugs which may affect electrolyte balance, there is a risk of cardiac events when methadone is taken concurrently.

Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with Odan-Methadone. Pharmacodynamic interactions may occur with concomitant use of Odan-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 Odan-Methadone concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.

Drug-Drug Interactions

Table 1 - Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Monoamine oxidase Inhibitors	C	Methadone	May also increase the risk of serotonin syndrome, a potentially life threatening condition.
Selective serotonin reuptake inhibitors	C	Methadone	May increase methadone plasma levels upon co-administration with Odan-Methadone and result in increased opioid effects and/or toxicity.
SSRIs, SNRIs, TCAs, MAOIs (including linezolide and methylene blue), triptans, other serotonergic drugs (e.g. lithium) and serotonin-precursors such as L-tryptophan	C, T	Methadone	May also increase the risk of serotonin syndrome, a potentially life threatening condition.
Alcohol and other CNS depressants	C	Methadone	May increase the general depressant effects of methadone when used concomitantly.

Proper name	Ref	Effect	Clinical comment
Potentially Arrhythmogenic Agents	T, C	Methadone	Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with Odan-Methadone. Pharmacodynamic interactions may occur with concomitant use of Odan-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 Odan-Methadone concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.
Abacavir, efavirenz, nelfinavir, nevirapine, ritonavir	CT, C	Methadone	Co-administration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone. Methadone-maintained patients beginning treatment with these anti-retroviral drugs should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly.
lopinavir + ritonavir combination	T	Methadone	Co-administration may result in increased clearance or decreased plasma levels of methadone.
Amprenavir	CT	Methadone	Methadone blood concentrations are decreased by the administration of abacavir plus amprenavir.
Histamine H2 antagonists such as cimetidine	T	Methadone	Can reduce the protein binding of methadone resulting in increased opioid action.
Delavirdine	T	Methadone	Dosage of methadone may need to be decreased when co-administered with delavirdine.
Rifampicin	C	Methadone	Reduced plasma levels and increased urinary excretion of methadone can occur with concurrent administration of rifampicin. Adjustment of the dose of methadone may be necessary.

Proper name	Ref	Effect	Clinical comment
Ciprofloxacin	C	Methadone	Plasma levels of methadone may increase with concurrent administration of ciprofloxacin due to inhibition of CYP 1A2 and CYP 3A4. Concomitant use may lead to sedation, confusion and respiratory depression.
Erythromycin	T, C	Methadone	Theoretically erythromycin may increase methadone levels due to decreased methadone metabolism.
Fluconazole	CT, C	Methadone	May raise methadone levels, due to decreased methadone metabolism.
Ketoconazole	T	Methadone	May raise methadone levels, due to decreased methadone metabolism.
Voriconazole	CT, C	Methadone	May raise methadone levels due to decreased methadone metabolism.
Phenytoin, Carbamazepine	C	Methadone	Induces methadone metabolism with the risk of precipitating withdrawal syndrome. Adjustment of the dose of methadone should be considered.
Phenobarbital	T	Methadone	Induces methadone metabolism with the risk of precipitating withdrawal syndrome.
Primidone	T	Methadone	Induces methadone metabolism with the risk of precipitating withdrawal syndrome.
Domperidone and metoclopramide	T	Methadone	May increase the speed of onset but not the extent of methadone absorption by reversing the delayed gastric emptying associated with opioids. Conversely, methadone may antagonise the effect of domperidone/metoclopramide on gastro-intestinal activity.
Methadone	T	Ciprofloxacin	Reduced serum concentrations of ciprofloxacin may occur.
Methadone	C	Didanosine Stavudine	Experimental evidence demonstrated that methadone decreased the area under the concentration-time curve (AUC) and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.
Methadone	CT	Zidovudine	Experimental evidence demonstrated that methadone increased the AUC of zidovudine which could result in toxic effects.
Methadone	C	Desipramine	Plasma levels of desipramine have increased with concurrent methadone administration.

Proper name	Ref	Effect	Clinical comment
Methadone	T	Domperidone and metoclopramide	Methadone may antagonise the effect of domperidone/metoclopramide on gastro-intestinal activity.
Methadone	T	Mexiletine	Methadone delays the absorption of mexiletine.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Opioid Antagonists, Mixed Agonist/Antagonists, and Partial Agonists
As with other μ-agonists, patients maintained on methadone may experience withdrawal symptoms when given opioid antagonists, mixed agonist/antagonists, and partial agonists. Examples of such agents are naloxone, naltrexone, pentazocine, nalbuphine, butorphanol, and buprenorphine.

Opioid antagonists:
Naloxone and naltrexone antagonises the analgesic, CNS and respiratory depressant effects of methadone and can rapidly precipitate withdrawal symptoms (see **OVERDOSE**). Similarly buprenorphine and pentazocine may precipitate withdrawal symptoms.

pH of Urine
Drugs that acidify or alkalinise the urine may have an effect on clearance of methadone as it is increased at acidic pH and decreased at alkaline pH.

Drug-Food Interactions
Pharmacokinetic studies show that concomitant grapefruit can cause a modest increase in methadone plasma levels. The clinical relevance of this is unknown.

Others
Methadone may have an effect on other drugs as a consequence of reduced gastro-intestinal motility.

Drug-Herb Interactions
St. John's Wort
Administration of Odan-Methadone along with other CYP3A4 inducers may result in withdrawal symptoms.

Drug-Laboratory Interactions
Pregnancy Tests
Methadone may interfere with urine testing for pregnancy.

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

Odan-Methadone may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery (see **WARNINGS AND**

PRECAUTIONS, Psychomotor Impairment).

DOSAGE AND ADMINISTRATION

USUAL ADULT DOSE: To be determined by the physician; may be diluted with water or other liquid before oral administration.

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

Dosing Considerations

Methadone differs from many other opioid agonists in several important ways. Methadone's pharmacokinetic properties, coupled with high inter-patient variability in its absorption, metabolism, and relative analgesic potency, necessitate a cautious and highly individualized approach to prescribing. **Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.**

The complexities associated with methadone dosing can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. **A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise. Deaths have been reported during conversion to methadone from chronic, high-dose treatment with other opioid agonists and during initiation of methadone treatment of addiction in subjects previously abusing high doses of other agonists.**

After interruption of chronic dosing, if methadone treatment is to be continued, re-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

The initial Odan-Methadone dose should be administered, under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgment. Initially, a single dose of 20 to 30 mg of Odan-Methadone will often be sufficient to suppress withdrawal symptoms. The initial dose should not exceed 30 mg. If same-day dosing adjustments are to be made, the patient should be asked to wait 2 to 4 hours for further evaluation, when peak levels have been reached. An additional 5 to 10 mg of Odan-Methadone may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily dose of Odan-Methadone on the first day of treatment should not ordinarily exceed 40 mg.

Over the first week of treatment, dose adjustments should be made based on control of withdrawal symptoms at the time of expected peak analgesic activity (e.g., 2 to 4 hours after dosing). **Prescribers are reminded that methadone's peak respiratory depressant effects typically occur later, and persist longer, than its peak analgesic effects.** Dose adjustment should be cautious; deaths have occurred in early treatment due to the cumulative effects of the first several days' dosing. Patients should be reminded that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate.

Patients Not Receiving Opioids at the Time of Initiation of Methadone Treatment
Initial doses should be lower for patients whose tolerance is expected to be low at treatment entry. Loss of tolerance should be considered in any patient who has not taken opioids for more than 5 days. Initial doses should not be determined by previous treatment episodes or dollars spent per day on illicit drug use.

Methadone Substitution Use: Maintenance Treatment or Detoxification Treatment
Methadone may be used in a maintenance treatment program of varying duration, or in a short-term detoxification protocol of gradually decreasing doses to the point of abstinence. Patients may remain in methadone maintenance treatment indefinitely, or may be ready for a medically-supervised taper at some point. Regardless of maintenance or detoxification treatment, increased risk of relapse following withdrawal of methadone treatment should be considered.

Prescribers are referred to clinical practice treatment standards and guidelines in their area.

Special Considerations for a Pregnant Woman
Caution should be taken in the maintenance treatment of pregnant patients. For opioid-dependent pregnant women, methadone maintenance should be provided at the lowest accepted dose which prevents withdrawal symptoms (usually less than 80 mg/day). In later pregnancy, it may be necessary to increase the dose, as increased clearance and reduced plasma levels have been reported during pregnancy (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**). An increase by 10 - 20 mg and/or divided dose may be required.

Treatment should be provided throughout pregnancy to protect the fetus and for a minimum of six months post-partum.

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**).

Geriatrics
Dosage adjustments should be based on the patient's clinical response (see **WARNINGS AND PRECAUTIONS, Geriatrics (> 65 years of age)**).

Adjustment or Reduction of Dosage

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Odan-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.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer desired or required for methadone maintenance treatment. Tapering should be individualized to the patient and carried out under medical supervision.

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

Disposal

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

Odan-Methadone should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired Odan-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 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 (acute or chronic) include sudden sensorial hearing loss, toxic leukoencephalopathy, 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 takes a large dose of methadone, effective opioid antagonists are available to counteract the potentially lethal respiratory depression. **The physician must remember,**

however, that methadone is a long-acting depressant (36 to 48 hours), whereas opioid 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.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or cardiovascular depression. In an individual physically dependent 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 dependent 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Methadone is an opioid agonist with actions predominantly at the μ receptor. The analgesic activity of the racemate is almost entirely due to the l-isomer, which is at least 10 times more potent as an analgesic than the d-isomer. The d-isomer lacks significant respiratory depressant activity but does have antitussive effects. Methadone also has some agonist actions at the κ and σ opioid receptors. These actions result in analgesia, depression of respiration, suppression of cough, nausea and vomiting (via an effect on the chemoreceptor trigger zone) and constipation. An effect on the nucleus of the oculomotor nerve, and perhaps on opioid receptors in the pupillary muscles causes pupillary constriction. All these effects are reversible by naloxone with a pA2 value similar to its antagonism of morphine. Like many basic drugs, methadone enters mast cells and releases histamine by a non-immunological mechanism. Similar to morphine, both isomers are 5-HT(3) receptor antagonists, although *l*-methadone producing greater inhibition than *d*-methadone. Methadone causes a dependence syndrome of the morphine type. Cross-tolerance between morphine and methadone has been demonstrated, as steady-state plasma methadone concentrations required for effectiveness ($C_{50\%}$) were higher in abstinent rats previously dosed with morphine, as compared to controls.

Some data indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to product neurotoxic effects in animals.

Prolongation of the QT interval associated with methadone can lead to potentially fatal ventricular arrhythmias and is caused by block of the rapid component of the cardiac delayed rectifier K(+) current (I(Kr)), which is encoded by hERG related gene. *In-vitro* effects of methadone have been

compared to heroin in human embryonic kidney cells expressing hERG currents, with methadone exhibiting 100-fold higher potency (IC_{50} 4.8 mcM) at inhibiting hERG than heroin (IC_{50} 427 mcM).

Central Nervous System
Methadone 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 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 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 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 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.

Pharmacokinetics

Absorption:
Methadone is one of the more lipid soluble opioids, and is well absorbed from the gastrointestinal tract. Following oral administration, the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 and 7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged between 65 to 630

ng/mL and the peak concentrations ranged between 124 to 1255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

Distribution:
Methadone undergoes fairly extensive first pass metabolism. It is bound to albumin and other plasma proteins and to tissue proteins (probably lipoproteins), the concentrations in lung, liver and kidneys being much higher than in the blood. Methadone is unusual in the opioid class, in that there is extensive binding to tissue proteins and fairly slow transfer between some parts of this tissue reservoir and the plasma. Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to a_1-acid glycoprotein (85% to 90%). Marked variations in plasma levels occur in dependent persons on a stable dose of oral methadone, without any relation to symptoms. Methadone is secreted in saliva, sweat, breast milk, amniotic fluid and umbilical cord plasma. The concentration in cord blood is about half the maternal levels.

Metabolism:
Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, CYP2C19, and to a lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine.

Excretion:
The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 and 126 L/h, and the terminal half-life (T½) was highly variable and ranged between 8 and 59 hours in different studies. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

Special Populations and Conditions

Pediatrics:
The pharmacokinetics of methadone hydrochloride has not been evaluated in the pediatric population. Individuals under 18 years of age should not take Odan-Methadone.

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

Gender:
The pharmacokinetics of methadone hydrochloride has not been evaluated for gender specificity.

Race:
The pharmacokinetics of methadone hydrochloride has not been evaluated for race specificity.

Hepatic Impairment:
Methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways, therefore patients with liver impairment may be at risk of accumulating methadone after multiple dosing (see also **WARNINGS AND PRECAUTIONS, Special Risk Patients, Patients with Hepatic Impairment**).

Renal Impairment:
Methadone pharmacokinetics has not been extensively evaluated in patients with renal insufficiency. Unmetabolized methadone and its metabolites are excreted in urine to a variable degree. Methadone is a basic (pKa=9.2) compound and the pH of the urinary tract can alter its disposition in plasma. Urine acidification has been shown to increase renal elimination of methadone. Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for increasing the elimination of methadone or its metabolites.

Pregnancy:
The disposition of oral methadone has been studied in approximately 30 pregnant patients in the second and third trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during second and third trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone (see **WARNINGS AND PRECAUTIONS, Labor, Delivery and Nursing Women** and **DOSAGE AND ADMINISTRATION**).

Pregnant women appear to have significantly lower trough plasma methadone concentrations, increased plasma methadone clearance, and shorter methadone half-life than after delivery. Dosage adjustment using higher doses or administering the daily dose in divided doses may be necessary in pregnant women treated with Odan-Methadone (see **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Teratogenic Effects – Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no controlled studies of methadone use in pregnant women that can be used to establish safety. However, an expert review of published data on experiences with methadone use during pregnancy by the Teratogen Information System (TERIS) concluded that maternal use of methadone during pregnancy as part of a supervised, therapeutic regimen is unlikely to pose a substantial teratogenic risk (quantity and quality of data assessed as "limited to fair"). However, the data are insufficient to state that there is no risk (TERIS, last reviewed October, 2002).

Pregnant women involved in methadone maintenance programs have been reported to have significantly improved prenatal care leading to significantly reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to women using illicit drugs. Several factors complicate the interpretation of investigations of the children of women who take methadone during pregnancy. These include the maternal adjunct use of illicit drugs,

other maternal factors such as nutrition, infection, and psychosocial circumstances, limited information regarding dose and duration of methadone use during pregnancy, and the fact that most maternal exposure appears to occur after the first trimester of pregnancy. Reported studies have generally compared the risk of methadone to the risk of untreated addiction to illicit drugs or to addiction-free pregnancies.

Drug Interactions (see **DRUG INTERACTIONS, Overview: Effects of CYP inhibitors and inducers**)

Methadone undergoes hepatic N-demethylation by cytochrome P450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Co-administration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone. Conversely, administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Pharmacokinetics of methadone may be unpredictable when coadministered with drugs that are known to both induce and inhibit CYP enzymes. Although anti-retroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir + ritonavir combination are known to inhibit some CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy before making a dosage adjustment.

STORAGE AND STABILITY

Dispense in tight containers, protected from light. Store at Room Temperature (15°C to 30°C). Keep out of reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

Dispense in tight containers, protected from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Odan-Methadone Oral Concentrate (methadone hydrochloride oral concentrate USP) 10 mg per mL is supplied as a red, cherry flavored liquid concentrate.

Odan-Methadone Sugar-Free Oral Concentrate (methadone hydrochloride oral concentrate USP) 10mg per mL is supplied as a dye-free, sugar-free, unflavored liquid concentrate.

Composition:

Odan-Methadone Oral Concentrate contains: Natural and artificial cherry flavor, citric acid anhydrous, FD&C Red No. 40, D&C Red No. 33, methylparaben, poloxamer 407, propylene glycol, propylparaben, purified water, sodium citrate dihydrate, and sucrose.

Odan-Methadone Sugar-Free Oral Concentrate contains: citric acid anhydrous, purified water, sodium benzoate.

Packaging:

Available in a 1 litre bottle.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

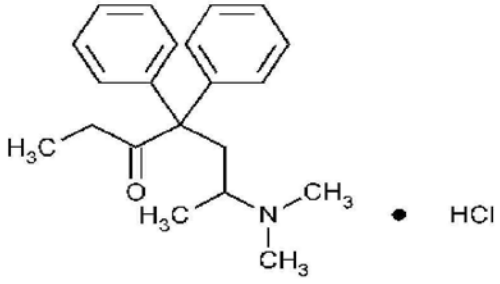
Drug Substance

Proper name: Methadone Hydrochloride

Chemical name: 6-(dimethylamino)-4,4-diphenylheptan-3-one hydrochloride

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

Structural formula:



Physicochemical properties:
Methadone hydrochloride is a white, essentially odorless, bitter-tasting crystalline powder. It is very soluble in water, soluble in isopropanol and in chloroform, and practically insoluble in ether and in glycerine. It is present in Odan-Methadone as the racemic mixture. Methadone hydrochloride has a melting point of 235°C, a pKa of 8.25 in water at 20°C, a solution (1 part per 100) pH between 4.5 and 6.5, a partition coefficient of 117 at pH 7.4 in octanol/wat.

Other ingredients of Odan-Methadone Oral Concentrate: Natural and artificial cherry flavor, citric acid anhydrous, FD&C Red No. 40, D&C Red No. 33, methylparaben, poloxamer 407, propylene glycol, propylparaben, purified water, sodium citrate dihydrate, sucrose.

Other ingredients of Odan-Methadone Sugar-Free Oral Concentrate: citric acid anhydrous, purified water, sodium benzoate.

DETAILED PHARMACOLOGY

See **ACTION AND CLINICAL PHARMACOLOGY** section.

TOXICOLOGY

In animals, methadone is 3 to 10 times more toxic than morphine, depending on the species, and 2 to 3 times more toxic than meperidine. In acute dose toxicity studies in rats, methadone 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 predominantly accounts for withdrawal suppression activity of the racemic mixture, demonstrates a similar toxicity to that seen with *d*-*l*-methadone. [Kristensen 1996; Pharmascience, 2005]

The following table summarizes the acute toxicity data for *d*-*l*-methadone obtained in rats and mice. [RTECS, 2011]

Route	**LD_{50} Values (mg/kg)**	
	Mouse	Rat
po	95	86
ip	31	18
sc	27	30
iv	24	11

Four of 6 monkeys (stumped tail macaques) orally administered methadone at a dose of 5 mg/kg three times per day (total daily dose 15 mg/kg) for two or more weeks developed sudden toxicity. In general, toxicity was associated with plasma methadone concentrations greater than 130 ng/mL (range 130 – 420 ng/mL) and in each case occurring after the first morning dose. Findings included respiratory depression, respiratory arrest resulting in death (1 monkey), shallow breathing, ataxia, fixed gaze, and EEG changes including attenuated visual evoked response waves. Two monkeys not developing toxicity had plasma methadone levels ranging from 20 to 123 ng/mL. [Snyder, 1977]

Morphine has been shown to elevate corticosterone and suppress the immune system. Methadone and morphine treatment in mice resulted in suppression of hepatic and splenic phagocytosis. [LeVier, 1995] However, immune response to parasitic, bacterial and yeast infections following methadone treatment was intact and, unlike morphine, phagocytosis by peripheral leukocytes and monocytes and alveolar macrophages was not altered. [De Waal, 1988; NTP, 1994; Tubaro, 1987] Chronic exposure to morphine and methadone produced tolerance and normal function in human cultured monocyte-derived macrophages, while withdrawal decreased phagocytic function in a similar manner to acute opioid exposure. [Delgado-Velez, 2008] Phagocytic activity in liver macrophages (Kupffer cells) from female mice dosed with 30 mg/kg methadone every 6 hours for 5 days, was decreased up to 59% and changes were dose-dependent. There was also a significant decrease in the ability of resident splenic macrophages to phagocytize RBCs. However these immunologic changes did not affect host resistance to bacteria. [NTP, 1994]

Carcinogenicity:
The results of carcinogenicity assessment in B6C2F1 mice and Fischer 344 rats following dietary administration of two doses of methadone hydrochloride have been published. Mice consumed 15 mg/kg/day or 60 mg/kg/day methadone for two years. These doses were approximately 0.6 and 2.5 times a human daily oral dose of 120 mg/day on a body surface area basis (mg/m^2). There was a significant increase in pituitary adenomas in female mice treated with 15 mg/kg/day but not with 60 mg/kg/day. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in male rats. Due to decreased food consumption in males at the high dose, male rats consumed 16 mg/kg/day and 28 mg/kg/day of methadone for two years. These doses were approximately 1.3 and 2.3 times a human daily oral dose of 120 mg/day, based on body surface area comparison. In contrast, female rats consumed 46 mg/kg/day or 88 mg/kg/day for two years. These doses were approximately 3.7 and 7.1 times a human daily oral dose of 120 mg/day, based on body surface area comparison. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in either male or female rats.

Mutagenicity:
There are several published reports on the potential genetic toxicity of methadone. 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. In contrast, methadone tested positive in the in vivo mouse dominant lethal assay and the in vivo mammalian spermatogonial chromosome aberration test. Additionally, methadone tested positive in the *E.coli* DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays.

Reproductive Studies:
Reproductive studies in rats revealed no evidence of teratogenicity. Multi-generational reproductive toxicity studies in male and female rats showed decreased body weight and number of pups (F1) and increased mortality (F2) with no changes in the F3 generation. [Walz, 1983] Subcutaneous doses of 20 to 28 mg/kg/day from gestation days 6 through 15 in CD-1 mice resulted in increased resorptions and decreased live births per litter as well as affecting fetal ossification of digits, sternum and skull. [Bui, 1993] Acute methadone dosing in male rats has been shown to increase the frequency of neonatal deaths. [Joffe, 1976] However, after chronic dosing, male rats showed no dominant lethal effect and spermatogenesis was not affected. [Soyka, 1978] Effects on the male reproductive system between rodent species show conflicting results. Methadone doses of 4 to 6 mg/kg/day for 3 days affected spermatogenesis in male mice. Germ cell chromosomal aberrations occurred in a dose-dependent manner and there were increased numbers of preimplantation deaths. [Badr, 1979]

Published animal data have reported increased neonatal mortality in the offspring of male rats that were treated with methadone prior to mating. In these studies, the female rats were not treated with methadone, indicating paternally-mediated developmental toxicity. Specifically, methadone administered to the male rat prior to mating with methadone-naïve females resulted in decreased weight gain in progeny after weaning. The male progeny demonstrated reduced thymus weights, whereas the female progeny demonstrated increased adrenal weights.

Furthermore, behavioral testing of these male and female progeny revealed significant differences in behavioral tests compared to control animals, suggesting that paternal methadone exposure can produce physiological and behavioral changes in progeny in this model.

Other animal studies have reported that perinatal exposure to opioids including methadone alters neuronal development and behavior in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociceptive responses and sensitivity to drugs. Additional animal data demonstrates evidence for neurochemical changes in the brains of methadone-treated offspring, including changes to the cholinergic, dopaminergic, noradrenergic and serotonergic systems. Additional studies demonstrated that methadone treatment of male rats for 21 to 32 days prior to mating with methadone-naïve females did not produce any adverse effects, suggesting that prolonged methadone treatment of the male rat resulted in tolerance to the developmental toxicities noted in the progeny. Mechanistic studies in this rat model suggest that the developmental effects of "paternal" methadone on the progeny appear to be due to decreased testosterone production. These animal data mirror the reported clinical findings of decreased testosterone levels in human males on methadone maintenance therapy for opioid addiction and in males receiving chronic intraspinal opioids.

Maternal exposure (5 mg/kg) of rats to *d-l*-methadone during gestation or lactation resulted in perinatal exposure in pups that produced reduced body weight, body length, head diameter and organ weights.[McLaughlin, 1978] Perinatal methadone treatment in rats results in dependence, developmental delays, and affects brain growth and development in their offspring. [Enters, 1991; Ford, 1979; Zagon, 1977] Chronic administration of methadone in pregnant Cynomolgus monkeys significantly reduced birth weight. [Hein, 1998] In the Guinea pig, prenatal methadone treatment resulted in decreased body weight and withdrawal symptoms in offspring. Morphine and methadone were associated with respiratory changes in Guinea pig pups with the effect of morphine being more prolonged. [Nettleton, 2008]

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 in pregnant hamsters indicated that a single subcutaneous dose of methadone ranging from 31 to 185 mg/kg (the 31 mg/kg dose is approximately twice a human daily oral dose of 120 mg/day on a mg/m^2 basis) on day 8 of gestation resulted in a decrease in the number of fetuses per litter and an increase in the percentage of fetuses exhibiting congenital malformations described as exencephaly, cranioschisis, and "various other lesions." The majority of the doses tested also resulted in maternal death. 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) administered on day 9 of gestation in mice also produced exencephaly in 11% of the embryos. However, no effects were 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) administered during days 6-15 and 6-18, respectively.

REFERENCES

1. Badr FM, Rabouh SA, Badr RS. On the mutagenicity of methadone hydrochloride. Induced dominant lethal mutation and spermatocyte chromosomal aberrations in treated males. Mutat Res 68(3):235-49. (1979).

2. Berkowitz BA. The relationship of pharmacokinetics to pharmacological activity: morphine, methadone and naloxone. Clin Pharmacokinet 1976; 1:219-30.

3. Berthschy G. Methadone maintenance treatment: an update. Eur Arch Psychiatry Clin Neurosci 1995; 245: 114-24.

4. Bui QQ, Sperling F, West WL. Developmental toxic effect after subcutaneous injections of methadone in Charles River CD-1 mice. Drug Chem Toxicol 6(1):41-70. (1983).

5. Cleary BJ, Donnelly JM, Strawbridge JD, Gallagher PJ, Fahey T, White MJ, Murphy DJ. Methadone and perinatal outcomes: a retrospective cohort study. Am J Obstet Gynecol. 2011;204(2):139.e1-9.

6. Deeb Tarek Z, Sharp D, Hales TG. Direct subunit-dependent multimodal 5-hydroxytryptamine3 receptor antagonism by methadone. Molecular Pharmacology 75(4):908-17. (2009).

7. Delgado-Velez M; Lugo-CA. Lizardo L; Morales I, Robles Y, Bruno N, Rodriguez JW, Rios-Olivares E, Correa M, Renaud FL. Chronic exposure of human macrophages in vitro to morphine and methadone induces a putative tolerant/dependent state. Journal of Neuroimmunology 196(1-2):94-100. (2008).

8. De Waal EJ, Van Der Laan JW, Van Loveren H. Effects of prolonged exposure to morphine and methadone on in vivo parameters of immune function in rats. Toxicology 129(2-3):201-10. (1988)

9. Dole VP. Implications of methadone maintenance for theories of narcotic addiction. JAMA 1988 Nov 25; 260 (20): 3025-9.

10. Eddy NB. A new morphine-like analgesic. J Amer Pharm Assoc, Prac Pharmacy Ed 1947; 8: 536-40.

11. Enters EK, Guo HZ,Pandey U, Ko DJ, Robinson SE. The effect of prenatal methadone exposure on development and nociception during the early postnatal period of the rat. Neurotoxicol Teratol 13(2):161-6. (1991)

12. Finnegan JK, Haag HB, Larson PS, Dreyfuss ML. Observations on the comparative pharmacologic actions of 6-dimethylamino-4,4-diphenyl-3-heptanone (amidone) and morphine. J Pharmacol Exp Ther 1948; 92: 269-76.

13. Ford DH, Rhines RK. Prenatal exposure to methadone HCl in relationship to body and brain growth in the rat. Acta Neurol Scand 59(5):248-62. (1979)

14. Fultz JM, Senay EC. Guidelines for the management of hospitalized narcotic addicts. Ann Intern Med 1975; 82: 815-18.

15. Gabrielsson JL, Johansson P, Bondesson U, Paalzow LK. Analysis of methadone disposition in the pregnant rat by means of physiological flow model. J Pharmacokinet Biopharm 13:355–372. (1985).

16. Garrido MJ, Trocóniz IF. Methadone: a review of its pharmacokinetic/pharmacodynamic properties. J Pharmacol Toxicol 42:61-66. (1999).

17. Gray TR, Choo RE, Concheiro M, Williams E, Elko A, Jansson LM, Jones HE, Huestis MA. Prenatal methadone exposure, meconium biomarker concentrations and neonatal abstinence syndrome. Addiction. 2010;105(12):2151-9.

18. Gupta MA, Mulvihill AO , Lascaratos GB, Fleck BW, George ND. Nystagmus and reduced visual acuity secondary to drug exposure in utero: Long-term follow-up. Journal of Pediatric Ophthalmology and Strabismus, 2012;49(1):58-63.

19. Hamilton R. McGlone L, MacKinnon JR, et al. Ophthalmic, clinical and visual electrophysiological findings in children born to mothers prescribed substitute methadone in pregnancy. Br J Ophthalmol. 2010;94:696-700.

20. Hassan HE, Myers AL, Coop A, Eddington ND. Differential involvement of P-glycoprotein (ABCB1) in permeability, tissue distribution, and antinociceptive activity of methadone, buprenorphine, and diprenorphine: in vitro and in vivo evaluation. J Pharm Sci 98(12):4928-40. (2009).

21. Hein PR, Schatorje JS, Frencken HJ. The effect of chronic methadone treatment on intra-uterine growth of the cynomolgus monkey (Macaca fascicularis). European Journal of Obstetrics, Gynecology, and Reproductive Biology 27(1):81-5 (1988).

22. Holmstrand J, Änggård E, Gunne L-M. Methadone maintenance: plasma levels and therapeutic outcome. Clin Pharmacol Ther 1978; 23: 175-80.

23. Hutchings DE. Methadone and heroin during pregnancy: a review of behavioural effects in human and animal offspring. Neurobehav Toxicol Teratol 1982; 4: 429-34.

24. Inturrisi CE. Role of opioid analgesics. Am J Med 1984; 77 (3A): 27-36.

25. Jaffe JH. Drug addiction and drug abuse. In: Gilman AG. Goodman LS, Rall TW, Murad F, eds. The pharmacological basis of therapeutics, ed 7. New York: Macmillan Publishing, 1985; 568-69 & 573-74.

26. Jaffe JH, martin WR. Opioid analgesics and antagonists. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. The pharmacological basis of therapeutics, ed 7. New York: Macmillan Publishing, 1985; 505, 517-19 & 1694-5.

27. Jansson LM, Di Pietro JA, Elko A, Williams EL, Milio L, Velez M. Pregnancies exposed to methadone, methadone and other illicit substances, and poly-drugs without methadone: A comparison of fetal neurobehaviors and infant outcomes. Drug Alcohol Depend. 2012 May 1;122(3):213-9.

28. Joffe JM, Peterson JM, Smith DJ, Soyka LF. Sub-lethal effects on offspring of male rats treated with methadone before mating. Res Commun Chem Pathol Pharmacol 13(4):611-21. (1976).

29. Johnson JH, Rosecrans JA. Blockade of ovulation by methadone in the rat: a central nervous system-mediated acute effect. J Pharmacol Exp Ther 1980; 213: 110-13.

30. Konijnenberg C, Melinder A. Prenatal exposure to methadone and buprenorphine: a review of the potential effects on cognitive development. Child Neuropsychol. 2011 Sep;17(5):495-519.

31. Kreek MJ. Substitution et produits: biological correlates of methadone maintenance pharmacotherapy. Ann Med Interne 1994; 145 (Suppl 3): 9-14.

32. Kristensen K, Blemmer TT, Angelo, HR, Christrup LL, Drenck NE, Rasmussen SN; Sjøgren P. Stereoselective Pharmacokinetics of Methadone in Chronic Pain Patients. Ther Drug Monitoring 18(3):221-227. (1996).

33. Langrod J, Lowinson J, Ruiz P. Methadone treatment and physical complaints: a clinical analysis. Int J Addict 1981; 16 (5): 947-52.

34. LeVier DG, Brown RD, Musgrove DL, Butterworth LF, McCay JA, White KL Jr, Fuchs BA, Harris LS, Munson AE. The effect of methadone on the immune status of B6C3F1 mice. Fundam Appl Toxicol 24(2):275-84. (1995).

35. McLaughlin PJ, Zagon IS, White WJ. Perinatal methadone exposure in rats. Effects on body and organ development. Biol Neonate 34(1-2):48-54. (1978).

36. Miby JB. Methadone maintenance to abstinence – how many make it? J Nervous Mental Dis 1988; 176: 409-22.

37. Nettleton RT, Wallisch M, Olsen GD. Respiratory effects of chronic in utero methadone or morphine exposure in the neonatal guinea pig. Neurotoxicol Teratol 30(5):448-54. (2008).

38. Olsen GD, Wendel HA, Livermore JD, Leger RM, Lynn RK, Gerber N. Clinical effects and pharmacokinetics of racemic methadone and its optical isomers. Clin Pharmacol Ther 1977; 21: 147-57.

39. Senay EC. Methadone Maintenance Treatment. Int J Addict 1985; 20 (6&7): 803-21.

40. Snyder EW, Dustman RE, Straight RC, Wayne AW, Beck EC. Sudden toxicity of methadone in monkeys: behavioral and electrophysiological evidence. Pharmacology, Biochemistry, and Behavior 6(1):87-92. (1977).

41. Soyka LF, Joffe JM, Peterson JM, Smith SM. Chronic methadone administration to male rats: tolerance to adverse effects on sires and their progeny. Pharmacol Biochem Behav 9(4):405-9. (1978).

42. Tennant F, Shannon J. Cocaine abuse in methadone maintenance patients is associated with low serum methadone concentrations. J Addict Dis 1995; 14(1): 67-74.

43. Verebely K, Volavka J, Mulé S, Resnick R. Methadone in man: pharmacokinetic and excretion studies in acute and chronic treatment. Clin Pharmacol Ther 1975; 18: 180-90.

44. Walz MA, Davis, WM, Pace HB. Parental methadone treatment: a multigenerational study of development and behavior in offspring. Dev Pharmacol Ther 6(2):125-37. (1983).

45. Winter CA, Flataker L. Studies on heptazone (6-morpholino-4,4-diphenyl-3-heptanone hydrochloride) in comparison with other analgesic drugs. J Pharmacol Exp Ther 1950; 98: 305-17.

46. Wouldes TA, Woodward LJ. Maternal methadone dose during pregnancy and infant clinical outcome. Neurotoxicology and Teratology. 2010;32(3):406-413.

47. Yaksh TL, Wallace MS. Chapter 18. Opioids, Analgesia, and Pain Management. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12nd ed. New York: McGraw-Hill; 2011. http://www.accessmedicine.com/content.aspx?aID=16663974. Accessed November 1, 2011.

48. Zagon IS, McLaughlin PJ. Effect of chronic maternal methadone exposure on perinatal development. Biol Neonate 31(5-6):271-82. (1977)

49. Zunkler BJ, Wos-Maganga M. Comparison of the effects of methadone and heroin on human ether-a-go-go-related gene channels. Cardiovascular Toxicology 10(3):161-5. (2010).

50. Zweben JE, Payte JT. Methadone maintenance in the treatment of opioid dependence – A current perspective, In Addiction Medicine [Special Issue]. West J Med 1990 May; 152: 588-99.

51. Product Monograph - Methadose™ (Methadone Hydrochloride Oral Concentrate, USP) 10 mg/mL, Mallinckrodt Canada ULC. Submission No. 245159; Date of Revision: March 24, 2021

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

[N] ODAN-METHADONE

Methadone Hydrochloride Oral Concentrate, USP (Cherry Flavor)
Methadone Hydrochloride Oral Concentrate, USP (Dye-Free, Sugar- Free, Unflavored)

Read this carefully before you start taking Odan-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 Odan-Methadone.

Serious Warnings and Precautions

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

- **You may get life-threatening breathing problems while taking Odan-Methadone. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing. This is less likely to happen if you take it as prescribed by your doctor. Because this effect is long-lasting, breathing problems can happen hours after taking your dose. Breathing problems may be most likely when starting Odan-Methadone and when the dose is increased. Get emergency medical help immediately if you:**

  - **Have trouble breathing, or have slow or shallow breathing;**
  - **Have a slow or irregular heartbeat;**
  - **Have severe sleepiness;**
  - **Have cold, clammy skin;**
  - **Feel faint, dizzy, confused, or cannot think, walk or talk normally;**
  - **Have a seizure;**
  - **Have hallucinations.**

Dangerous side effects and death may occur when Odan-Methadone is used with alcohol or with other medications that may cause drowsiness such as anti-depressants, anti-histamines, muscle relaxants or sleeping medications.

In some patients, Odan-Methadone may cause heartbeat problems that can be life-threatening in rare cases. Symptoms may include fainting, palpitations (feeling a rapid, pounding or irregular heartbeat), or loss of consciousness.

- **You should never give anyone your Odan-Methadone. They could die from taking it. If a person has not been prescribed Odan-Methadone, taking even one dose can cause a fatal overdose. This is especially true for children.**

- **If you took Odan-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 Odan-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 Odan-Methadone used for?
Odan-Methadone is used in conjunction with appropriate social and medical services as a substitution treatment for opioid drug dependence. Only a qualified doctor can prescribe Odan-Methadone. Odan-Methadone needs to be taken under daily supervision of a healthcare professional.

How does Odan-Methadone work?
Methadone belongs to a class of drugs that is commonly referred to as opioids or narcotics which also includes the illicit drug heroin, and the prescription drugs codeine, fentanyl, hydromorphine and morphine.

Methadone acts to suppress symptoms of opioid withdrawal without producing a "high", while the long-acting nature of the drug allows for once-a-day maintenance dosing.

What are the ingredients in Odan-Methadone?
Medicinal ingredients: Methadone hydrochloride
Non-medicinal ingredients:

- Odan-Methadone Oral Concentrate contains: Natural and artificial cherry flavor, citric acid anhydrous, FD&C Red No. 40, D&C Red No. 33, methylparaben, poloxamer 407, propylene glycol, propylparaben, purified water, sodium citrate dihydrate, sucrose.
- Odan-Methadone Sugar-Free Oral Concentrate contains: citric acid anhydrous, purified water, and sodium benzoate.

Odan-Methadone comes in the following dosage forms:
Oral concentrate, cherry flavor: 10 mg/mL
Oral concentrate, dye-free, sugar-free, unflavored: 10 mg/mL

Do not use Odan-Methadone if:

- you are allergic to methadone hydrochloride or any of the other ingredients in Odan-Methadone
- you have severe asthma, trouble breathing, or other breathing problems
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you have severe diarrhea caused by antibiotics
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Odan-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, lung disease
- have heart disease
- have low blood pressure
- have or had depression
- have problems with your thyroid, adrenal or prostate gland
- suffer from chronic or severe constipation
- have, or had in the past, hallucinations or other severe mental problems
- suffer from migraines
- you are going to have a planned surgery
- you are pregnant or plan to become pregnant

Other warnings you should know about:

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery: The use of Odan-Methadone during labour or delivery is not recommended. Opioids can be transferred to your baby through breast milk, or while still in the womb. Odan-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 Odan-Methadone. Odan-Methadone can cause:

- drowsiness
- dizziness or
- lightheadedness

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 Odan-Methadone.

Serotonin toxicity (also known as serotonin syndrome): Odan-Methadone can cause serotonin toxicity, 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 Odan-Methadone with certain anti-depressants or migraine medications.

Serotonin toxicity symptoms include:

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

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

- You should call your doctor immediately if you feel dizzy, lightheaded, or faint or have palpitations (feeling a rapid, pounding or irregular heartbeat) after taking Odan-Methadone;
- You should not drink alcohol or take medicines that may cause drowsiness and/or slow, shallow breathing (like sleeping aids or muscle relaxers) when taking Odan-Methadone;
- If you become pregnant or plan to become pregnant, talk with your doctor about the risks related both to taking Odan-Methadone during pregnancy, and to stopping Odan-Methadone;
- Stopping treatment with Odan-Methadone may result in a return to narcotic drug use;
- If you suddenly stop taking Odan-Methadone, you may experience withdrawal symptoms. If you and your doctor decide that you should stop taking Odan-Methadone, consider slowly lowering the dose instead of suddenly stopping the treatment. Your doctor can provide you with an appropriate dosing schedule.
- If you are pregnant or breastfeeding, then speak with your doctor about the risks and benefits of breastfeeding while taking Odan-Methadone such as the following:
    - Your baby will receive a small amount of Odan-Methadone through your breast milk;
    - Your baby may experience withdrawal symptoms if you suddenly stop breastfeeding.
    - Talk with your doctor about developing a plan to slowly wean your baby;
    - You should not drink alcohol or use drugs of abuse while breastfeeding, because doing so will expose your baby to additional risks;
    - When starting Odan-Methadone treatment or increasing the dose while breastfeeding, closely watch your baby for changes in behavior or breathing patterns.

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).

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 Odan-Methadone:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol.
  Do not drink alcohol while you are taking Odan-Methadone. It can lead to:
  - drowsiness
  - unusually slow or weak breathing
  - serious side effects or
  - a fatal overdose
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- anti-depressants (for depression and mood disorders). **Do not** take Odan-Methadone with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- drugs used to treat migraines (e.g. triptans)
- anti-epileptic drugs (used to treat seizures)
- anti-retroviral drugs (used to treat HIV)
- anti-fungal drugs (used to treat fungal infections)
- antibiotic drugs (used to treat bacterial infections)
- some heart medication (such as beta-blockers, anti-arrhythmic agents and calcium channel blockers)
- grapefruit juice
- St. John's Wort

Be sure to tell your doctor, dentist, pharmacist and all other health professionals who are treating you that you are taking Odan-Methadone.

How to take Odan-Methadone:

Usual Adult Starting Dose

Dosing of Odan-Methadone is patient-specific and varies based on use and symptoms. Take exactly as directed by your doctor. The dose should be taken all at once, and preferably at the same time every day.

The dose of Odan-Methadone will "hold" for longer periods of time as your treatment progresses. You should not change your dose of Odan-Methadone unless you discuss this with your doctor and your doctor recommends a dose change. Taking higher doses can lead to more side effects and a greater chance of overdose.

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

If you have been taking Odan-Methadone for more than a few days you should not stop taking it all of a sudden.

Your doctor will monitor and guide you on how to slowly stop taking Odan-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 sleeping
- an unusual increase in sweating
- an unexplained fever
- weakness
- yawning

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

Refilling your Prescription for Odan-Methadone:
A new written prescription is required from your doctor each time you need more Odan-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.

Occasionally, the brand of methadone prescribed by your doctor or dispensed by your pharmacist may change. Should you experience any side effects, discuss with your doctor or pharmacist.

Overdose:

If you think you, or a person you are caring for have taken too much Odan-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. If you miss one dose, take your next dose at your usual time. 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 Odan-Methadone?
These are not all the possible side effects you may feel when taking Odan-Methadone. If you experience any side effects not listed here, contact your healthcare professional. Side effects may include:
- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement

- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

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

Get emergency medical help right away if you have:

- Fast or slow or skipped heartbeat, chest pain, chest tightness, fainting or feel very dizzy;
- Serotonin Syndrome: a combination of most or all of the following symptoms: agitation, confusion, delirium, rapid heart rate and high blood pressure, stiffness, lack of coordination, nausea, vomiting, diarrhea, sweating, fever, shivering, seizure and coma.

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	
Overdose: confusion, hallucinations, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
Respiratory Depression: Slow, shallow or weak breathing.			√
Serotonin Toxicity: 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			√
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			√
Fast, Slow or Irregular Heartbeat: heart palpitations.			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
Low Blood Pressure: dizziness, fainting, lightheadedness.		√	

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:

Your pharmacist or other health professional will store this product.

In the case of take-home doses:

- **You should store Odan-Methadone, like other opioids, in a locked, secure place and out of the sight and reach of children and pets.**
- **Never take medicine in front of small children as they may want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidently takes Odan-Methadone, get emergency help right away.**
- **Odan-Methadone is a federally-controlled drug because of the potential for abuse. Protect your Odan-Methadone from theft or any other access, and never provide your Odan-Methadone to anyone else.**
- **Keep unused or expired Odan-Methadone in a secure place to prevent theft, misuse or accidental exposure.**
- Store at room temperature (15° - 30°C) in tight containers, protected from light.

Disposal:

Odan-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 Odan-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) or by contacting the sponsor, Odan Laboratories Ltd. at 1-888-666-6326.

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