NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Rubifen LA 10 mg, 20 mg, 30 mg, 40 mg and 60 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is methylphenidate hydrochloride (INN for alpha-phenyl-2-piperidine acetic acid methyl ester).

Rubifen LA modified release capsules contain 10 mg, 20 mg, 30 mg, 40 mg or 60 mg methylphenidate hydrochloride.

Excipient(s) with known effect: sugar (sucrose)

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

Rubifen modified release capsules are presented as follows:

Rubifen LA 10 mg modified release capsules:

Hard gelatin capsule size 2, with a dark yellow opaque cap and a white opaque body, imprinted with "RUB" in red ink on the cap and "M10" in red ink on the body, containing 10 mg white and whitish pellets.

Rubifen LA 20 mg modified release capsules:

Hard gelatin capsule size 2, white opaque capsule, imprinted with "RUB" in red ink on the cap and "M20" in red ink on the body, containing 20 mg white and whitish pellets.

Rubifen LA 30 mg modified release capsules:

Hard gelatin capsule size 2, ivory opaque capsule, imprinted with "RUB" in red ink on the cap and "M30" in red ink on the body, containing 30 mg white and whitish pellets.

Rubifen LA 40 mg modified release capsules:

Hard gelatin capsule size 1, dark yellow opaque, imprinted with "RUB" in red ink on the cap and "M40" in red ink on the body, containing 40 mg white and whitish pellets.

Rubifen LA 60 mg modified release capsules:

Hard gelatin capsule size 0, with a dark yellow opaque cap and an ivory opaque body, imprinted with "RUB" in red ink on the cap and "M60" in red ink on the body, containing 60 mg white and whitish pellets.

Not all presentations are available.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention-Deficit/Hyperactivity Disorder (ADHD, DSM-IV)

Rubifen LA is indicated in the treatment of Attention-Deficit/Hyperactivity Disorder in children aged 6 years or older and in adults.

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. Ritalin is indicated as part of a comprehensive treatment programme 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 in children

The specific aetiology 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, and 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.

Special Diagnostic Considerations for ADHD in adults

Adults with ADHD have symptom patterns characterised by shifting activities, being bored easily, restlessness, impatience, and inattentiveness. Symptoms such as hyperactivity tend to diminish with increasing age possibly due to adaptation, neurodevelopment and self-medication. Inattentive symptoms are more prominent and have a greater impact on adults with ADHD. Diagnosis in adults should include a structured patient interview to determine current symptoms. The pre-existence of childhood ADHD is to be determined retrospectively. Diagnosis should not be made solely on the presence of one or more symptoms. The decision to use a stimulant in adults must be based on a very thorough assessment of the severity and chronicity of the symptoms and their impact on the daily life of the patient.

Narcolepsy

Rubifen LA modified release capsules **should not** be used for the treatment of narcolepsy in adults.

4.2 Dose and method of administration

Dosage regimen

Daily doses above 80 mg are not recommended for the treatment of ADHD in adults.

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.

Special populations

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 older)

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

Pre-treatment screening

Treatment should only be initiated by specialist physicians with experience in the use of the drug. Before initiating Rubifen LA treatment, patients should be assessed for pre-existing cardiovascular and psychiatric disorders and a family history of sudden death, ventricular arrhythmia and psychiatric disorders. Weight and height should also be measured before treatment and documented on a growth chart (**Section 4.3 Contraindications** and **Section 4.4. Special warnings and precautions for use**).

Periodic assessment of the treatment in ADHD

Drug treatment does not need to be indefinite. Physicians should periodically re-evaluate the treatment with trial periods off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

When used in children with ADHD, treatment can usually be discontinued during or after puberty.

Target population

ADHD

Children (6 years and over) and adolescents

Rubifen LA (methylphenidate hydrochloride modified-release capsules) are for oral administration once daily in the morning. The recommended starting dose of Rubifen LA is 20 mg. When in the judgement of the clinician a lower initial dose is appropriate, patients may begin treatment with Rubifen LA 10 mg.

A maximum daily dose of 60 mg should not be exceeded.

Adults

Only the modified release formulation should be used for the treatment of ADHD in adults.

Rubifen LA is administered as a single dose once daily.

- ***Patients new to methylphenidate***

(See Section 5.2 Pharmacokinetic properties) The recommended starting dose of Rubifen LA in patients who are not currently taking methylphenidate is 20 mg once daily.

- ***Patients currently using methylphenidate***

Treatment may be continued with the same daily dose. If the patient was previously treated with an immediate release formulation, a conversion to an appropriate recommended dose of Rubifen LA should be made (see Switching patients from methylphenidate immediate release tablets to Rubifen LA capsules).

A maximum daily dose of 80 mg should not be exceeded.

There is no difference in dosing recommended between male and female adult patients (see Section 5.1 Pharmacodynamics).

Switching patient's treatment from methylphenidate immediate release tablets to Rubifen LA modified release capsules

The recommended dose of Rubifen LA should be equal to the total daily dose of the immediate release formulation not exceeding a total dose of 60 mg in children and 80 mg in adults. Examples involving switch from methylphenidate immediate release tablets are provided in **Table 1.**

Table 1: Recommended daily dose when switching treatment to Rubifen LA

Previous dose of methylphenidate immediate release tablets	Recommended dose of Rubifen LA modified release capsules
5 mg twice daily	10 mg once daily
10 mg twice daily	20 mg once daily
15 mg twice daily	30 mg once daily
20 mg twice daily	40 mg once daily
30 mg twice daily	60 mg once daily

For other methylphenidate regimens, clinical judgement should be used when selecting the starting dose. Rubifen LA dosage may be adjusted at weekly intervals in 10 mg increments for children and in 20 mg increments for adults.

Administration

Rubifen LA capsules and/or their contents should not be crushed, chewed, or divided.

Rubifen LA capsules may be administered with or without food.

They may be swallowed whole or alternatively may be administered by sprinkling the contents over a small amount of food (see the instructions: Administration by sprinkling LA capsule contents on food).

Sprinkling Rubifen LA capsule contents on food
The capsules may be carefully opened and the beads sprinkled over soft food (e.g. apple-sauce). The food should not be warm because this could affect the modified-release properties of this formulation.

The mixture of drug and food should be consumed immediately in its entirety. The drug and food mixture should not be stored for future use.

4.3 Contraindications

Rubifen LA is contraindicated in patients with the following:

- anxiety and tension states
- agitation
- a family history or diagnosis of Tourette's syndrome
- glaucoma
- hyperthyroidism
- pre-existing cardiovascular disorders including uncontrolled hypertension, angina pectoris, arterial occlusive disease especially coronary arteries; heart failure, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, cardiac arrhythmia and channelopathies (disorders caused by the dysfunction of ion channels)
- treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO inhibitor (hypertensive crisis may result)
- pheochromocytoma
- known drug dependence or alcohol abuse
- severe depression, anorexia nervosa, psychotic symptoms or suicidal tendency, since Rubifen might worsen these conditions
- known hypersensitivity to methylphenidate or to any component of the formulation.

4.4 Special warnings and precautions for use

General

Treatment with Ritalin 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 Ritalin should depend on an assessment of the severity of symptoms and in paediatric patients, the 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 Ritalin 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 Ritalin treatment, patients should be assessed for pre-existing cardiovascular disorders and a family

history of sudden death and ventricular arrhythmia (see section 4.2 Posology and method of administration).

Cardiovascular conditions:

Ritalin is contraindicated in patients with severe hypertension (see Section 4.3 Contraindications). Ritalin 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 Contraindications).

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

Misuse and Cardiovascular Events:

Misuse of stimulants of the central nervous system, including Ritalin, 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 Ritalin. 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 Ritalin (see above, paragraph on Cardiovascular Conditions and Section 4.5 Interaction with other medicinal products and other forms of interaction).

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 Ritalin, patients should be assessed for pre-existing psychiatric disorders and a family history of psychiatric disorders (see section 4.2 Method of administration).

Treatment of ADHD with stimulant products including Ritalin 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, Ritalin 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 Ritalin (see section 4.8 Undesirable effects). Physicians should consider treatment discontinuation.

Aggressive behaviour:

Emergent aggressive behaviour or an exacerbation of baseline aggressive behaviour has been reported during stimulant therapy, including Ritalin. 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 and caregivers of patients should be alerted about the need to monitor for clinical worsening, suicidal behaviour or thoughts or unusual changes in behaviour and to seek medical advice immediately if these symptoms appear. The physician should initiate appropriate treatment of any underlying psychiatric condition and consider a possible discontinuation or change in the ADHD treatment.

Tics:

Ritalin is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported (see section 4.8 Undesirable effects). Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in patients should precede use of methylphenidate for ADHD treatment. Ritalin is contraindicated in case of diagnosis or family history of Tourette's syndrome (see Section 4.3 Contraindications). Patients should be regularly monitored for the emergence or worsening of tics during treatment with Ritalin.

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, hyperthermia), neuromuscular symptoms (e.g. tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g. nausea, vomiting, 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 Interaction with other medicinal products and other forms of interaction).

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 Ritalin, in children (see section 4.8 Undesirable effects).

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

Seizures

Ritalin 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, Ritalin should be discontinued.

Drug abuse and dependence

Chronic abuse of Ritalin 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 Ritalin 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 Ritalin 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 Undesirable effects).

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.

NON-CLINICAL SAFETY DATA

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 Interactions with other medicines and other forms of interactions

Pharmacodynamic interactions

Anti-hypertensive drugs

Rubifen LA may decrease the effectiveness of drugs used to treat hypertension.

Use with drugs that elevate blood pressure

Methylphenidate should be used with caution in patients being treated with drugs that elevate blood pressure due to the risk of severe hypertension (see Section 4.4 Special warnings and precautions for use – Cerebrovascular conditions).

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

Use with alcohol

Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including Rubifen LA. 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 LA 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 dopaminergic drugs

As an inhibitor of dopamine reuptake, methylphenidate may be associated with pharmacodynamic interactions when coadministered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) as well as dopamine antagonists (antipsychotics, e.g. haloperidol).

Concomitant use of methylphenidate with antipsychotics is not recommended due to its counteracting mechanism of action. If upon medical assessment the combination is deemed necessary, monitoring for extrapyramidal symptoms (EPS) is recommended, as the concomitant use of methylphenidate with antipsychotics may increase the risk of EPS when there is a change (increase or decrease) in dosage of either or both medications.

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 Special warnings and precautions for use). Methylphenidate has been shown to increase extracellular serotonin and noradrenaline and appears to have weak potency in binding serotonin transporter.

Pharmacokinetic interactions

Ritalin 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 Ritalin pharmacokinetics. Conversely, the d- and l-enantiomers of methylphenidate in Ritalin did not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

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

Case reports suggested a potential interaction of Ritalin 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 Ritalin 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

Women of child-bearing potential

There are no data to support special recommendation in women of child-bearing potential.

Pregnancy

There is insufficient experience with use of methylphenidate in pregnant women. Ritalin should not be given to pregnant women unless the potential benefit outweighs the risk to the foetus. Methylphenidate is potentially teratogenic in rabbits (see Non-clinical Safety Data below).

NON-CLINICAL SAFETY DATA

Reproductive toxicity

Methylphenidate is considered to be possibly teratogenic in rabbits. Spina bifida with malrotated hind limbs 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 Pharmacokinetic properties).

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 Ritalin and/or its metabolites pass into breast milk, but for safety reasons, breast-feeding mothers should not use Ritalin.

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 (see Non-clinical safety data below).

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

Ritalin may cause dizziness, drowsiness, blurred vision, hallucinations or other CNS side effects (see section 4.8 Undesirable Effects).

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

4.8 Undesirable effects

Nervousness and insomnia are very common adverse reactions which occur at the beginning of Ritalin treatment but can usually be controlled by reducing the dosage and/or omitting the afternoon or evening dose.

Decreased appetite is also very common but usually transient. Abdominal pain, nausea and vomiting are common to very common, usually occur at the beginning of treatment and may be alleviated by concomitant food intake.

Tabulated summary of adverse drug reactions

The adverse reactions listed in Table 2 are listed by MedDRA (v15.1) system organ class. Within each organ class, the adverse drug reactions are ranked by frequency, using the following convention: very common ≥ 10%, common ≥ 1% to < 10%; uncommon ≥ 0.1% to < 1%; rare ≥ 0.01% to < 0.1%; very rare < 0.01%.

Table 2: Adverse reactions reported with methylphenidate tablets/ capsules use from clinical studies, spontaneous reports and literature

Infections and infestations	
Very common	Nasopharyngitis*
Blood and the lymphatic system disorders	
Very rare	Leucopenia, thrombocytopenia, anaemia
Immune system disorders	
Very rare	Hypersensitivity reaction, including angioedema and anaphylaxis
Metabolism and nutrition disorders	
Very common	Decreased appetite**
Rare	Moderately reduced weight gain during prolonged use in children
Psychiatric disorders	
Very common	Nervousness, insomnia

Common	Anxiety*, restlessness*, sleep disorder*, agitation*, depression, aggression, bruxism
Very rare	Hyperactivity, psychosis (sometimes with visual and tactile hallucinations), transient depressed mood
Nervous system disorders	
Common	Dyskinesia, tremor*, headache, drowsiness, dizziness
Very rare	Convulsions, choreoathetoid movements, tics or exacerbation of existing tics and Tourette's syndrome, cerebrovascular disorders including vasculitis, cerebral haemorrhages and cerebrovascular accidents
Eye disorders	
Rare	Difficulties in visual accommodation, blurred vision
Cardiac disorders	
Common	Tachycardia, palpitation, arrhythmias, changes in blood pressure and heart rate (usually an increase)
Rare	Angina pectoris
Respiratory, thoracic and mediastinal disorders	
Common	Cough*
Gastrointestinal disorders	
Very common	Nausea**, dry mouth**
Common	Abdominal pain, vomiting (which may be alleviated by concomitant food intake), dyspepsia*, toothache*
Hepatobiliary disorders	
Very rare	Abnormal liver function, ranging from transaminase elevation to hepatic coma
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus, urticaria, fever, scalp hair loss, hyperhidrosis*
Very rare	Thrombocytopenic purpura, exfoliative dermatitis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Uncommon	Trismus
Very rare	Muscle cramps
General disorders and administration site conditions	
Common	Feeling jittery*
Rare	Slight growth retardation during prolonged use in children
Investigations	
Common	Weight decreased*
Vascular disorders	
Common	Raynaud's phenomenon**, peripheral coldness**

* 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 Ritalin 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.

Table 3: Adverse drug reactions from spontaneous reports and literature (frequency not known)

Reproductive system and breast disorders:	Priapism
Psychiatric disorders:	Dysphemia, suicidal ideation or attempt (including completed suicide)
Renal and urinary disorders:	Enuresis

Additional adverse reactions reported with other methylphenidate-containing products

The list below shows adverse reactions not listed for methylphenidate immediate release tablets that have been reported with other methylphenidate-containing products based on clinical trials data and post-market spontaneous reports.

Blood and lymphatic disorders:	Pancytopenia
Immune system disorders:	Hypersensitivity reactions such as auricular swelling
Psychiatric disorders:	Irritability, affect lability, abnormal thinking or behaviour, anger, mood altered, mood swings, hypervigilance, mania, disorientation, libido disorder, apathy, repetitive behaviours, over-focussing, confusional state, dependence. Cases of abuse and dependence have been described, more often with immediate release formulations
Nervous system disorders:	Reversible ischaemic neurological deficit, migraine
Eye disorders:	Diplopia, mydriasis, visual disturbance
Cardiac disorders:	Cardiac arrest, myocardial infarction
Respiratory, thoracic and mediastinal disorders:	Pharyngolaryngeal pain, dyspnoea
Gastrointestinal disorders:	Diarrhoea, constipation
Skin and subcutaneous tissue disorders:	Angioneurotic oedema, erythema, fixed drug eruption
Musculoskeletal, connective tissue and bone disorders:	Myalgia, muscle twitching
Renal and urinary disorders:	Haematuria, incontinence
Reproductive system and breast disorders:	Gynaecomastia
General disorders and administration site conditions:	Chest pain, fatigue, sudden cardiac death
Investigations:	Cardiac murmur

Reporting suspected adverse effects

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

Symptoms

Signs and symptoms of acute overdosage, mainly due to over-stimulation of the central nervous system and from excessive sympathomimetic effects, may include: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitation, cardiac arrhythmias, hypertension, mydriasis, dryness of mucous membranes and rhabdomyolysis.

Management

When treating an overdose, practitioners should bear in mind that a second release of methylphenidate from Ritalin LA (methylphenidate hydrochloride modified-release capsules) occurs approximately four hours after administration.

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 Ritalin 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

Pharmacotherapeutic group: Psychostimulants
ATC classification: N06BA04

5.1 Pharmacodynamics

Methylphenidate 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 and norepinephrine reuptake into presynaptic neurons and thereby increasing these neurotransmitters in the extraneuronal space reuptake in the striatum, without triggering the release of dopamine.

The mechanism by which methylphenidate 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.

The l-enantiomer is thought to be pharmacologically inactive.

The effect of treatment with 40 mg dexmethylphenidate hydrochloride, the pharmacologically active d-enantiomer of Ritalin, on QT/QTc interval was evaluated in a study in 75 healthy volunteers. The maximum mean prolongation of QTcF intervals was <5 ms, and the upper limit of the 90% confidence interval was below 10 ms for all time matched comparisons versus placebo. This was below the threshold of clinical concern and no exposure response relationship was evident.

Clinical efficacy and safety

Ritalin has been used for over 50 years in the treatment of ADHD. Its effectiveness in the treatment of ADHD is well established. In addition to improving core symptoms of ADHD, methylphenidate also improves behaviours associated with ADHD such as impaired academic performance and social function.

Studies in the published literature have shown Ritalin to significantly improve daytime sleepiness and cataplexy.

Children with ADHD

Ritalin LA was evaluated in a randomized, double-blind, placebo-controlled, parallel group clinical study in which 134 children, ages 6 to 12, with DSM-IV diagnoses of Attention Deficit Hyperactivity Disorder (ADHD) received a single morning dose of Ritalin LA in the range of 10-40 mg/day, or placebo, for up to 2 weeks. The optimal dose for each patient was determined in a dose titration phase of the study prior to randomization.

The primary efficacy variable was the change from baseline to the final rating in the ADHD/DSM-IV Scale for Teachers (CADS-T) total subscale score. The CADS-T assesses symptoms of hyperactivity and inattention. The analysis of the primary efficacy variable showed a significant treatment difference in favour of Ritalin LA ($p < 0.0001$). A statistically significant treatment effect for Ritalin LA relative to placebo was also found in all analyses of the secondary CADS efficacy variables, as well as in two post-hoc analyses for the ADHD diagnostic subtypes (combined type, inattentive type). The results of the primary and secondary efficacy analyses are summarized in Table 4.

Table 4: ADHD/DSM-IV subscales for teachers and parents, change from baseline (ITT population, LOCF analysis)

	Methylphenidate modified release capsules		Placebo		
	n	Mean change[1] (SD[2])	n	Mean change[1] (SD[2])	p-value
CADS-T subscale					
Total	62[3]	10.7 (15.7)	70[3]	-2.8 (10.6)	< 0.0001
Inattentive	62	5.3 (8.25)	70	-1.5 (5.67)	< 0.0001
Hyperactive-Impulsive	62	5.4 (7.95)	70	-1.3 (5.93)	< 0.0001
CADS-P subscale					
Total	63	6.3 (13.5)	70	0.5 (13.55)	0.0043
Inattentive	63	2.8 (7.28)	70	0.2 (6.4)	0.0213
Hyperactive-Impulsive	63	3.5 (6.87)	70	0.3 (7.66)	0.0015

[1] Score at end of placebo-washout period minus final score

[2] Standard deviation

[3] Two patients (one in each treatment group) had no CADS-T baseline values but had post-randomisation values. They are, therefore, not included in the descriptive statistics.

Adults with ADHD

Methylphenidate modified release capsules were evaluated in a randomised, double-blind, placebo-controlled, multicentre study in the treatment of 725 adult patients (395 male and 330 female) diagnosed with ADHD according to DSM-IV ADHD criteria. The study was designed to:

1) Confirm the clinically effective and safe dose range of methylphenidate modified release capsules for adults (18 – 60 years old) in a 9-week, double-blind, randomised, placebo-controlled, parallel group period (Period 1) consisting of a 3-week titration stage followed by a 6-week fixed dose stage (40, 60, 80 mg/day or placebo). Subsequently patients were re-titrated to their optimal dose of methylphenidate modified release capsules (40, 60 or 80 mg/day) over a 5-week period (Period 2).
2) Evaluate the maintenance of effect of methylphenidate modified release capsules in adults with ADHD in a 6-month, double-blind, randomized, withdrawal study (Period 3).

Efficacy was assessed using the DSM-IV ADHD rating scale (DSM-IV ADHD RS) for symptomatic control and Sheehan Disability Score (SDS) for functional improvement as change in respective total scores from baseline to the end of the first period. All dose levels of methylphenidate modified release capsules showed significantly greater symptom control ($p < 0.0001$ for all dose levels) compared to placebo as measured by a reduction in DSM-IV ADHD RS total score. All doses of methylphenidate modified release capsules showed significantly greater functional improvement ($p = 0.0003$ at 40 mg, $p = 0.0176$ at 60 mg, $p < 0.0001$ at 80 mg) compared to placebo as measured by reduction in SDS total score (see **Table 5**).

Table 9: Analysis of improvement from baseline 1 to end of Period 1 in DSM IV ADHD RS total score and SDS total score by treatment/(LOCF*) for Period 1

		40 mg methylphenidate modified release capsules	60 mg methylphenidate modified release capsules	80 mg methylphenidate modified release capsules	Placebo
Change in DSM-IV ADHD RS from baseline	n	160	155	156	161
	LS mean*	15.45	14.71	16.36	9.35
	p-value	< 0.0001	< 0.0001	< 0.0001	
	Significance level	0.0167	0.0208	0.0313	
Change in SDS total score from baseline	n	151	146	148	152
	LS mean	5.89	4.9	6.47	3.03
	p-value	0.0003	0.0176	< 0.0001	
	Significance level***	0.0167	0.0208	0.0313	

* LOCF – Last Observation Carried Forward using the final visit for each patient with data in the 6-week fixed-dose phase of Period 1

**LS mean – Least Square mean changes from Analysis of Covariance (ANCOVA) model with treatment group and centre as factors and baseline DSM-IV ADHD RS total score and SDS total score as covariate

***Significance level = the final two-sided level of significance (alpha) for the test following the extended gatekeeping procedure

Significant clinical efficacy was demonstrated in all three methylphenidate modified release capsule dose levels using physician rated scales [Clinical Global Impression-Improvement (CGI-I) and Clinical Global Improvement-Severity (CGI-S)], self-rated scales [Adult Self-Rating Scale (ASRS)] and observer-rated scales [Conners' Adult ADHD Rating Scale Observer Short Version (CAARS O:S)]. The results were consistently in favour of methylphenidate modified release capsules over placebo across all assessments in Period 1.

Maintenance of effect of methylphenidate modified release capsules was evaluated by measuring the percentage of treatment failure in methylphenidate modified release capsules compared to the placebo group at the end of a 6-month maintenance period (see Table 6). Once the methylphenidate modified release capsules dose was optimized in Period 2, approximately 79 % of patients continued to maintain disease control for a period of at least 6 months ($p < 0.0001$ vs. placebo). An odds ratio of 0.3 suggested that patients treated with placebo had a 3 times higher chance of becoming a treatment failure compared to methylphenidate modified release capsules.

Table 6: Percentage of treatment failures during Period 3

			All methylphenidate modified release capsules vs. placebo	
	All methylphenidate modified release capsules n = 352 n (%)	**Placebo n = 115 n (%)**	**Odds ratio (95% CI)**	**p-value* (significance level**)**
Treatment failure	75 (21.3)	57 (49.6)	0.3 (0.2, 0.4)	< 0.0001 (0.0500)
Not treatment failure	277 (78.7)	58 (50.4)		

* Two-sided p-value based on comparison between each methylphenidate modified release capsules group and placebo using the logistic regression model.

**Significance level = the final two-sided level of significance (alpha) for the test following the extended gatekeeping procedure.

Patients who entered Period 3 had completed a total of between 5 14 weeks of methylphenidate modified release capsules treatment in Periods 1 and 2. Patients then assigned to placebo in Period 3

did not experience increased signs of withdrawal and rebound compared to patients who continued on methylphenidate modified release capsules treatment.

The study performed in adults did not suggest any difference in efficacy or safety amongst gender subgroups (see section 4.2 Posology and method of administration).

The long-term efficacy and safety of methylphenidate modified release capsules in adult patients was further evaluated in a 26-week open label extension study of methylphenidate modified release capsules in 298 adult patients with ADHD. Combining all patients in both studies, a total of 354 patients continuously received methylphenidate modified release capsules for > 6 months and 136 patients for > 12 months.

The safety profile of methylphenidate modified release capsules did not change with the longer duration of treatment of adult ADHD patients. The safety profile seen in this study was similar to that observed in previous study. No unexpected serious adverse events or adverse events were observed in this extension study and the commonly observed adverse events were expected and driven by the pharmacologic activity.

Furthermore, methylphenidate modified release capsules treatment during the study consistently demonstrated clinical efficacy when using self-rated scales (SDS) and physician-rated scales (ie, DSM-IV ADHD RS, CGI-I, and CGI-S). The results were consistently in favor of methylphenidate modified release capsules treatment across all assessments. Patients continued to show symptomatic improvement and a reduction in functional impairment throughout the study as shown by the mean change in DSM-IV ADHD total score by -7.2 points and the mean change in SDS total score by 4.8 points when assessed against the extension baseline.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of methylphenidate modified release capsules to children diagnosed with Attention-Deficit Hyperactivity Disorder (ADHD) and adults, methylphenidate is rapidly absorbed and produces a bimodal plasma concentration-time profile (i.e. two distinct peaks approximately four hours apart). The relative bioavailability of methylphenidate modified release capsules administered once daily is comparable to the same total dose of immediate release methylphenidate HCl tablets administered twice daily in children and in adults.

The fluctuations between peak and trough plasma methylphenidate concentrations are smaller for methylphenidate modified release capsules administered once daily compared to methylphenidate HCl tablets administered twice daily.

Food effects

Methylphenidate modified release capsules may be administered with or without food. There were no significant differences in AUC when methylphenidate modified release capsules were administered with either a high fat breakfast or applesauce, compared to administration in the fasting condition, although a high fat meal and applesauce reduced C_{max2} by 25% and 13% respectively. There is no evidence of dose dumping in the presence or absence of food.

For patients unable to swallow the capsule, the contents may be sprinkled on applesauce and administered (see **Section 4.2 Dosage and method of administration**).

Distribution

In the blood, methylphenidate and its metabolites become distributed in the plasma (57%) and the erythrocytes (43%). Binding to plasma proteins is low (10 to 33 %). The apparent volume of distribution (Vd) has been calculated at 13.1 L/kg after an oral dose. The volume of distribution was 2.65 ± 1.11 L/kg for *d*-MPH and 1.80 ± 0.91 L/kg for *l*-MPH, following intravenous administration of 10 mg methylphenidate.

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 (see **Section 4.6 Fertility, pregnancy and lactation – Use in Lactation**). Adverse events were not noted in either infant (6 months and 11 months of age).

Metabolism

Biotransformation of methylphenidate, primarily by the carboxyl esterase CES1A1, is rapid and extensive. Peak plasma concentrations of the main, de-esterified, metabolite, α-phenyl-2-piperidine acetic-acid (ritalinic acid), are attained about 2 hours after administration and are 30 to 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. 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.

Excretion

Methylphenidate is eliminated from the plasma with a mean half-life of 2 to 3 hours, and the calculated mean systemic clearance is 4 to 10 L/h/kg after an oral dose. The systemic clearance is 0.40 ± 0.12 L/h/kg for *d*-MPH and 0.73 ± 0.28 L/h/kg for *l*-MPH. Within 48 to 96 hours, 78 to 97% of the dose administered is excreted in the urine and 1 to 3% in the faeces in the form of metabolites. Unchanged methylphenidate appears in the urine only in small quantities (< 1%). Most of the dose is excreted in the urine as α-phenyl-2-piperidine acetic acid (60 – 86%).

Special populations

Effect of age

There are no apparent differences in the pharmacokinetics of methylphenidate between hyperactive children (6-13 years) and healthy adult volunteers.

Patients with renal impairment

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 alpha-phenyl-2-piperidine acetic acid may be reduced.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Rubifen LA 10 mg modified release capsules:

Povidone
Surinerts sugar spheres (sucrose and maize starch)
Purified talc
Methacrylic acid copolymer

Ammonio methacrylate copolymer
Triethyl citrate
Gelatin (from bovine bones)
Titanium dioxide
Iron oxide yellow
Red ink (shellac, propylene glycol, iron oxide red, strong ammonia solution, potassium hydroxide)

Rubifen LA 20 mg modified release capsules:

Povidone
Surinerts sugar spheres (sucrose and maize starch)
Purified talc
Methacrylic acid copolymer
Ammonio methacrylate copolymer
Triethyl citrate, gelatin (from bovine bones)
Titanium dioxide
Red ink (shellac, propylene glycol, iron oxide red, strong ammonia solution, potassium hydroxide)

Rubifen LA 30 mg modified release capsules:

Povidone
Surinerts sugar spheres (sucrose and maize starch)
Purified talc
Methacrylic acid copolymer
Ammonio methacrylate copolymer
Triethyl citrate
Gelatin (from bovine bones)
Titanium dioxide
Iron oxide yellow, red ink (shellac, propylene glycol, iron oxide red, strong ammonia solution, potassium hydroxide)

Rubifen LA 40 mg modified release capsules:

Povidone
Surinerts sugar spheres (sucrose and maize starch)
Purified talc
Methacrylic acid copolymer
Ammonio methacrylate copolymer
Triethyl citrate
Gelatin (from bovine bones)
Titanium dioxide
Iron oxide yellow
Red ink (shellac, propylene glycol, iron oxide red, strong ammonia solution, potassium hydroxide)

Rubifen LA 60 mg modified release capsules:

Povidone
Surinerts sugar spheres (sucrose and maize starch)
Purified talc
Methacrylic acid copolymer
Ammonio methacrylate copolymer
Triethyl citrate
Gelatin (from bovine bones)
Titanium dioxide
Iron oxide yellow

Red ink (shellac, propylene glycol, iron oxide red, strong ammonia solution, potassium hydroxide)

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this drug.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

Rubifen LA modified release capsules are supplied in PVC/Aclar-PET/Alu foil peelable blister packs of 30.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Controlled Drug B2

8 SPONSOR

AFT Pharmaceuticals Ltd
Auckland
New Zealand

Phone: 0800-423-823

Email: customer.service@aftpharm.com

9 DATE OF FIRST APPROVAL

18 January 2024

10 DATE OF REVISION

22 January 2024

Summary table of changes

Date	Section changed	Update
22 January 2024	6.3 Shelf-life	Shelf-life changed to 48 months