

# ADECURE SYRUP 5MG/ML

## **NAME AND STRENGTH OF ACTIVE INGREDIENT(s):**

Each ml contains:

Methadone Hydrochloride.....5mg

## **PRODUCT DESCRIPTION:**

A red colour liquid.

## **PHARMACODYNAMICS:**

Methadone is primarily a  $\mu$  opioid agonist with multiple actions quantitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle.

## **PHARMACOKINETICS:**

Methadone is well absorbed from the gastrointestinal tract. Oral administration of methadone delays its onset of action, lowers its peak concentrations, prolongs its duration of action and reduces its potency by about half compared to parenteral administration. When administered orally, its onset of action is 30-60 minutes, duration of action 4-6 hours and the time taken to reach its peak effect is 1.5-2 hours. The duration of action of methadone is extended in patients physically dependent on oral methadone. Repeated administration of methadone increases its duration of action to approximately 22-48 hours in patients on methadone maintenance because of the accumulation of methadone or active metabolites. This may decrease as tolerance develops with chronic treatment. The depressant effects from methadone overdosage may continue for 36-48 hours.

Methadone is highly bound to tissue protein. This may explain its cumulative effects and slow elimination.

The half-life of orally administered methadone is 13-47 hours, with an average of 25 hours. This may increase with repeated administration. Methadone is primarily metabolized in the liver where it undergoes N-demethylation and does not appear to be conjugated. It is mainly excreted renally and undergoes renal reabsorption. The renal excretion of methadone is dose dependent and also increases when renal reabsorption decreases in acidic urine. Methadone metabolites are also excreted in the faeces via the bile.

Methadone abstinence syndrome is qualitatively similar to that of morphine but has a slower onset, a more prolonged course and the symptoms are less severe.

## **INDICATION:**

For detoxification treatment or maintenance treatment of narcotic addiction.

## **RECOMMENDED DOSAGE:**

### **DETOXIFICATION TREATMENT**

**Adecure Syrup should be administered daily under close supervision.**

The duration of detoxification treatment courses should not exceed 21 days and should not be repeated in less than 4 weeks after completion of a preceding course. Methadone is administered when there are significant symptoms of withdrawal and the recommended dosage can be adjusted according to clinical judgement.

Initially, a single oral dose of 15-20mg methadone should often be sufficient to suppress the withdrawal symptoms. If withdrawal symptoms are not suppressed or reappear, additional methadone can be administered. In patients physically dependent on high doses, these recommended levels may not be sufficient and can be exceeded. 40mg daily in a single or divided doses is recommended as a stabilizing dosage level. After a stabilization period of 2 to 3 days, the dosage can be reduced gradually, at a rate that will be determined separately for each patient. The dosage can be decreased on a daily basis or at 2 day intervals, but the dosage must be sufficient for the withdrawal symptoms to be at a tolerable level. In patients who are hospitalized, a gradual daily reduction of 20 percent of the total daily dose may be tolerated and cause little discomfort. In ambulatory patients however, the reduction may need to be slower.

If administered for over 3 weeks, the procedure will be considered to have progressed from detoxification or treatment of acute withdrawal symptoms to maintenance treatment despite the goal of eventual total withdrawal.

### **MAINTENANCE TREATMENT**

In maintenance treatment programmes, the initial dosage of methadone should be sufficient to control the withdrawal symptoms but low enough so that it does not cause sedation, respiratory depression or other effects of acute intoxication. The initial dosage should be adjusted for each patient based on the narcotic tolerance of the patient. If the patient enters treatment as a heavy user of heroin, a dose of 20mg 4 to 8 hours later or 40mg as a single oral dose may be given. If the patient enters treatment with little or no narcotic tolerance (eg. a patient who has recently been released from jail or other confinement), the initial dosage may be one-half of these quantities. If there is any doubt, a smaller dose should be used initially, with the patient kept under observation and additional 10mg doses administered as required if the withdrawal symptoms are not tolerable. After that, the dosage should be adjusted individually, as tolerated and required, up to a maximum dose of 120mg daily. For the first 3 months, methadone should be ingested by the patient under observation daily, or for a minimum of 6 days a week. Drug ingestion under observation can be reduced to a minimum of 3 times weekly after that if the patient has demonstrated satisfactory adherence to the programme's requirements. The dosage level

should be reviewed regularly, with the dosage reduced as indicated on an individual basis. A new dosage level is only a test level until stability is achieved.

#### Pregnant Patients

Exercise caution in the maintenance treatment of pregnant patients. If methadone treatment is necessary, the dosage should be kept as low as possible.

#### **ROUTE OF ADMINISTRATION:**

Oral route.

#### **CONTRAINDICATIONS:**

Hypersensitivity to methadone. Paediatric use. Obstetric use because of the increased risk of neonatal depression during labour due to methadone's long duration of action. Respiratory depression, obstructive airway disease, ulcerative colitis, severe hepatic impairment. Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of monoamine oxidase inhibitor treatment discontinuation. The use of methadone should be avoided in acute asthma attacks, acute alcoholism and risk of paralytic ileus and raised intracranial pressure or head injury.

#### **WARNINGS AND PRECAUTIONS:**

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| This preparation may be habit forming on prolonged use. Avoid alcoholic beverages. |
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**Serotonin Syndrome with Concomitant use of Serotonergic Drugs.** Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of Ade cure Syrup with serotonergic drugs (See Interactions with Other Medicaments). This may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental-status changes (eg. agitation, hallucinations, coma), autonomic instability (eg. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg. hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg. nausea, vomiting, diarrhoea) and can be fatal (See Interactions with Other Medicaments). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Ade cure Syrup if serotonin syndrome is suspected.

**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, decreased appetite, 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 dosing 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.

**Sexual Function/Reproduction.** Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See Postmarketing Experience).

**Risk from Concomitant Use with Benzodiazepines.** Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Ade cure Syrup with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patient closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Ade cure Syrup is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine 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 benzodiazepines (See Drugs Interactions).

**Dependence.** Physical dependence, psychic dependence and tolerance may develop with repeated administration of methadone. It can produce drug dependence similar to morphine and should be prescribed and administered with the same degree of caution appropriate to the use of morphine.

**Asthma and respiratory conditions.** Use methadone with caution in patients have an acute asthmatic attack and in patients with chronic obstructive pulmonary disease or cor pulmonale, significantly decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia. In these patients, even the usual therapeutic doses of methadone can decrease respiratory drive while increasing airway resistance to the point of apnea.

**Head injury and increased intracranial pressure.** In patients with increased intracranial pressure, methadone's respiratory depressant and cerebrospinal fluid pressure elevation effects may be significantly exaggerated. Besides this, the

side effects of methadone may obscure the clinical course of patients with head injuries. Methadone should only be used in these patients if it is essential and must be used with caution.

**Hypotensive effects.** Methadone administration may cause severe hypotension in patients whose ability to maintain their blood pressure is compromised by pre-existing conditions such as depleted blood volume or concurrent administration of drugs such as phenothiazines or certain anaesthetics.

**Anxiety.** The use of methadone in maintenance treatment is limited to the control of withdrawal symptoms and is not a tranquilizer, ineffective for the relief of general anxiety. In methadone maintenance treatment, methadone is used by tolerant patients at a constant maintenance dosage who will react to life problems and stresses with the same symptoms of anxiety as other individuals. These symptoms of anxiety should not be confused with symptoms of narcotic abstinence and should not be treated by increasing the methadone dosage.

**Use in ambulatory patients.** Methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery. In ambulatory patients, methadone may produce orthostatic hypotension.

**Acute abdominal conditions.** The use of methadone may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

**Special risk patients.** In patients such as the elderly or debilitated and in those with severe renal or hepatic impairment, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture, methadone should be administered with caution and the initial dose reduced.

**Use in children.** Methadone is not recommended for children.

### **INTERACTIONS WITH OTHER MEDICAMENTS:**

**Serotonergic Drugs.** The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Adecur Syrup if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT<sub>3</sub> receptor antagonists, drugs that affect the serotonin neurotransmitter system (eg. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See Warnings and Precautions).

**Benzodiazepines** Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death. The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at  $\mu$ -receptors, and benzodiazepines interact at GABA<sub>A</sub> sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions). Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

**Other central nervous system depressants.** Use methadone with caution and in reduced doses in patients concurrently receiving other narcotic analgesics, tranquilizers, phenothiazines, sedatives or hypnotics, tricyclic antidepressants, or other central nervous system depressants, including alcohol. There is a risk of respiratory depression, hypotension, profound sedation or coma.

**Pentazocine.** Pentazocine may cause withdrawal symptoms in patients on methadone maintenance treatment.

**Rifampin.** Although the mechanism by which it occurs is not fully understood, concurrent administration of rifampin may reduce the plasma concentrations of methadone to levels sufficient to produce withdrawal symptoms.

**Monoamine oxidase inhibitors.** Therapeutic doses of meperidine have been reported to cause severe reactions in patients concurrently receiving monoamine oxidase inhibitors or in patients who have received monoamine oxidase inhibitors within 14 days. Although similar reactions have not been reported with methadone, a sensitivity test should be performed in which repeated small incremental doses are administered over a few hours while monitoring the patient's condition and vital signs, if the use of methadone is necessary in these patients.

**Naloxone.** Naloxone antagonises the analgesic, central nervous system and respiratory depressant effects of methadone.

**Naltrexone.** Naltrexone will rapidly precipitate long term withdrawal symptoms in patients addicted to methadone.

**Antivirals.** Methadone increases the plasma concentrations of zidovudine.

### **PREGNANCY AND LACTATION:**

**Pregnancy.** The safe use of methadone in pregnancy has not been established in terms of possible teratogenic effects. It is contraindicated in obstetric use because of the increased risk of neonatal depression during labour due to methadone's long duration of action.

**Lactation.** Theoretically, methadone is likely to be excreted in breast milk. The risks and benefits of methadone treatment in nursing women must be weighed because the use of maintenance doses may cause physical dependence in the infant.

### **SIDE EFFECTS:**

THE MAJOR HAZARD OF METHADONE IS RESPIRATORY DEPRESSION, CIRCULATORY DEPRESSION, RESPIRATORY ARREST, SHOCK AND CARDIAC ARREST HAVE ALSO BEEN REPORTED.

**Initial administration.** Initially, the dosage of methadone should be titrated to the individual patient. Induction too rapid for the patient is more likely to produce these side effects.

**Most common side effects.** Lightheadedness, dizziness, sedation, nausea, vomiting and sweating, which are more prominent in ambulatory patients and patients who are not suffering from severe chronic pain. In these patients, lower doses are advisable. Some of these side effects can be alleviated if the ambulatory patient lies down.

**Other side effects.**

- Central nervous system: Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, visual disturbances, increased intracranial pressure.
- Gastrointestinal: Dry mouth, anorexia, constipation, biliary tract spasm.
- Cardiovascular: Facial flushing, bradycardia, palpitations, faintness, syncope, hypotension.
- Genito-urinary: Urinary retention or hesitancy, antidiuretic effect, reduced libido and/or potency.
- Allergic: Pruritus, urticaria, other skin rashes, edema and rarely hemorrhagic urticaria.

**Maintenance on a stabilized dose.** Most of the side effects of methadone treatment (except sweating and constipation) often gradually and progressively disappear over a period of several weeks with the prolonged administration of methadone.

**Postmarketing experience:**

Serotonin syndrome (See Warnings and Precautions)

Adrenal insufficiency (See Warnings and Precautions)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. 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.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

**SYMPTOMS AND TREATMENT OF OVERDOSE:**

**Symptoms:** Serious cases of methadone overdose is characterized by respiratory depression (decrease in respiratory rate and/or tidal volume, Cheyne-stokes syndrome, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin and occasionally, bradycardia and hypotension. Apnea, circulatory collapse, cardiac arrest and death may occur in cases of severe methadone overdose, particularly by the intravenous route.

**Treatment:** Primary attention should be given to reestablishing adequate respiratory exchange via a patent airway and assisted controlled ventilation. If a non-tolerant person, especially a child, has taken a large dose of methadone, effective narcotic antagonists are available to counteract the potentially lethal respiratory depression effects of methadone. However, the antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

NARCOTIC ANTAGONISTS ACT FOR MUCH SHORTER PERIODS (1 TO 3 HOURS) COMPARED TO THE LONG DURATION OF ACTION OF METHADONE (36 TO 48 HOURS).

The patient must be continuously monitored for the recurrence of respiratory depression and treated with the narcotic antagonist as required. To reverse signs of intoxication, intravenously administered narcotic antagonists eg. naloxone hydrochloride, nalorphine hydrochloride or levallorphan tartrate are the drugs of choice. The risk of the narcotic antagonist further depressing respiration is less likely with naloxone compared to the other antagonists. The patient should be treated repeatedly with the antagonist as required until the patient's status is satisfactory.

Symptomatic and supportive treatment e.g. oxygen, intravenous fluids and vasopressors should be administered if necessary. A respiratory stimulant would not be necessary in cases where methadone overdose is the sole cause of the respiratory depression.

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| IF THE PATIENT IS PHYSICALLY DEPENDENT ON NARCOTICS, THE USUAL DOSE OF A NARCOTIC ANTAGONIST WILL PRECIPITATE AN ACUTE WITHDRAWAL SYNDROME, THE SEVERITY OF WHICH WILL DEPEND ON THE DEGREE OF PHYSICAL DEPENDENCE AND THE ANTAGONIST DOSE. IF POSSIBLE, THE USE OF NARCOTIC ANTAGONISTS SHOULD BE AVOIDED IN SUCH PATIENTS. IF NECESSARY FOR THE TREATMENT OF SEVERE RESPIRATORY DEPRESSION, THE ANTAGONIST SHOULD BE ADMINISTERED WITH EXTREME CARE AND IN SMALLER DOSES THAN USUAL. |
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**EFFECT ON ABILITY TO DRIVE AND USE MACHINE:**

This can be severely affected during and after methadone treatment. Patients must be cautioned accordingly. The time that these activities can be safely resumed is extremely patient dependent and must be decided by the physician.

**PRECLINICAL SAFETY DATA**

Not applicable

**INSTRUCTION FOR USE**

For oral use only

**DOSAGE FORMS AND PACKAGING AVAILABLE:**

Dosage Form: Liquid

Packaging Available: 100ml & 1L in white round plastic bottle

**NAME AND ADDRESS OF MANUFACTURER / PRODUCT REGISTRATION HOLDER:**

MALAYSIAN PHARMACEUTICAL INDUSTRIES SDN BHD (101323-U)

Plot 14, Lebuhraya Kampung Jawa, 11900 Bayan Lepas,

Pulau Pinang, Malaysia.

**DATE OF REVISION:**

20/02/2018