Opioid Antagonists, Mixed Agonist/Antagonists, and Partial Agonists
Patients maintained on methadone may experience withdrawal symptoms when given opioid antagonists, mixed agonist/antagonists, and partial agonists just like other μ-agonists. For examples, naloxone, naltrexone, pentazocine, nalbuphine, butorphanol, and buprenorphine.

Anti-retroviral Agents
Abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination: An increased clearance or decrease plasma levels of methadone will be observed when it is coadministered with these anti-retroviral agents. Evidence of withdrawal effects in methadone-maintained patients who begin treatment with antiretroviral drugs should be monitored. The methadone dose should be adjusted accordingly as well.

Didanosine and Stavudine: Experimental evidence have demonstrated that among didanosine and stavudine, the reduction effect of methadone on AUC and peak levels is more significant for didanosine. Other than this, methadone disposition was not significantly altered.

Zidovudine: Experimental evidence demonstrated that methadone could result in toxic effects as it increased the area under the concentration-time curve (AUC) of zidovudine.

Cytochrome P450 Inducers
At the initiation treatment with CYP3A4 inducers, methadone-maintained patients should be monitored for evidence of withdrawal effects. Dosage of methadone should be adjusted accordingly.

Following are the drug interactions observed after coadministration of methadone with inducers of cytochrome P450 enzymes:

Rifampin: Concomitant administration of rifampin with methadone reduced the methadone levels in serum and resulted a concurrent appearance of withdrawal symptoms in patients well-stabilized on methadone.

Phenytoin: Phenytoin administration (250 mg b.i.d. initially for 1 day followed by 300 mg QD for 3 to 4 days) caused methadone level to be reduced by approximately 50% and withdrawal symptoms occurred at the same time. However, the withdrawal symptoms will decrease and methadone exposure will rise back to a level comparable to that prior to phenytoin administration after discontinuation of phenytoin treatment.

St. John's Wort, Phenobarbital, Carbamazepine
Withdrawal symptoms may be observed if methadone is coadministered with other CYP3A4 inducers.

Cytochrome P450 Inhibitors
Administration of drugs that inhibit CYP3A4 activity concomitantly with methadone may results in decreased clearance of methadone. Opioid effects would then increase. Thus, patients should be carefully monitored when methadone is given concurrently with strong inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole). Dosage should be adjusted when deemed necessary.

Some of the selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine) might increase opiate effects and/or toxicity when taken concomitantly with methadone.

Others
Monoamine Oxidase (MAO) Inhibitors: Therapeutic doses of meperidine have lead to severe reactions in patients coadministered with monoamine oxidase inhibitors or those who have taken such agents within 14 days time. Similar drug reactions of methadone with MAO inhibitors have not been reported.

For patients on monoamine oxidase (MAO) inhibitors, a sensitivity test should be performed if treatment of methadone is necessary in such patients. The treatment of methadone in repeated small, incremental doses can be given over the course of several hours and the patient's condition and vital signs are monitored with care.

Desipramine: Coadministration of methadone will increase the level of desipramine in blood.

Potentially Arrhythmogenic Agents
Extreme caution should be taken when administering methadone together with drugs which can prolong The QT interval. For example: antiarrhythmics, some neuroleptics, tricyclic antidepressants and calcium channel blockers.

Caution should also be taken when coadministered together with drugs which disturbs the electrolyte balance, eg diuretics and laxatives.

Pregnancy and Lactation:
There are no controlled studies done on pregnant women. Methadone is detected in amniotic fluid, cord plasma and also in newborn urine.

According to retrospective study done on 101 pregnant, opiate-dependant women who were under opiate detoxification with methadone, there is no increased risk of miscarriage in 2nd trimester and premature delivery in 3 trimester.

Children born to narcotic-addicted women have been found to have decreased fetal growth and deficits in performance on psychometric and behavioral tests.

These babies may also be dependent on the opioid and may demonstrate withdrawal symptoms after birth, which may prolong between a few days to a few months.

Methadone should only be used during pregnancy if the potential benefit outweighs the risk to the fetus.

Methadone should not be used during labor or prior to delivery.

Methadone is excreted in breast milk. Therefore breast feeding is not recommended during methadone treatment.

Side Effects:
Heroin Withdrawal
The typical withdrawal symptoms of heroin withdrawal shown during the induction phase of methadone maintenance treatment should be distinguished from methadone-induced side effects. They are lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, 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
Initial titration of dose should be done carefully, to minimize adverse effects.

Side effects are lightheadedness, dizziness, sedation, nausea, vomiting, constipation, exacerbation of existing asthma, miosis, reversible thrombocytopenia, urinary retention, reduced libido and sweating.

Other side effects such as respiratory depression, cardiovascular effects, systemic hypotension, respiratory arrest, shock, cardiac arrest, death have occurred.

Below are other adverse reactions that may be observed in patients:

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

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

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

Hematologic and Lymphatic: In opioid addicts with chronic hepatitis, reversible thrombocytopenia has been observed.

Metabolic and Nutritional: hypokalemia, hypomagnesemia, weight gain.

Nervous: agitation, confusion, disorientation, dysphoria, euphoria, insomnia, seizures.

Respiratory: pulmonary edema.

Skin and Appendages: pruritis, urticaria, other skin rashes. Hemorrhagic urticaria rarely occurs.

Special Senses: visual disturbances.

Urogenital: antidiuretic effect, amenorrhea, urinary retention or hesitancy, reduced libido and/or potency.

Maintenance on a Stabilized Dose: The side effects will usually disappeared over a period of several weeks during prolonged administration of methadone (such as in the methadone maintenance treatment program). However, constipation and sweating often persist.

Symptoms and Treatment of Overdose:
Symptoms
Serious overdose may cause respiratory depression, extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin, bradycardia and hypotension. In severe overdosage, apnoea, circulatory collapse, cardiac arrest and death may occur.

Treatment
Adequate respiratory exchange should be established, through provision of a patent airway and controlled ventilation.

Narcotic antagonists such as naloxone or nalmefene may be administered. It should be kept in mind that methadone is long acting and its effects may lasts up to 36-48 hours. The antagonists act for only 1-3 hours. Therefore the treatment with antagonists must be repeated as needed. The antagonist needs to be administered with extreme care and by titration starting from a small dose. However, in the absence of respiratory or cardiac depression, an antagonist should not be administered.

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

Storage Condition:
Keep the container tightly closed. Store in a dry place (below 30°C). Protect from light.

Pack Size:
Alphadone Syrup 5mg/ml:
60ml, 90ml, 100ml and 120ml in plastic bottles.

Alphadone Syrup 10mg/ml:
60ml, 90ml, 100ml and 120ml in plastic bottles.

Registration Numbers:
Alphadone Syrup 5mg/ml: MAL06081185AZ
Alphadone Syrup 10mg/ml: MAL06081186AZ

Further information can be obtained from your doctor or pharmacist.

ROYCE®

Product Holder/Manufactured by:
ROYCE PHARMA MFG SDN. BHD. 650435-X
PT 1663, Nilai Industrial Estate,
71800 Nilai, Negeri Sembilan, Malaysia.

Revision date: 101017

ROYCE®

ALPHADONE SYRUP
(Methadone HCl-Analgesic)

Presentation:
Alphadone Syrup 5mg/ml
A red / dark brown coloured syrup.
Each ml contains Methadone HCl 5mg.

Alphadone Syrup 10mg/ml
An orange coloured and fruity flavoured syrup.
Each ml contains Methadone HCl 10mg.

Pharmacological Information:
Methadone hydrochloride is a μ-agonist as well as a synthetic opioid analgesic. It has multiple actions that qualitatively similar to morphine, which will affect the central nervous system and organs composed of smooth muscle. Methadone hydrochloride's primary therapeutic value is analgesia and sedation as well as detoxification or maintenance in opioid addiction. Although the methadone abstinence syndrome is qualitatively similar to that of morphine, but the symptoms are less severe for methadone addiction as the onset will be slower with a more prolonged course.

Meanwhile, methadone also shows the antagonist character at the N-methyl-D-aspartate (NMDA) receptor but the contribution of NMDA receptor antagonism to methadone's efficacy is not established. However, other NMDA receptor antagonists have shown neurotoxic effects in animals.

Absorption
The bioavailability of methadone ranges between 36 to 100% after being administered orally and achieves the peak plasma concentrations in 1 to 7.5 hours. The steady-state plasma concentrations and the peak concentrations of methadone can be observed in the range of 65 to 630 ng/mL and 124 to 1255 ng/mL respectively after daily oral administration of doses ranging from 10 to 225 mg. The effect of dose proportionality on methadone pharmacokinetics is unclear. Other than that, effect of food on the bioavailability of methadone is also not known.

Distribution
Methadone can be found in saliva, breast milk, amniotic fluid and umbilical cord plasma. The steady state volume of methadone distribution ranges between 1.0 to 8.0 L/kg. It is lipophilic and extensively bound to alpha 1-acid glycoprotein (85% to 90%) in plasma.

Metabolism
Methadone will be metabolized primarily to 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidene (EDDP) by Cytochrome P450 enzymes like CYP3A4, CYP2B6, CYP2C19, CYP2C9 and CYP2D6 in N-demethylation. Then, the EDDP will be excreted predominantly in urine along with other inactive metabolites produced in this process.

Excretion
After going through extensive biotransformation, methadone will be metabolize to inactive metabolites and excreted through renal and fecal system.
Plasma clearance of methadone ranges from 1.4 to 126 L/h while the terminal half-life (T1/2) ranges between 7 to 59 hours after multiple dose administration.
Methadone persists in the liver and other tissues because of its lipophilic nature. Thus, it will have longer action duration due to its slow release from the liver and other tissues despite low plasma concentrations.

Pharmacokinetics in Special Populations
Pregnancy
Pharmacokinetic studies of parenteral methadone in pregnancy are not available.

Studies on the disposition of oral methadone have been conducted in about 30 patients during the 2nd and 3rd trimester of pregnancy.

Pregnancy significantly changed the behavior of elimination of methadone. Pregnant patients have a higher rate of total body clearance of methadone compared to the same patients postpartum and non-pregnant opioid-dependent women. Besides, a decrease trend of methadone terminal half-life can also be observed during the second and third trimesters. In other words, the decrease in plasma half-life and increased clearance of methadone will lead to a lower methadone through levels during pregnancy causing the withdrawal symptoms in some pregnant patients. Thus, increase in methadone dosage or decrease in the dosing interval in pregnant patients receiving methadone might be necessary.

Renal impairment
There are no significant studies of methadone pharmacokinetics in patients with renal insufficiency. Methadone is basic (pKa=9.2) and the elimination of methadone is extensively affected by the pH of the urinary tract, which can alter its disposition in plasma. Hence, metabolized and unmetabolized methadone are excreted in urine in an unpredictable level. Renal elimination of methadone will be increased by urine acidification. The efficacy of forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion in increasing methadone or metabolite elimination has not been established.

Hepatic Impairment
There are no significant studies of Methadone in patients with hepatic insufficiency. Patients with liver impairment may be at risk of accumulating methadone after multiple dosing because methadone is metabolized by hepatic pathways.

Gender, Race, Geriatric and Pediatric
There are no significant studies of methadone pharmacokinetics in patients of gender or race specificity.

Studies of methadone pharmacokinetics in geriatric or pediatric population have not been evaluated as well.

Indication:
Alphadone is indicated for detoxification and maintenance treatment of opioid addiction (heroin or other morphine-like drugs) together with appropriate social and medical services.

Dosage and Administration:
Adults:
Induction/Initial Dosing: Initially 20-30mg. The initial dose should not exceed 30mg. If the same day dosing adjustment is to be made, the patient is to wait for 2-4 hours until peak levels have been reached. An additional 5-10mg methadone may be given if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily dose on the first day should not exceed 40mg/day. Dose adjustment is to be done over the first week of treatment. Dose adjustment should be cautious due to the cumulative effects of the first several days' dosing.

Short-term detoxification: 40mg daily in divided doses for 2 to 3 days. The dose of methadone should be gradually decreased at a rate depending on patient's condition, either on daily basis or at 2-day intervals. Daily reduction of 20% of the total daily dose may be tolerated in hospitalized patients. A slower schedule may be needed in ambulatory patients.

Maintenance treatment: A dose at which opioid symptoms are prevented for 24 hours, drug hunger or craving is reduced, the euphoric effects of self-administered opioids are blocked or attenuated, and the patient is tolerant to the sedative effects of methadone should be titrated. Clinical stability usually can be observed at doses ranged from 80-120mg daily.

Medically supervised withdrawal after a period of maintenance: For patients who choose to taper off methadone, it is generally suggested that the dose reduction should be less than 10% of the established tolerance or maintenance dose, and that 10-14 day intervals should elapse between dose reductions.

Elderly: Dose should be given with caution.

Children: Not recommended in children.

Contraindication:
Antidone is contraindicated in patients with a known hypersensitivity to methadone hydrochloride and in any situation where opioids are contraindicated. For example, in patients with respiratory depression where the presence of resuscitative equipment or monitored settings are not available and in patients with acute bronchial asthma or hypercarbia.

Warning and Precautions:
Warning
Alphadone Syrup is for oral administration only and it should not be injected.
Keep out of reach of children.

Cardiac Conduction Effects
This information is provided to assist the prescribing physician for the appropriate use of methadone in patients with a history of cardiac disease. Evidence from both in vivo and in vitro studies showed that the cardiac potassium channels will be inhibited by methadone and the QT interval will be prolonged.

During treatment with methadone, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed. These appear to have a close relation to higher dose treatment (> 200 mg/day). However, these effects can be observed in patients receiving doses commonly used in maintenance treatment of opioid addiction as well as patients who were treated for pain with large and multiple daily doses of methadone. For typical maintenance doses, concomitant medications and/or clinical conditions such as hypokalemia are

contributing factors. Nevertheless, methadone possesses the potential for adverse cardiac conduction effects in some patients.

Caution should be given when methadone is administered in patients already at risk for development of prolonged QT interval such as cardiac hypertrophy, concomitant diuretic use, hypokalemia and hypomagnesemia.

Patients with a history of cardiac conduction disease, patients taking medications affecting cardiac conduction, and patients with history or physical exam that suggest an increased risk of dysrhythmia should be closely monitored when treated with methadone.

During methadone treatment, the presence of modifiable risk factors (concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities, and drugs which might act as inhibitors of methadone metabolism) should be assessed for patients developing QT prolongation.

The risks of discontinuing methadone treatment should be weighed against the possible risks of methadone like the risk of life-threatening arrhythmias. A very high probability of relapse to illicit drug use will occur following methadone discontinuation in these patients.

Significant studies on use of methadone in patients with a prolonged QT interval have not been conducted. The potential risks of methadone should be evaluated against the significant morbidity and mortality associated with untreated opioid addiction.

Respiratory Depression
The major hazard associated with methadone hydrochloride administration is respiratory depression especially in elderly or debilitated patients and in patients suffering from conditions accompanied by hypoxia or hypercapnia. In these patients, even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

In the meantime, extreme caution should be given to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, and CNS depression or coma. Their respiratory drive will be decreased and airway resistance will be increased to the point of apnea even when treated with usual therapeutic doses of methadone.

Thus, non-opioid analgesics should be considered as an alternate treatment. Methadone should be employed only under careful medical supervision at the lowest effective dose in these patients.

In the short-term use setting, methadone's peak respiratory depressant effects typically occur later and persist longer than its peak analgesic effects. At the beginning of treatment and during dose titration, these characteristics can contribute to cases of iatrogenic overdose.

Incomplete Cross-tolerance between Methadone and other Opioids Incompletely tolerant to methadone might occur in patients who are tolerant to other opioids.

Determination of dosing during opioid conversion is complex and difficult. For patients tolerant to other μ-opioid agonists who are being converted to methadone, incomplete cross-tolerance is of particular concern.

Cases of deaths during conversion from chronic, high-dose treatment with other opioid agonists have been reported. High "opioid tolerance" will not eliminate the possibility risk of methadone overdose, iatrogenic or otherwise.

Misuse, Abuse, and Diversion of Opioids
Similar to morphine and other opiod, methadone has a high abuse liability. Clinician and healthcare professionals should consider the risk of misuse, abuse, or diversion when dispensing methadone.

Head Injury and Increased Intracranial Pressure
In the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure, the respiratory depressant effects of opioids and their capacity to elevate cerebrospinal-fluid pressure may be amplified. Moreover, treatment for patients with head injuries might be affected as opioids produce effects that may obscure the clinical course. In such patients, methadone must be used with caution in such patients when only the benefits go beyond the risk.

Acute Abdominal Conditions
The diagnosis or clinical course of patients with acute abdominal conditions will be obscured by opoids.

Hypotensive Effect
Severe hypotension might occur in patients whose ability to maintain normal blood pressure is compromised after treatment with methadone.

Precaution
Special caution should be given to elderly and debilitated patients; patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease; and in patients with comorbid conditions or concomitant medications which may predispose to dysrhythmia or reduced ventilatory drive when administered with methadone.

Physical Dependence
Generally, opioids should not be abruptly discontinued. Physical dependence can be observed during opioid agonist therapy of opioid addiction. Some of the opioid abstinence or withdrawal symptoms are: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms such as irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate also may develop.

Interaction With Other Medicaments
Methadone is eliminated in liver through N-demethylation by cytochrome P-450 isoforms, mainly CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Higher rate of methadone metabolism might be observed when it is administered concomitantly with the inducers of these enzymes. This will possibly decreased the effect of methadone. On the contrary, coadministration of methadone with inhibitors may reduce metabolism and promote methadone's effects.

The interaction potential of methadone with other drug taken concomitantly should be considered and evaluated. Clinicians might also need to consider individual response to drug therapy.

Interactions with other CNS Depressants
Patients may suffer from respiratory depression, hypotension, profound sedation, or coma when treated concomitantly with methadone and other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with methadone.

Interactions with Alcohol and Drugs of Abuse
When used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression methadone is expected to have additive effects. Death due to illegal administration of methadone usually associated with concomitant use of benzodiazepine.