NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Rubifen: Methylphenidate hydrochloride (USP) 5 mg, 10 mg and 20 mg

Rubifen SR**:** Methylphenidate hydrochloride (USP) 20 mg sustained release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5mg tablet contains methylphenidate 5mg

Each 10mg tablet contains methylphenidate 10mg

Each 20mg tablet contains methylphenidate 20mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Rubifen immediate release 5, 10 and 20 mg tablets: round white tablet with slightly bevelled edges, marked RU-5, RU-10 or RU-20 containing 5 mg, 10 mg and 20 mg methylphenidate respectively with a score mark on the 10 mg tablets.

Rubifen sustained release 20 mg tablets: oblong white or white-cream smooth tablet containing 20 mg methylphenidate in a modified release formulation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention Deficit/Hyperactivity Disorder (ADHD)
ADHD was previously known as attention-deficit disorder or minimal brain dysfunction. Other terms used to describe this behavioural syndrome include: hyperkinetic disorder, minimal brain damage, minimal cerebral dysfunction, minor cerebral dysfunction and psycho-organic syndrome of children.

Rubifen is indicated as part of a comprehensive treatment program which typically includes psychological, educational and social measures and is aimed at stabilising children with a behavioural syndrome characterised by moderate to severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity. The diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10. Non-localising (soft) neurological signs, learning disability and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Special Diagnostic Considerations for ADHD
The specific etiology of this syndrome is unknown, and there is no single diagnostic test. Proper diagnosis requires medical and neuropsychological, educational and social investigation.

Characteristics commonly reported include: history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics. Drug treatment is not indicated in all children with this syndrome. Stimulants are not indicated in children with symptoms secondary to environmental factors (child abuse in particular) and/or primary psychiatric disorder, including psychosis. Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms.

Narcolepsy

Symptoms include daytime sleepiness, inappropriate sleep episodes, and sudden loss of voluntary muscle tone.

4.2 Dosage and method of administration

Dose titration

Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest possible dose.

Other strengths of this medicinal product and other methylphenidate-containing products may be available.

The maximum daily dosage of methylphenidate is 60 mg.

Immediate release tablets

The dosage of Rubifen should be individualised according to the patient's clinical needs and responses. Do not halve tablets. Dose equivalence when the tablet is divided has not been established.

In the treatment of ADHD, an attempt should be made to time administration to coincide with the periods of greatest academic, behavioural and social stress.

Rubifen should be started at a low dose, with increments at weekly intervals. Daily doses above 60 mg are not recommended.

If symptoms do not improve after dose titration over a period of one month, the drug should be discontinued.

If symptoms worsen or other adverse effects occur, the dosage should be reduced or, if necessary, the drug discontinued.

If the effect of the drug wears off too early in the evening, disturbed behaviour and/or inability to go to sleep may recur. A small evening dose of the normal tablet or an afternoon dose of the SR tablet may help to solve this problem.

Rubifen should be discontinued periodically to assess the child's condition. Improvement may continue when the drug is temporarily or permanently discontinued.

Drug treatment should not, and need not, be indefinite. It can usually be discontinued during or after puberty. However, ADHD may continue into adulthood and treatment with Rubifen may be beneficial to those patients after puberty.

Pre-treatment screening
Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment height and weight on a growth chart (see sections 4.3 and 4.4)

Ongoing monitoring
Growth, psychiatric and cardiovascular status should be continuously monitored (see also Section 4.4).

Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months;

Height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart;

Development of de novo or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then least every 6 months and at every visit.

Patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate.

Long-term (more than 12 months) use in children and adolescents
The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferable during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation
Treatment must be stopped if the symptoms do not improve after appropriate dosage adjustment over a one-month period. If paradoxical aggravation of symptoms or other serious adverse events occur, the dosage should be reduced or discontinued.

In the treatment of narcolepsy, the usual oral dose is 20 to 30 mg daily in divided doses, normally 30 to 45 minutes before meals, but the effective dose may range from 10 to 60 mg daily.

In hyperactivity disorders in children aged 6 years and over, the usual initial dose is 5 mg once or twice daily by mouth, increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily in divided doses. Methylphenidate maybe given before breakfast and lunch. A later dose may be considered if the effect wears off in the evening causing rebound hyperactivity.

Sustained release tablets
Rubifen SR Tablets have a duration of action of about 8 hours. They may therefore be used when a prolonged effect is desired exceeding the duration of action of conventional Rubifen tablets. Rubifen SR tablets must be swallowed whole and never crushed or chewed. Rubifen SR tablets should not be split or divided. They should be taken after meals, preferably after a substantial breakfast (see Section 5.2) for maximum duration of effect.

It may be necessary to use a combination of the standard immediate release and SR tablets in some patients to achieve the optimal clinical response. As the duration of action of Rubifen SR tablets is variable from patient to patient, it may not be possible to avoid administration of a Rubifen dose during the middle part of the day in all patients. The total absorption and duration of action of Rubifen SR tablets are maximised when it is taken with a meal.

The total daily dose should be similar to that required if the immediate formulation is used. In the fasted state, Rubifen SR 20 mg gives similar blood concentration to that expected following two Rubifen 10 mg immediate release tablets (with the second being taken four hours after the first).

4.3 Contraindications

- Hypersensitivity to methylphenidate or to any of the excipients
- Anxiety, tension
- Agitation
- Hyperthyroidism
- Pre-existing cardiovascular disorders including severe hypertension, angina, arterial occlusive disease; heart failure, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels)
- During treatment with monoamine oxidase (MAO) inhibitors, or within a minimum of 2 weeks of discontinuing those drugs, due to risk of hypertensive crisis (see Section 4.5)
- In patients with poorly-controlled open-angle or angle-closure glaucoma
- Phaeochromocytoma
- Diagnosis or family history of Tourette's syndrome.

4.4 Special warnings and precautions for use

Treatment with Rubifen is not indicated in all cases of Attention-Deficit/Hyperactivity disorder, and should be considered only after detailed history-taking and evaluation. The decision to prescribe Rubifen should depend on an assessment of the severity of symptoms and their appropriateness to the child's age, and not simply on the presence of one or more abnormal behavioural characteristics. Where these symptoms are associated with acute stress reactions, treatment with Rubifen is usually not indicated.

Cardiovascular
Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems
Sudden death has been reported in association with the use of stimulants of the central nervous system

at usual doses in patients with structural cardiac abnormalities or other serious problems. A causal relationship with stimulant products has not been established since some of these conditions alone may carry an increased risk of sudden death. Stimulant products generally should not be used in patients with known structural cardiac abnormalities or other serious cardiac disorders that may increase the risk of sudden death due to sympathomimetic effects of a stimulant drug. Before initiating Rubifen treatment, patients should be assessed for pre-existing cardiovascular disorders and a family history of sudden death and ventricular arrhythmia (see Section 4.2).

Cardiovascular Conditions

Rubifen is contraindicated in patients with severe hypertension (see Section 4.3). Methylphenidate increases heart rate and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension. Severe cardiovascular disorders are contraindicated (see Section 4.3).

Blood pressure should be monitored at appropriate intervals in all patients taking Rubifen, especially those with hypertension. Patients who develop symptoms suggestive of cardiac disease during Rubifen treatment should undergo a prompt cardiac evaluation.

Misuse and Cardiovascular Events

Misuse of stimulants of the central nervous system, including Rubifen, may be associated with sudden death and other serious cardiovascular adverse events.

Cerebrovascular

Cerebrovascular conditions

Patients with pre-existing central nervous system (CNS) abnormalities, e.g., cerebral aneurysm and/or other vascular abnormalities such as vasculitis or pre-existing stroke should not be treated with Rubifen. Patients with additional risk factors (history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed regularly for neurological/psychiatric signs and symptoms after initiating treatment with Rubifen (see above, paragraph on Cardiovascular Conditions and Section 4.5).

Aggression, anxiety and agitation

Aggressive behaviour, marked anxiety, or agitation are often observed in patients with ADHD, and have been reported in patients treated with methylphenidate tablets (see section 4.8 Undesirable effects). Anxiety led to discontinuation of methylphenidate tablets in some patients. It is recommended to monitor patients beginning treatment with methylphenidate tablets for the appearance of, or worsening of, aggressive behaviour, marked anxiety, or agitation.

Psychiatric

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. Prior to initiating treatment with Rubifen, patients should be assessed for pre-existing psychiatric disorders and a family history of psychiatric disorders (see Section 4.2).

Treatment of ADHD with stimulant products including Rubifen should not be initiated in patients with acute psychosis, acute mania or acute suicidality. These acute conditions should be treated and controlled before ADHD treatment is considered.

In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric symptoms, Rubifen should not be given to patients unless the benefit outweighs the potential risk.

Psychotic symptoms
Psychotic symptoms, including visual and tactile hallucinations or mania have been reported in patients administered usual prescribed doses of stimulant products, including Rubifen (see Section 4.8). Physicians should consider treatment discontinuation.

Aggressive behaviour
Emergent aggressive behaviour or an exacerbation of baseline aggressive behaviour has been reported during stimulant therapy, including Rubifen. However, patients with ADHD may experience aggression as part of their medical condition. Therefore causal association with treatment is difficult to assess. Physicians should evaluate the need for adjustment of treatment regimen in patients experiencing these behavioural changes, bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency
Patients with emergent suicidal ideation and behaviour during treatment for ADHD should be evaluated immediately by their physician. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen.

Tics and worsening of Tourette's syndrome
Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. It is recommended that the family history be assessed, and that the patient is clinically evaluated for tics or Tourette's syndrome before initiating methylphenidate. Regular monitoring for the emergence or worsening of tics or Tourette's syndrome during treatment with methylphenidate is recommended at every dose adjustment and every visit, and treatment discontinued if clinically appropriate.

Serotonin syndrome
Serotonin syndrome has been reported following co-administration of methylphenidate with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) and serotonin- norepinephrine reuptake inhibitors (SNRIs). The concomitant use of methylphenidate and serotonergic drugs is not recommended as this may lead to the development of serotonin syndrome. The symptoms of serotonin syndrome may include mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g. tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, and hyperthermia), neuromuscular symptoms (e.g. tremor, rigidity, myoclonus, hyperreflexia, and incoordination), seizures, and/or gastrointestinal symptoms (e.g. nausea, vomiting, and diarrhoea). Prompt recognition of these symptoms is important so that treatment with methylphenidate and serotonergic drugs can be immediately discontinued and appropriate treatment instituted (see Section 4.5).

Priapism
Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both paediatric and adult patients. Priapism generally developed after some time on the drug, often subsequent to an increase in dose. Priapism has also been reported during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Growth retardation
Moderately reduced weight gain and slight growth retardation have been reported with the long-term use of stimulants, including Rubifen, in children (see Section 4.8).

Growth should be monitored as clinically necessary during treatment with Rubifen, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures
Rubifen should be used with caution in patients with epilepsy as clinical experience has shown that it can cause an increase in seizure frequency in a small number of such patients. If seizure frequency increases, Rubifen should be discontinued.

Drug abuse and dependence
Chronic abuse of Rubifen can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur, especially with parenteral abuse. Clinical data indicate that children given Rubifen are not more likely to abuse drugs as adolescents or adults.

Caution is called for in emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because they may increase the dosage on their own initiative.

Withdrawal
Careful supervision is required during drug withdrawal, since this may unmask depression as well as the effects of chronic over activity. Some patients may require long-term follow-up.

Haematological effects

The long-term safety and efficacy profiles of Rubifen are not fully known. Patients requiring long-term therapy should therefore be carefully monitored and complete and differential blood counts and a platelet count performed periodically. In the event of haematological disorders appropriate medical intervention should be considered (see Section 4.8).

Renal impairment

No studies have been performed in renally impaired patients (see section 5.2 Pharmacokinetic properties).

Hepatic impairment

No studies have been performed in hepatically impaired patients (see section 5.2 Pharmacokinetic properties).

Geriatric patients (65 years or above)

No studies have been performed in patients over 60 years of age (see section 5.2 Pharmacokinetic properties).

Paediatric patients (under 6 years of age)
Methylphenidate should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

<u>*NON-CLINICAL SAFETY DATA*</u>
In a conventional study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When the animals were tested as adults (postnatal weeks 13-

14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose of 100 mg/kg/day (about 58-fold higher than the MRHD on a mg/kg basis).

Genotoxicity
With methylphenidate, sister chromatid exchange and chromosome aberrations were elevated in one in vitro study in Chinese Hamster Ovary (CHO) cells. However, no genotoxicity effects were seen in several other assays, including no mutagenic effects in three in vitro tests (Ames reverse mutation test, mouse lymphoma forward mutation test, human lymphocyte chromosome aberration test) and no evidence of clastogenic or aneugenic effects in two in vivo mouse bone marrow (micronucleus tests, at doses up to 250 mg/kg . B6C3F1 mice from the same strain that showed liver tumours in the cancer bioassay were used in one of these studies. Additionally, there was no genotoxic potential as assessed by measuring cII mutations in the liver and micronuclei in peripheral reticulocytes in the Big Blue mouse, micronuclei in peripheral blood reticulocytes, HPRT mutations and chromosomal aberrations in peripheral blood lymphocytes of rhesus monkeys. Pig A locus mutations in adolescent rats, micronucleated reticulocyte frequencies in blood and DNA damage in blood, brain, and liver cells of adult male rats treated for 28 consecutive days, and by measuring micronuclei in mouse peripheral blood erythrocytes.

Carcinogenicity
In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas (a benign tumour) and, in males only, an increase in hepatoblastomas (a malignant tumour) at daily doses of approximately 60 mg/kg/day (about 35- fold-higher than the MRHD on a mg/kg basis). Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no overall increase in the number of malignant hepatic tumours. The mouse strain used is particularly sensitive to the development of hepatic tumours. It is thought that hepatoblastomas might be due to non-genotoxic mechanisms such as an increase in hepatic cell proliferation. This is consistent with the increase in liver weights observed in this mouse carcinogenicity study.

Methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day (about 26-fold higher than the MRHD on a mg/kg basis).

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions
Anti-hypertensive drugs
Rubifen may decrease the effectiveness of drugs used to treat hypertension.

Use with drugs that elevate blood pressure
Rubifen should be used with caution in patients being treated with drugs that elevate blood pressure (see also paragraph on Cerebrovascular Conditions in Section 4.4).

Because of possible hypertensive crisis, Rubifen is contraindicated in patients being treated (currently or within the preceding 2 weeks) with MAO-inhibitors (see Section 4.3).

Use with alcohol
Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including Rubifen. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with anaesthetics
There is a risk of sudden blood pressure and heart rate increase during surgery. If surgery is planned, Rubifen should not be taken on the day of surgery.

Use with centrally acting alpha-2 agonists (e.g. clonidine)
Serious adverse events including sudden death, have been reported in concomitant use with clonidine, although no causality for the combination has been established.

Use with domaminergic drugs
As an inhibitor of dopamine reuptake, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) as well as dopamine antagonists (antipsychotics, e.g. haloperidol). The co-administration of Rubifen with antipsychotics is not recommended because of the counteracting mechanism of action.

Use with serotonergic drugs
The concomitant use of methylphenidate and serotonergic drugs is not recommended as this may lead to the development of serotonin syndrome (see Section 4.4).

Methylphenidate has been shown to increase extracellular serotonin and norepinephrine and appears to have weak potency in binding serotonin transporter.

Pharmacokinetic interactions
Methylphenidate is not metabolized by cytochrome P450 to a clinically relevant extent. Inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on Rubifen pharmacokinetics. Conversely, the d- and l-enantiomers of methylphenidate in Rubifen did not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

Rubifen co-administration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

Case reports suggested a potential interaction of methylphenidate with coumarin anticoagulants, some anticonvulsants (e.g. phenobarbital, phenytoin, primidone), phenylbutazone, and tricyclic antidepressants but pharmacokinetic interactions were not confirmed when explored at larger sample sizes. The dosage of these drugs might have to be reduced.

An interaction with the anticoagulant ethyl biscoumacetate in 4 subjects was not confirmed in a subsequent study with a larger sample size (n=12).

Other specific drug-drug interaction studies with m have not been performed in vivo.

Drug/Laboratory test
Methylphenidate may induce false positive laboratory tests for amphetamines, particularly with immunoassays screen test.

4.6 Fertility, pregnancy and lactation

Pregnancy
Methylphenidate is potentially teratogenic in rabbits (see non-clinical safety data).
The safety of methylphenidate for use during human pregnancy has not been established. Data from a

cohort study of in total approximately 3,400 pregnancies exposed in the first trimester do not suggest an increased risk of overall birth defects. There was a small increased occurrence of cardiac malformations (pooled adjusted relative risk, 1.3; 95 % CI, 1.0-1.6) corresponding to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies.

Medicines should only be prescribed in pregnancy when the expected benefits to the mother outweigh any potential risks to the mother and foetus. If possible, medicines should be used at the lowest effective dose for the shortest possible duration. Careful consideration and discussion of the risks and benefits of the medicines should be taken in the management of pregnant women or women intending to become pregnant. Women of child-bearing potential should be fully informed of the risks and benefits of the use of methylphenidate during pregnancy.

Non-clinical safety data

Reproductive toxicity

Methylphenidate is considered to be possibly teratogenic in rabbits. Spina bifida with malrotated hindlimbs was observed in two separate litters at a dose of 200 mg/kg/day. Exposure (AUC) at this dose was approximately 5.1 times higher than the extrapolated exposure at the maximum recommended human dose (MRHD). Exposure at the next lower dose, wherein no spina bifida was found, was 0.7 times the extrapolated exposure at MRHD. A second study was conducted with a high dose of 300 mg/kg, which was considered maternally toxic. No spina bifida was seen, however, in 12 litters (92 foetuses) surviving. Exposure (AUC) at 300 mg/kg was 7.5 times the extrapolated exposure at MRHD.

Methylphenidate is not teratogenic in rats. Development foetal toxicity was noted at a high dose of 75 mg/kg (20.9 times higher than the AUC at MRHD) and consisted of an increase of the instance of foetuses with delayed ossification of the skull and hyoid bones as well as foetuses with short supernumerary ribs.

When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day (about 26-fold higher than the MRHD on a mg/kg basis), offspring body weight gain was decreased at the highest dose, but no other effects on postnatal development were observed.

Lactation

Case reports showed that methylphenidate was distributed into breast milk reaching a milk-to-plasma ration of approximately 2.5 (see Section 5.2).

A decision should be made whether to abstain from breast-feeding or to abstain from methylphenidate therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the mother.

It is not known whether the active substance of Rubifen and/or its metabolites pass into breast milk, but for safety reasons, breast-feeding mothers should not use Rubifen.

Non-clinical safety data

When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day (about 26-fold higher than the MRHD on a mg/kg basis), offspring body weight gain was decreased at the highest dose, but no other effects on postnatal development were observed.

Fertility

No human data on the effect of methylphenidate on fertility are available. Methylphenidate did not impair fertility in male or female mice.

Non-clinical safety data

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week continuous breeding study. The study was conducted over two generations of mice continuously receiving methylphenidate doses of up to 160 mg/kg/day (about 90-fold higher than the MRHD on a mg/kg basis).

4.7 Effects on ability to drive and use machines

Rubifen may cause dizziness, drowsiness, blurred vision, hallucinations or other CNS side effects (see Section 4.8).

Patients experiencing such side effects should refrain from driving, operating machinery, or engaging in other potentially hazardous activities.

4.8 Undesirable effects

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of methylphenidate based on the comprehensive assessment of the available adverse event information. A causal relationship with methylphenidate cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data

Double-Blind Data – Adverse Drug Reactions Reported at ≥1% Frequency

Adverse Drug Reactions (ADRs) in either the paediatric or adult double-blind studies may be relevant for both patient populations.

Paediatric Patients

The safety of methylphenidate tablets was evaluated in 639 paediatric patients (children and adolescents) with ADHD who participated in 4 placebo-controlled, double-blind clinical trials. The information presented in this section was derived from pooled data.

Adverse Drug Reactions (ADRs) reported by ≥1% of methylphenidate tablets -treated children and adolescent subjects and more frequently than placebo in these trials are shown in below table.

Adverse Drug Reactions Reported by ≥1% of methylphenidate tablets -Treated Children and Adolescent Subjects and More Frequently than Placebo in 4 Placebo-Controlled, Double-Blind Clinical Trials

System/Organ Class Adverse Drug Reaction	Methylphenidate tablets (n = 321) %	Placebo (n = 318) %
Infections and Infestations Nasopharyngitis	2.8	2.2
Psychiatric Disorders Insomnia	2.8	0.3

System/Organ Class Adverse Drug Reaction	Methylphenidate tablets (n = 321) %	Placebo (n = 318) %
Nervous System Disorders		
Headache	10.6	11.9
Dizziness	1.9	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.9	0.9
Oropharyngeal Pain	1.2	0.9
Gastrointestinal Disorders		
Abdominal Pain upper	6.2	3.8
Vomiting	2.8	1.6
General Disorders and Administration Site Conditions		
Pyrexia	2.2	0.9

*Terms of Initial insomnia (methylphenidate tablets=0.6%) and Insomnia (methylphenidate tablets = 2.2%) are combined into Insomnia

The majority of ADRs were mild to moderate in severity.

Adult Patients

The safety of methylphenidate tablets was evaluated in 905 adult subjects with ADHD who participated in 3 placebo-controlled, double-blind clinical trials. The information presented in this section was derived from pooled data.

Adverse Drug Reactions (ADRs) reported by ≥1% of methylphenidate tablets-treated adult subjects in these trials are shown in below table.

Adverse Drug Reactions Reported by ≥1% of methylphenidate tablets -Treated Adult Subjects in 3 Placebo-Controlled, Double-Blind Clinical Trials

System/Organ Class Adverse Drug Reaction	Methylphenidate tablets (n = 596) %	Placebo (n = 309) %
Infections and Infestations		
Upper respiratory tract infection	1.7	1.0
Sinusitis	1.3	1.0
Metabolism and Nutrition Disorders		
Decreased appetite	24.8	6.1
Anorexia	4.2	1.3

System/Organ Class Adverse Drug Reaction	Methylphenidate tablets (n = 596) %	Placebo (n = 309) %
Psychiatric disorders		
Insomnia	13.3	7.8
Anxiety	8.4	2.9
Initial insomnia	5.7	2.6
Depressed mood	4.4	2.6
Restlessness	4.0	0
Agitation	3.2	0.6
Nervousness	2.3	0.6
Bruxism	1.5	0.6
Depression	1.5	0.6
Affect lability	1.3	0.6
Libido decreased*	1.5	0.6
Panic attack	1.3	0.3
Tension	1.3	0.3
Aggression	1.2	0.6
Confusional state	1.0	0.3
Nervous system disorders		
Headache	24.2	18.8
Dizziness	7.4	5.5
Tremor	3.4	0.6
Paraesthesia	1.2	0
Tension headache	1.0	0.3
Eye disorders		
Accommodation disorder	1.3	0
Vision blurred	1.3	1.0
Ear and labyrinth disorders		
Vertigo	2.0	0.3
Cardiac disorders		
Tachycardia	6.0	0
Palpitations	4.5	0.6
Vascular Disorders		
Hypertension	2.2	1.6
Hot flush	1.3	0.6
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	1.5	1.3
Cough	1.2	1.0
Dyspnoea	1.2	0.6
Gastrointestinal disorders		
Dry mouth	15.1	3.6
Nausea	14.3	4.9
Dyspepsia	2.0	1.9
Vomiting	1.8	0.6
Constipation	1.5	0.6
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	5.7	1.3
Musculoskeletal and Connective Tissue Disorders		
Muscle tightness	1.3	0
Muscle spasm	1.0	0.3

System/Organ Class Adverse Drug Reaction	Methylphenidate tablets (n = 596) %	Placebo (n = 309) %
Reproductive System and Breast Disorders		
Erectile dysfunction	1.0	0.3
General Disorders and Administration Site Conditions		
Irritability	5.2	2.9
Fatigue	4.7	4.2
Thirst	1.8	0.6
Asthenia	1.2	0
Investigations		
Weight decreased	8.7	3.6
Heart rate increased	3.0	1.9
Blood pressure increased	2.5	1.9
Alanine aminotransferase increased	1.0	0

*The adverse reaction libido decreased includes the preferred term loss of libido

The majority of ADRs were mild to moderate in severity.

Open-Label Data – Adverse Drug Reactions Reported at ≥1% Frequency

The safety of methylphenidate tablets was evaluated in 3782 paediatric and adult subjects with ADHD who participated in 12 open-label clinical trials. The information presented in this section was derived from pooled data.

Adverse Drug Reactions (ADRs) reported by ≥1% of methylphenidate tablets -treated subjects in these trials and not listed in above tables are shown in the below table.

Adverse Drug Reactions Reported by ≥1% of methylphenidate tablets -Treated Subjects in 12 Open-Label Clinical Trials

System/Organ Class Adverse Drug Reaction	Methylphenidate tablets (n = 3782) %
Psychiatric Disorders	
Tic	2.0
Mood swings	1.1
Nervous System Disorders	
Somnolence	1.0
Gastrointestinal disorders	
Diarrhea	2.4
Abdominal discomfort	1.3
Abdominal pain	1.2
Skin and Subcutaneous Tissue Disorders	
Rash	1.3
General Disorders and Administration Site Conditions	
Feeling jittery	1.4

The majority of ADRs were mild to moderate in severity.

Double Blind and Open-Label Data – Adverse Drug Reactions Reported at <1% Frequency

Additional ADRs that occurred in <1% of methylphenidate tablets-treated paediatric and adult subjects in the double-blind and open-label clinical datasets are listed in the below table.

Adverse Drug Reactions Reported by <1% of methylphenidate tablets -Treated Pediatric and Adult Subjects in Either Double-Blind or Open-Label Clinical Trials

Blood and Lymphatic System Disorders
Leukopenia
Psychiatric Disorders
Anger, Sleep disorder, Hypervigilance, Tearfulness, Mood altered
Nervous System Disorders
Psychomotor hyperactivity, Sedation, Lethargy
Eye Disorders
Dry eye
Skin and Subcutaneous Tissue Disorders
Rash macular
Investigations
Cardiac murmur

Postmarketing Data

ADRs identified during postmarketing experience with methylphenidate tablets are included in the below table. The frequencies are provided according to the following convention:
Very common ≥1/10
Common ≥1/100 and <1/10
Uncommon ≥1/1000 and <1/100
Rare ≥1/10000 and <1/1000
Very rare <1/10000, including isolated reports

Adverse Drug Reactions Identified During Postmarketing Experience with methylphenidate tablets by Frequency Category Estimated from Spontaneous Reporting Rates

Infections and infestations
Very common Nasopharyngitis**
Blood and Lymphatic System Disorders
Very rare Pancytopenia, Thrombocytopenia, Thrombocytopenic, Purpura, Leucopenia. Anaemia
Immune System Disorders
Rare Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions and Exanthemas NEC
Metabolism and nutrition disorders
Rare Moderately reduced weight gain during prolonged use in children
Psychiatric Disorders
Very common insomnia
Very rare Hyperactivity, Disorientation, Psychosis, Hallucination, Hallucination Auditory, Hallucination Visual, Mania, Logorrhoea, libido disorder*, Transient depressed mood.**Nervous System Disorders**
Common Drowsiness.
Very rare Convulsion, Grand Mal Convulsion, Dyskinesia, Choreoathetoid Movements, Tics or exacerbation of existing tics and Tourette's syndrome, Cerebrovascular disorder (including cerebral vasculitis, cerebral haemorrhage, cerebral arteritis, cerebral vascular occlusion)
Eye Disorders
Very rare Diplopia, Mydriasis, Visual Impairment
Cardiac Disorders
Very rare Angina Pectoris, Bradycardia, Extrasystoles, Supraventricular Tachycardia, Ventricular Extrasystoles
Vascular Disorders
Common Raynaud's Phenomenon***, Peripheral coldness***
Respiratory, thoracic, and mediastinal disorders
Common Cough**
Very rare Epistaxis
Gastrointestinal disorders

Common Toothache**	
Skin and Subcutaneous Tissue Disorders	
Common Pruritus, Urticaria, Fever.	
Very rare Alopecia, Erythema, Exfoliative dermatitis, Hyperhidrosis	
Hepatobiliary Disorders	
Very rare Hepatocellular injury, Acute hepatic failure	
Musculoskeletal, and Connective Tissue Disorders	
Very rare Arthralgia, Myalgia, Muscle cramps	
Reproductive System and Breast Disorders	
Very rare Priapism, Gynecomastia	
General Disorders and Administration Site Conditions	
Rare Therapeutic Response Decreased	
Very rare Chest Pain, Chest Discomfort, Drug Effect Decreased, Hyperpyrexia	
Investigations	
Very rare Blood Alkaline Phosphatase Increased, Blood Bilirubin Increased, Hepatic Enzyme Increased, Platelet Count Decreased, White Blood Cell Count Abnormal	

NEC = not elsewhere classified
*The adverse reaction libido disorder includes terms apart from those associated with decreases in libido
** ADRs reported from the clinical trials performed in adult ADHD patients
*** The reported frequency of ADRs was based on the frequency observed higher in the adult ADHD clinical study which was higher than that previously reported for children.

Very rare reports of poorly documented neuroleptic malignant syndrome (NMS) have been received. In most of these reports, patients were also receiving other medications. It is uncertain what role methylphenidate played in these cases.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with methylphenidate via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Psychiatric disorders
Dysphemia, suicidal ideation or attempt (including completed suicide)
Renal and urinary disorders
Enuresis

Additional adverse reactions reported with other methylphenidate-containing products

Others adverse reactions that have been reported with other methylphenidate-containing products based on clinical studies data and post-market spontaneous reports included:

Psychiatric disorders
Irritability, abnormal behaviour or thinking, apathy, repetitive behaviours, over-focussing, dependence. Cases of abuse and dependence have been described, more often with immediate release formulations.
Nervous System Disorders
Reversible ischaemic neurological deficit, Migraine
Cardiac Disorders
Cardiac arrest, myocardial infarction
Skin and Subcutaneous Tissue Disorders
Angioneurotic oedema, Fixed drug eruption
Renal and urinary disorders
Haematuria
General Disorders and Administration Site Conditions

sudden cardiac death

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://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Symptoms
Signs and symptoms of acute overdosage, mainly due to overstimulation of the central and sympathetic nervous systems, may include: vomiting, agitation, tremor, hyperreflexia, muscle twitching, convulsions (possibly followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitation, cardiac arrhythmias, hypertension, mydriasis, dryness of mucous membranes and rhabdomyolysis.

Management
Management consists in providing supportive measures, and symptomatic treatment of life-threatening events, e.g. hypertensive crisis, cardiac arrhythmias, convulsions. For the most current guidance for treatment of symptoms of overdose, the practitioner should consult a certified Poison Control Centre or current toxicological publication.

Supportive measures include preventing self-injury and protecting the patient from external stimuli that would exacerbate the overstimulation already present. If the overdose is oral and the patient is conscious, the stomach could be evacuated by induction of vomiting, followed by administration of activated charcoal. Airway protected gastric lavage is necessary in hyperactive or unconscious patients, or those with depressed respiration. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required to reduce hyperpyrexia.

The efficacy of peritoneal dialysis or extracorporeal haemodialysis for Rubifen overdosage has not been established. Clinical experience with acute overdosage is limited. Patients who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an infusion of calcium gluconate.

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

Pharmacotherapeutic group: Psychostimulants.

Rubifen is a mild CNS stimulant with more prominent effects on mental than on motor activities. Its mode of action in humans is not completely understood, but its stimulant effects are thought to be due to an inhibition of dopamine reuptake in the striatum, without triggering the release of dopamine.

The mechanism by which Rubifen exerts its mental and behavioural effects in children is not clearly established, nor is there conclusive evidence showing how these effects relate to the condition of the central nervous system.

5.2 Pharmacokinetic properties

Absorption
Immediate release tablets: After oral administration the active substance (methylphenidate hydrochloride) is rapidly and almost completely absorbed. Owing to extensive first-pass metabolism its systemic availability is only 30 % (11-51 %) of the dose. Ingestion with food accelerates absorption, but has no effect on the amount absorbed.

Peak plasma concentrations of about 40 nmol/L (11 ng/mL) are reached on average 1-2 hours after administration of 0.30 mg/kg. Peak plasma concentrations vary markedly between patients. The area under the concentration-time curve (AUC) and the peak plasma concentration (C_{max}) are proportional to the dose.

SR Tablets: in the fasted state, absorption of methylphenidate from Rubifen 20 mg SR tablets is 37 % slower than with the conventional tablets and results in a smaller fluctuation of plasma concentration. C_{max} is lower (by 40 %) and is attained later (at 3 hours) but the total amount absorbed (AUC) is the same.

After a high-fat meal, both AUC (by 25 %) and C_{max} (by 27 %) are significantly higher, although the rate of absorption (C_{max}/AUC ratio) remains the same. Time to C_{max} (T_{max}) is also slightly faster after a high-fat meal (median T_{max} = 2.5 hrs.) as compared to without food (median T_{max} = 3 hrs.). As with immediate release tablets, there is considerable variation in plasma methylphenidate concentrations between patients.

Distribution
In blood, methylphenidate and its metabolites are distributed between plasma (57 %) and erythrocytes (43 %). Binding to plasma proteins is low (10-33 %). The apparent distribution volume is about 13.1 L/kg.

Methylphenidate excretion into breast milk has been noted in two case reports, where the calculated relative infant dose was ≤ 0.2 % of the weight adjusted maternal dose. Adverse events were not noted in either infant (6 months of age and 11 months of age).

Biotransformation
Biotransformation of methylphenidate is rapid and extensive. Peak plasma concentrations of the main, de-esterified metabolite α-phenyl-2-piperidine acetic acid are attained about 2 hours after administration and are 30-50 times higher than those of the unchanged substance. The half-life of α-phenyl-2-piperidine acetic acid is about twice that of methylphenidate, and its mean systemic clearance is 0.17 L/h/kg. Only small amounts of hydroxylated metabolites (e.g. hydroxymethylphenidate and hydroxyritalinic acid) are detectable. Therapeutic activity seems to be principally due to the parent compound.

Elimination
Methylphenidate is eliminated from the plasma with a mean half-life of 2 hours. The apparent mean systemic clearance is 10 L/h/kg. After oral administration, 78-97 % of the dose is excreted in the urine and 1-3 % in the faeces in the form of metabolites within 48-96 hours. Only small quantities (<1 %) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as α-phenyl-

2-piperidine acetic acid (60-86 %).

The elimination half-life and the cumulative urinary excretion of α-phenyl-2-piperidine acetic acid are not significantly different for SR tablets. Hence, in the fasted state, the total amount absorbed from one SR tablet and 20 mg in conventional tablet form is equal.

Special Populations

There are no apparent differences in the pharmacokinetics of methylphenidate between hyperactive children and healthy adult volunteers.

Elimination data from patients with normal renal function suggest that renal excretion of unchanged methylphenidate would hardly be diminished in the presence of impaired renal function. However, renal excretion of the metabolite α-phenyl-2-piperidine acetic acid may be reduced.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Rubifen (5 mg, 10 mg and 20 mg) contains calcium hydrogen phosphate dehydrate magnesium stearate, maize starch, and microcrystalline cellulose.

Rubifen SR (20 mg) contains cetyl alcohol, ethylcellulose, lactose, magnesium stearate, and opadry white Y-1-7000.

6.2 Incompatibilities

None known.

6.3 Shelf life

Rubifen (5 mg, 10 mg and 20 mg): 24 months.

Rubifen SR (20 mg): 36 month.

6.4 Special precautions for storage

Store at or below 25°C and protect from moisture.

6.5 Nature and contents of container

Rubifen (5 mg, 10 mg and 20 mg): Blister pack, PVC/Al, 30 tablets

Rubifen SR (20 mg): Blister pack, PVC/PVdC AL (10 tbs/blister), 30 tablets

6.6 Special precautions for disposal

Not applicable

7. MEDICINE SCHEDULE

Class B2 Controlled Drug

8. SPONSOR

AFT Pharmaceuticals Limited
PO Box 33-203
Takapuna
Auckland 0740
Phone: 0800 423 823

9. DATE OF FIRST APPROVAL

16/03/2000

10. DATE OF REVISION OF THE TEXT

January 2026

Summary table of changes

Date	Section(s) Changed	Change (s)
January 2026	4.8	Addition of Hyperhidrosis to ADR table