NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Methatabs, Tablet, 5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Name and strength of the active substance

Methadone hydrochloride BP 5 mg

Excipient(s) with known effect

Lactose monohydrate
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral – tablet

Presentation

Methatabs are white, 7 mm, normal convex tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Methatabs is indicated for:

The treatment of severe pain
Methadone is indicated for relief of severe pain. Methadone is sometimes used as an antitussive when severe pain is present, and coughing cannot be relieved by other means. Methadone is not recommended for obstetric analgesia because its long duration of action increases the risk of neonatal respiratory depression.

The treatment of dependence on opioid drugs
Methadone is indicated as a suppressant to permit detoxification. Oral Methadone is also indicated as maintenance therapy to discourage addicts from returning to illicit use of other opioid drugs.

4.2 Dose and method of administration

Treatment of severe pain
Starting oral doses of Methadone may range from 5 to 10mg (1 to 2 tablets) given every 6 to 8 hours or longer and thereafter adjusted as necessary.

Treatment of dependence on opioid drugs

A dose of 10 to 20 mg (2 to 4 tablets) by mouth may be given initially and increased as necessary by 5 to 10 mg daily. The dose must not be increased by more than 5 to 10mg daily, and by no more than 30 mg in any 7-day period. After stabilisation, which can often be achieved with a dose of 30 to 50 mg daily (up to a maximum of 80 mg daily), the dose of Methadone is gradually decreased until total withdrawal is achieved. Some treatment schedules for opioid dependence involved prolonged maintenance therapy with Methadone where the daily dose is adjusted carefully for the individual.

4.3 Contraindications

Methadone is contraindicated in individuals who are hypersensitive to Methadone or other components in Methadone Tablets:
Like other opioids, Methadone is contraindicated in patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions. Methadone should not be given during an attack of bronchial asthma. Methadone is contraindicated in the presence of acute alcoholism, head injury and raised intracranial pressure.

Methadone is contraindicated in individuals receiving monoamine oxidase inhibitors or within 14 days of stopping such treatment (see Interactions Section 4.5).

As with other opioids, Methadone is contraindicated in patients with ulcerative colitis, since it may precipitate toxic dilation or spasm of the colon. As with all narcotics, Methadone should not be administered to patients with severe hepatic impairment as it may precipitate hepatic encephalopathy (Refer section 4.4 Special warnings and precautions for use).

Methadone is contraindicated in biliary and renal tract spasm.

4.4 Special warnings and precautions for use

Cardiac Conduction Effects:
Laboratory studies, both in vivo and in vitro, have demonstrated that Methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with Methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (> 100 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of Methadone although cases have been reported in patients receiving doses commonly used for maintenance of opioid addiction.
Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval. These risks include cardiac hypertrophy, history of cardiac conduction abnormalities, advanced heart disease or ischaemic heart disease, liver disease, family history of sudden death, hypokalaemia, hypomagnesaemia, concomitant treatments with medicines that have a potential for QT prolongation, concomitant treatment with medicines which may cause electrolyte abnormalities (e.g., diuretics) and concomitant treatment with CYP3A4 inhibitors.

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.

In patients with recognised risk factors of QT prolongation, or in case of concomitant treatment with medicines that have a potential for QT prolongation, ECG monitoring is recommended prior to methadone treatment, at dose stabilisation, after dose increases, or after starting any potentially interacting medicine. In patients without recognised risk factors for QT prolongation, ECG monitoring is recommended before dose titration above 100 mg/day, and at seven days after titration.

For use of Methadone to treat pain, the risk of QT prolongation and development of dysrhythmias should be weighed against the benefit of adequate pain management and the availability of alternative therapies.

Serotonin Syndrome:
The development of serotonin syndrome, which is potentially life-threatening, has been reported with opioid use, including with methadone. This is mainly applicable to the use of methadone at higher doses such as in opioid substitution therapy. Serotonin syndrome has generally occurred when methadone was used concomitantly with other serotonergic drugs (see section 4.5 Interactions with other medicines and other forms of interactions).

Serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma, confusion), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia, diaphoresis), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity, tremor, myoclonus), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, a dose reduction or discontinuation of at least one of the serotonergic medicines being taken should be considered depending on the severity of the symptoms.

Mutagenicity:
Methadone did not exhibit demonstrable mutagenic activity in a wide range of standard in vitro and in vivo mutagenicity assays. However, in a Dominant Lethal assay in mice, treatment with Methadone at doses of 1 to 6 mg/kg was associated with increased pre-implantation deaths and chromosomal aberrations of sperm cells, when compared with controls.

Carcinogenicity:
Long term carcinogenicity tests in rodents did not reveal any evidence of Methadone- related neoplasia.

Teratogenicity:
No teratogenic effects have been observed in standard teratogenicity studies in rats and rabbits given Methadone at doses from 10 to 50 times the average daily human maintenance dose. Developmental abnormalities of the central nervous system have been reported in hamsters and mice given high doses in early pregnancy.

Use in Children:

Methadone is not recommended for use in children less than 18 years of age since documented clinical experience has been insufficient to establish a suitable dosage regimen; furthermore, children are particularly sensitive to the respiratory and central nervous system effects of Methadone.

Use in the Elderly:
Methadone has a long plasma half-life which may lead to accumulation, particularly if renal function is impaired (see Renal Impairment Section 4.5).
In common with other opioids, Methadone may cause confusion in this age group, therefore careful monitoring is advised.

Hepatic Impairment:
Particular care should be taken when Methadone is to be used in patients with hepatic impairment as these patients metabolise Methadone more slowly than normal patients. Where not contraindicated, Methadone should be given at less than the normal recommended dose and the patient's response used as a guide to further dosage requirements (see Contraindications Section 4.3).

Renal Impairment:
Methadone should be used with caution in patients with renal dysfunction.

4.5 Interaction with other medicines and other forms of interaction

The medicines listed below are known to affect methadone metabolism and should therefore be used with caution by those being treated with methadone.

NOTE: Patients with hepatitis C may have impaired liver function. This needs to be taken into account when the use of medicines metabolised by the liver is considered. The dose of paracetamol, for example, needs to be well within the standard 4 g per day.

Drug	Status of effect	Interaction	Mechanism
Alcohol	Clinically important	Increased sedation, increased respiratory depression, combination may also have increased hepatotoxic potential.	Additive central nervous system depression.
Benzodiazepines	Clinically important	Enhanced sedative effect	Additive CNS depression
Buprenorphine	Clinically important	Antagonistic effect or enhanced sedative and respiratory depression	Partial agonist of opiate receptors
Carbamazepine	Clinically important	Reduced methadone levels.	Stimulates hepatic enzymes involved in methadone metabolism
Chlormethiazole	Clinically important	Enhanced sedative	Additive CNS

		effect	depression
Cimetidine	Two cases have been shown in patients taking methadone as analgesia.	Possible increase in methadone plasma levels.	Inhibits hepatic enzymes involved in methadone metabolism
Cisapride Domperidone Metoclopramide	Theoretical	Theoretically might increase the speed of onset of methadone absorption, but not the extent.	Possibly by reversing the delayed gastric emptying associated with opioids.
Cyclizine and other sedating antihistamines	Clinically important	Anecdotal reports of injection of cyclizine with opioids causing hallucinations.	Additive psychoactive effects, anti-muscarinic effects at high doses.
Desipramine	Clinically important	Raised desipramine levels by up to a factor or two.	Unknow interaction not seen with other tricyclic antidepressants
Other tricyclic antidepressants	Theoretical	Enhanced sedative effect which is dependent.	Additive CNS dose depression
Erythromycin	In theory should interact but combination has not been studied.	Increase in methadone levels.	Decreased methadone metabolism.
Fluconazole	In theory the same as ketoconazole.		
Fluoxetine	Clinically important	Raised methadone levels but not as significant as for fluvoxamine.	Decreased methadone metabolism.
Fluvoxamine, other SSRs	Clinically important, theoretical	Raised plasma methadone levels.	Decreased methadone metabolism.
Grapefruit juice	Should interact in theory and there have been several anecdotal reports.	Raised methadone levels.	Decreased methadone metabolism.
Indinavir	Clinically important	Raised methadone levels.	Decreased methadone metabolism.
Ketoconazole	Clinically important	Raised methadone levels.	Decreased methadone metabolism.
MAOI (including selegiline and moclobemide)	Severe with pethidine though unlikely with methadone and has never been described.	CNS excitation delirium, hyperpyrexia, convulsions, hypotension or respiratory depression.	Unclear, avoid the combination if possible.
Naltrexone	Clinically important	Blocks effect to	Opioid agonist –

		methadone (long acting).	competes for opiate receptors.
Naloxone	Clinically important	Blocks effect to methadone (long acting) but may be needed if overdose suspected.	Opioid agonist – competes for opiate receptors.
Nevirapine	Clinically important	Decreased methadone levels	Increased methadone metabolism
Nifedipine	Has been demonstrated *in vitro* only.	Increased nifedipine levels; no effect on methadone levels.	Methadone decreases the metabolism of nifedipine.
Omeprazole	To date, demonstrated only in animals.	Increased methadone levels.	Possibly affects methadone absorption from the gut.
Phenobarbitone	Clinically important	Reduced methadone levels; increased sedation, additive CNS depression	Barbiturates stimulate hepatic enzymes involved in methadone metabolism.
Phenytoin	Clinically important	Reduced methadone levels	Phenytoin stimulates hepatic enzymes involved in methadone metabolism.
Rifampicin	Very important: most patients are likely to be affected.	Reduced methadone levels.	Rifampicin stimulates hepatic enzymes involved in methadone metabolism
Rifabutin	Occasionally clinically important.	Decreased methadone levels.	Increased methadone metabolism.
Ritonavir	Clinically important.	Ritonavir may increase plasma methadone levels.	Inhibits methadone metabolism.
Other protease inhibitors	Theoretical	May raise or lower plasma methadone levels.	Inhibits methadone metabolism.
Urine acidifiers (e.g., ascorbic acid/ vitamin C)	Clinically important	Reduced plasma methadone levels.	Raised urinary excretion of methadone.
Urine alkalinisers (e.g., sodium bicarbonate)	Clinically important	Increased plasma methadone levels.	Reduced urinary excretion of methadone.
Zidovudine	Clinically important	Raised plasma levels of zidovudine; no effect on methadone levels.	Unknown
Zopiclone	Clinically important	Enhanced sedative effects.	Additive CNS depression.

Other opioids	May be clinically important	Enhanced sedative effects.	Additive CNS depression; enhanced respiratory depression.
Other CNS depressant medicines (e.g., neuroleptics, hyoscine)	Clinically important	Enhanced sedative effects, which are dose dependent.	Additive CNS depression.

Serotonergic drugs:
Co-administration of methadone with serotonergic drugs may increase the risk of serotonin syndrome, a potentially life-threatening condition (see section 4.4).

Drugs the affect the serotonergic neurotransmitter system include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

4.6 Fertility, pregnancy and lactation

Fertility:
Methadone does not appear to impair human female fertility. Studies in men on Methadone maintenance programmes have shown that Methadone reduces serum testosterone and markedly depresses the ejaculate volume and sperm motility. The sperm counts of Methadone subjects were twice that of controls, reflecting the lack of dilution through reduced seminal secretions.

Use in Pregnancy and Lactation:

Use in Pregnancy
There is inadequate evidence of the safety of Methadone in human pregnancy although it has been in selected use for many years without apparent ill consequence. Autopsies on five infants who died in utero did not reveal any abnormality attributable to Methadone use by their dependent mothers. Nevertheless, the use of methadone in pregnancy should be avoided unless there is no safer alternative.

Narcotics may cause respiratory depression in the newborn infant. During the last 2 to 3 hours before expected delivery, narcotics should therefore only be used after weighing the needs of the mother against the risk to the foetus.

Use in Lactation
Assays of breast milk from mothers taking methadone for opioid substitution treatment showed Methadone concentrations of 0.17 to 5.6 mcg/ml.

Breastfeeding mothers receiving methadone for opioid substitution treatment should be under specialist care from obstetric and paediatric staff with experience in monitoring for neonatal abstinence syndrome. The baby should be monitored for sedation and poor feeding particularly during the first three weeks of life. Breastfeeding mothers should receive specific information on how to identify respiratory depression and sedation in their babies and when it may be necessary to seek immediate medical care. Breastfeeding mothers should be advised to wean slowly off breastfeeding when they decide to stop to reduce the possibility of withdrawal symptoms in the baby.

The evaluation of the risks and benefits of breastfeeding while on methadone for opioid substitution treatment should be done jointly by the prescriber and patient.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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

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

Other adverse reactions include the following:

Body as a whole: weakness, oedema, headache

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

Endocrine: hypogonadism

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

Hematologic: reversible thrombocytopenia has described in opioid addicts with chronic hepatitis

Metabolic: hypokalaemia, hypomagnesaemia, weight gain, hypoglycaemia (frequency not known)

Musculoskeletal: decreased muscle mass and strength, osteoporosis and fractures

Nervous system disorders: raised intracranial pressure, sedation

Psychiatric: agitation, changes of mood, dependence, disorientation, dysphoria, euphoria, hallucinations, insomnia

Renal: antidiuretic effect, urinary retention or hesitancy

Reproductive: amenorrhoea, reduced libido and/or potency, reduced ejaculate volume,

reduced seminal vesicle and prostate secretions, decreased sperm motility, abnormalities in sperm morphology

Respiratory: pulmonary oedema, respiratory depression

Skin and subcutaneous tissue: pruritus, urticaria, other skin rashes, and rarely, haemorrhagic urticaria

Maintenance on a stabilised dose: during prolonged administration of methadone, as in a methadone maintenance programme, constipation and sweating often persist and hypogonadism, decreased serum testosterone and reproductive effects are thought to be related to chronic opioid use.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions
https://nzphvc.otago.ac.nz/reporting/}

4.9 Overdose

Signs and Symptoms:
The symptoms and signs of overdosage with Methadone parallel those for other opioids, namely profound respiratory depression, pin-point pupils, hypotension, circulatory failure and pulmonary oedema and coma.
Mydriasis may replace miosis as asphyxia intervenes. Drowsiness, floppiness, pin-point pupils and apnoea have been reported in children.

Rare events of leukoencephalopathy may occur in serious cases of overdosage.

Hypoglycaemia has been reported.

Treatment:
General supportive measures should be employed as required. The specific opioid antagonist naloxone is the treatment of choice for the reversal of coma and the restoration of spontaneous respiration. A dose of 0.4 to 2mg is given by intravenous injection repeated at intervals of 2 to 3 minutes, if necessary, up to 10mg. Naloxone may also be given by subcutaneous or intramuscular injection or intravenous infusion. Patients should be monitored closely for at least 48 hours after apparent recovery in case of relapse since the duration of action of the antagonist may be substantially shorter than that of Methadone. The use of other respiratory or central stimulants is not recommended. Acidification of the urine will enhance urinary excretion of Methadone. Methadone is not dialysable by either peritoneal dialysis or haemodialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Actions
Methadone hydrochloride is a synthetic opioid analgesic. Methadone is a racemic mixture and levo-methadone is the active isomer.

The pharmacological actions of Methadone are qualitatively similar to those of morphine. Significant quantitative differences are its effective analgesic activity after administration by the oral route and its tendency to show persistent effects with repeated administration.

5.2 Pharmacokinetic properties

Methadone hydrochloride is readily absorbed after administration by mouth and has high oral bioavailability. Peak plasma concentrations have been reported 1 to 5 hours after oral administration of a single dose in tablet form. It undergoes considerable tissue distribution, and protein binding is reported to be 60 to 90% with oc-acid glycoprotein being the main binding protein in plasma. Metabolism to the major metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenyl-5 –methypyrrolidine, both of them inactive, occurs in the liver. The metabolites are excreted in the faeces and urine together with unchanged Methadone. Other metabolites, including methanol and nor- methadol (reported to be pharmacologically active), have also been described, but account for a small proportion of the dose. The liver may also serve as a major storage site of unchanged Methadone which is taken up, bound non-specifically by the liver and released again mainly unchanged.

Marked inter individual variation in kinetics have been observed with Methadone. Elimination half-lives vary considerably (a range of 15-to 60 hours has been reported) and careful adjustment of dosage is necessary with repeated administration.

Plasma concentrations have been found to vary widely during Methadone maintenance therapy with large differences between patients and wide fluctuations in individual patients.

Declining concentrations have been reported during Methadone maintenance suggesting that tolerance occurs, possibly as a result of auto-induction of hepatic microsomal enzymes.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Maize starch

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

Bottle pack: 60 months from date of manufacture.
Blister pack: 36 months from date of manufacture.

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Pack of 10 tablets in a glass bottle.
Pack of 10 tablets in a blister pack.

Note: Not all pack types are marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Controlled Drug B3.

8. SPONSOR

Noumed Pharmaceuticals Limited
Auckland, New Zealand

Freephone 0800 527 545

9. DATE OF FIRST APPROVAL

31/12/1969

10. DATE OF REVISION OF THE TEXT

23/10/2023

SUMMARY TABLE OF CHANGES

Section changes	Summary of new information
Sponsor	Updated sponsor details.