ARTIGE®
(methylphenidate HCl)

DRUG DEPENDENCE: Artige should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow up.

NAME OF THE MEDICINE

Active ingredient: Methylphenidate hydrochloride

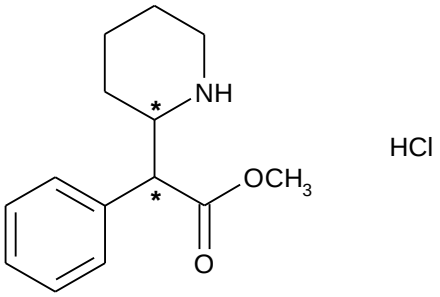
Chemical names: Methyl (R*, R*)-(±)-α-phenyl-2-piperidineacetate hydrochloride; 2-piperidineacetic acid, α-phenyl-, methyl ester, hydrochloride; or methyl α-phenyl-2-piperidineacetate hydrochloride

Molecular formula: $C_{14}H_{19}NO_2$. HCl

Molecular weight: 269.8

CAS number: 298-59-9

Chemical structure:



DESCRIPTION

Methylphenidate hydrochloride is a white, finely crystalline, odourless powder; freely soluble in water and methanol, soluble in ethanol and slightly soluble in chloroform and acetone. It is a racemic mixture comprised of the *d*- and *l-threo* enantiomers.

One Artige tablet contains 10 mg of methylphenidate hydrochloride.

Excipients: lactose, calcium phosphate, gelatin, magnesium stearate, purified talc and wheat starch.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: psychostimulants
ATC code: NO6B AO4.

Pharmacodynamics

Artige is a racemate consisting of a 1:1 mixture of *d-threo* methylphenidate (*d*-MPH) and *l-threo* methylphenidate (*l*-MPH).

Mechanism of Action

Methylphenidate is a central nervous system (CNS) stimulant. Its mode of action in humans is not completely understood but methylphenidate presumably exerts its stimulant effect by an inhibition of dopamine reuptake in the striatum, without triggering the release of dopamine.

There is neither specific evidence which clearly establishes the mechanism whereby methylphenidate produces its mental and behavioural effects in children, nor conclusive evidence as to how these effects relate to the condition of the central nervous system.

The *l*-enantiomer is thought to be pharmacologically inactive.

Repeated oral administration of methylphenidate to young rats was associated with decreased spontaneous locomotor activity at systemic exposures (plasma AUC) about 3-fold that at the maximum clinical dose, due to an exaggerated pharmacological activity of methylphenidate. A deficit in the acquisition of a specific learning task was also observed, only in females, at systemic exposures (plasma AUC) 8-fold that at the maximum clinical dose. The clinical relevance of these findings is unknown**.**

Pharmacokinetics

Absorption:

Following oral administration of Artige tablets, the active substance, methylphenidate hydrochloride, is rapidly and almost completely absorbed from the tablets. Owing to extensive first-pass metabolism, the absolute bioavailability was 22±8 % for the *d*-enantiomer and 5±3 % for the *l*-enantiomer. Ingestion with food increased both the C_{max} (23%) and the AUC (15%) of methylphenidate, but had no effect on the rate of absorption. Peak plasma concentrations of approx. 40 nmol/litre (11 ng/mL) are attained, on the average, 2 hours after administration. The peak plasma concentrations, however, vary markedly from one person to another. The area under the plasma concentration curve (AUC), as well as the peak plasma concentration, are proportional to the size of the dose administered.

Distribution:

In the blood, methylphenidate and its metabolites become distributed in the plasma (57%) and the erythrocytes (43%). Methylphenidate and its metabolites have low plasma protein-binding (approximately 15%). 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 MPH.

Methylphenidate excretion into breast milk has been noted in two case reports (see PRECAUTIONS – Use in Lactation).

Metabolism:

Biotransformation of methylphenidate is primarily by the carboxylesterase CES1A1. Peak plasma concentrations of the main, deesterified, 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.

Elimination:

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%). The bulk of the dose is excreted in the urine as α-phenyl-2-piperidine acetic acid (60-86%).

Special populations

Effects of age: There are no apparent differences in the pharmacokinetic behaviour of methylphenidate in hyperactive children 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 α-phenyl-2-piperidine acetic acid may be reduced.

INDICATIONS

Attention-Deficit Hyperactivity Disorder (ADHD)

Artige tablets are indicated for the treatment of ADHD.

ADHD was previously known as attention-deficit disorder. Other terms used to describe this behavioural syndrome include: minimal brain dysfunction in children, hyperkinetic child syndrome, minimal brain damage, minimal cerebral dysfunction, minor cerebral dysfunction and psycho-organic syndrome of children.

Artige is indicated as part of a comprehensive treatment programme which typically includes other remedial measures (psychological, educational, social) for achieving a beneficial effect in children with a behavioural syndrome characterised by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity (not always present) and impulsivity. The diagnosis of this syndrome should not be made when these symptoms are only of recent origin. Non-localising (soft) neurological signs, emotional lability, learning disability and an 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 aetiology of this syndrome is unknown and there is no single diagnostic test. Adequate diagnosis requires the use, not only of medical, but also of psychological, educational and social resources. Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and an 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 for all children with this syndrome. Stimulants are not intended for use in children who exhibit symptoms secondary to environmental factors (e.g. child abuse in particular) or primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Narcolepsy

Artige tablets are also indicated for the treatment of narcolepsy. The symptoms include daytime sleepiness, inappropriate sleep episodes and rapidly occurring loss of voluntary muscle tone. Artige is effective for symptoms of sleepiness but not for loss of voluntary muscle tone.

CONTRAINDICATIONS

Artige 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 inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase (MAO) inhibitor (hypertensive crises may result)
- phaeochromocytoma
- known drug dependence or alcohol abuse
- severe depression, anorexia nervosa, psychotic symptoms or suicidal tendency, since Artige might worsen these conditions
- known hypersensitivity to methylphenidate or to any component of the formulation.

PRECAUTIONS

General

Treatment with methylphenidate is not indicated in all cases of ADHD and should be considered only after detailed history taking and evaluation of the patient. The decision to prescribe methylphenidate should depend on the physician's assessment of the chronicity and severity of the symptoms and in paediatric patients, the appropriateness to the child's age. Prescription should not depend solely on the presence of isolated behavioural characteristics. When the symptoms are associated with acute stress reactions, treatment with methylphenidate is usually not indicated.

Sudden death and pre-existing structural cardiac abnormalities or other serious heart problems

It is essential that patients with pre-existing structural cardiac abnormalities or other serious heart problems being considered for treatment are assessed by a cardiologist before initiating treatment. Ongoing cardiological supervision should be maintained throughout treatment in these patients.

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Stimulant products, including methylphenidate, generally should not be used in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may increase the risk of sudden death due to the sympathomimetic effects of a stimulant drug. Before initiating methylphenidate treatment, patients should be assessed for pre-existing cardiovascular disorders and a family history of sudden death and ventricular arrhythmia (see DOSAGE AND ADMINISTRATION).

Adults

Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Cardiovascular Conditions:

Artige is contraindicated in patients with severe hypertension. Artige 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 CONTRAINDICATIONS).

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

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease. Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Misuse and Cardiovascular Events:

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

<u>Cerebrovascular</u>

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 Artige. Patients with additional risk factors (history of cardiovascular disease, concomitant medicines that elevate blood pressure) should be assessed regularly for neurological/psychiatric signs and symptoms after initiating treatment with Artige (see PRECAUTIONS – Cardiovascular Conditions and INTERACTIONS WITH OTHER MEDICINES).

Psychiatric Conditions

Artige should not be used to treat severe depression or for the prevention or treatment of normal fatigue states. In psychotic patients administration of methylphenidate may exacerbate symptoms of behaviour disturbance and thought disorder.

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

Treatment of ADHD with stimulant products including Artige 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. Methylphenidate should not be used as treatment for severe depression of either exogenous or endogenous origin.

In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric symptoms, Artige 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 Artige (see ADVERSE EFFECTS). Physicians should consider treatment discontinuation if psychotic symptoms occur.

Bipolar Illness:

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients.

Aggressive behaviour:

Emergent aggressive behaviour or an exacerbation of baseline aggressive behaviour has been reported during stimulant therapy, including Artige. 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.

Motor and verbal tics:

CNS stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported (see ADVERSE EFFECTS).Therefore, clinical evaluation for tics in patients should precede use of stimulant medicine. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate for ADHD treatment. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate.

Serotonin syndrome:

Serotonin syndrome has been reported when methylphenidate was co-administered 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 INTERACTIONS WITH OTHER MEDICINES).

Paediatric use:

Methylphenidate should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established. Medicines should be kept out of the reach of children.

Growth retardation

Moderately reduced weight gain and slight growth retardation have been reported with the long term use of stimulants, including methylphenidate, in children (see ADVERSE EFFECTS). Growth should be monitored as clinically necessary during treatment with methylphenidate and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Careful follow up of weight and height in children aged 7 to 10 years who were randomised to either methylphenidate or non-medicine treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medicine treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e. treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Published data are inadequate to determine whether chronic use of amphetamines may cause similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

The retardation of growth referred to under ADVERSE EFFECTS is usually followed by catch-up growth when the medicine is discontinued. In order to minimise such complications, drug-free periods over weekends, school holidays and long vacations are advocated by some specialists.

Fatigue:

Methylphenidate should not be employed for the prevention or treatment of normal fatigue states.

Seizures:

There is some clinical evidence that methylphenidate may lower the convulsion threshold in patients with a history of seizures, with prior EEG abnormalities in the absence of seizures and, rarely, in the absence of a history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and methylphenidate has not been established. In the presence of seizures, the drug should be discontinued.

Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both paediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Drug abuse and dependence:

Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because they may increase the dosage on their own initiative. Chronic abuse can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur, especially in response to parenteral abuse.

Clinical data indicate that children given Artige are not more likely to abuse drugs as adolescents or adults. Methylphenidate abuse or dependence does not appear to be a problem in adolescents or adults who were treated with methylphenidate for ADHD as children.

Use with alcohol

Alcohol may exacerbate the CNS adverse reactions of psychoactive drugs, including methylphenidate. Therefore, it is advisable for patients to abstain from alcohol during treatment.

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

Data on safety and efficacy of long-term use of methylphenidate are not complete. Therefore, patients requiring long-term therapy should be carefully monitored and periodic complete blood counts, differential and platelet counts are advisable during prolonged therapy. In the event of haematological disorders appropriate medical intervention should be considered (see ADVERSE EFFECTS)

Carcinogenicity

In a lifetime carcinogenicity study carried out in $B6C3F_1$ mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 4 times the maximum recommended human dose of methylphenidate on a mg/m^2 basis. Hepatoblastoma is a relatively rare rodent malignant tumour type. The mouse strain used is sensitive to the development of hepatic tumours, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumours in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 50 mg/kg/day, which is approximately 7 times the maximum recommended human dose of methylphenidate on a mg/m^2 basis.

In a 24-week carcinogenicity study in the transgenic mouse strain $p53^{+/-}$, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; approximately 60 and 74 mg/kg/day of methylphenidate, respectively, which is approximately 4 and 5 times the maximum recommended human dose of methylphenidate on a mg/m^2 basis, respectively.

Comment: The US Food and Drug Administration examined data from the Surveillance, Epidemiology and End Results (SEER) database for the years 1973 to 1991 and found that the estimated incidence of hepatoblastoma in the general population was not greater than 1 in 10 million person-years.

A total of 174 cases of hepatoblastoma were reported by the SEER for the period 1973 to 1995. The age-adjusted incidence rate is very low (IR=0.0382 per 100,000 person-years). The majority of cases (149 out of 174) were diagnosed among the age group 0 to 4 years old, which is in accordance with the natural history of the disease. For the age group 5 to 24 years old the rates of hepatoblastoma are very low with 14 cases reported. For the 0 to 4 years old age group, incidence rates of hepatoblastoma have risen slowly, ranging from 0.3032 per 100,000 in 1973 to 0.4889 per 100,000 in 1995. On the basis of experience since marketing Artige, there is no evidence that the incidence is higher in patients receiving Artige.

Genotoxicity

Methylphenidate was not mutagenic in assays *in vitro* (Ames reverse mutation assay and the mouse lymphoma cell forward mutation assay). Methylphenidate showed evidence of a weak

clastogenic response *in vitro* (Chinese Hamster Ovary cells) but was negative *in vivo* (mouse bone marrow micronucleus assay).

Effects on fertility

No human data on the effect of methylphenidate on fertility are available.

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 at doses up to 160 mg/kg/day, approximately 11-fold the highest recommended human dose of methylphenidate on a mg/m^2 basis.

Women of child-bearing potential

Methylphenidate should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks (see Use in Pregnancy).

Use in Pregnancy (Category B3)

There are no adequate and well-controlled studies in pregnant women. Methylphenidate should not be prescribed to pregnant women unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

As a general rule no drugs should be taken during the first 3 months of pregnancy, and the benefits and risks of taking drugs should be carefully considered throughout the whole of the pregnancy.

Reproductive animal toxicity

Adequate animal reproduction studies to establish safe use of methylphenidate during pregnancy have not been conducted. Oral administration of methylphenidate to rabbits during the period of organogenesis has produced teratogenic effects at systemic exposures (plasma AUC) approximately 3 times clinical exposure at the maximum recommended human dose. The exposure at the no-effect dose was less than human exposure. In rats, teratogenic effects were not seen at systemic exposures (plasma AUC) approximately 12 times clinical exposure at the maximum recommended human dose (MRHD).

Use in Lactation

Case reports showed that methylphenidate was distributed into breast milk. For safety reasons, mothers taking methylphenidate should refrain from breast-feeding their infants. A decision should be made by the prescriber whether the mother must abstain from breast-feeding or abstain from methylphenidate therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the mother.

Effects on laboratory tests:

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

Effects on ability to drive and use machines:

Artige may cause dizziness, drowsiness, blurred vision, hallucinations or other CNS side effects (see ADVERSE EFFECTS). Patients experiencing such side effects should refrain from driving, operating machinery, or engaging in other potentially hazardous activities.

INTERACTIONS WITH OTHER MEDICINES

Anti-hypertensive drug

Artige 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 PRECAUTIONS - Cerebrovascular Conditions).

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

Use with anaesthetics

There is a risk of sudden blood pressure and heart rate increase during surgery. If surgery is planned, Artige 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, Artige 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). The coadministration of Artige 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 PRECAUTIONS). Methylphenidate has been shown to increase extracellular serotonin and norepinephrine and appears to have weak potency in binding serotonin transporter.

Pharmacokinetic interactions

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

Artige coadministration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

Case reports have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbitone, primidone, phenytoin), phenylbutazone and tricyclic antidepressants (imipramine, desipramine), but pharmacokinetic interactions were not confirmed when explored at higher sample sizes. Reduction in the dosage of these drugs may be required when they are given concomitantly with methylphenidate.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

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

ADVERSE EFFECTS

Post-marketing Experience

Nervousness and insomnia are very common adverse reactions which occur at the beginning of Artige treatment and are usually controlled by reducing the dosage and omitting the drug in the afternoon or evening.

Loss of appetite is very common but usually transient. Abdominal pain, insomnia and tachycardia are common, usually at the beginning of treatment and may be alleviated by concomitant food intake.

Tabulated summary of adverse drug reactions

Adverse drug reactions listed in Table 2 are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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 use

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, irritability
Common	Anxiety, restlessness, sleep disorder, agitation
Very rare	Hyperactivity, psychosis (sometimes with visual and tactile hallucinations), transient depressed mood.
Nervous system disorders	
Common	Headache, drowsiness, dizziness, dyskinesia, tremor
Very rare	Convulsions, choreoathetoid movements, tics or exacerbation of existing tics and Tourette's syndrome, cerebrovascular disorders including vasculitis, cerebral haemorrhages and cerebrovascular accidents, reports of poorly documented neuroleptic malignant syndrome

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, hyperhydrosis
Very rare	Thrombocytopenic purpura, exfoliative dermatitis, erythema multiforme.
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
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

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 events reported since market introduction in patients taking methylphenidate include suicide, suicide attempt and suicidal ideation. No causal relationship between methylphenidate and these events has been established.

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.

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

Reproductive system and breast disorders
Priapism

Additional adverse reactions reported with other methylphenidate-containing products

The list below shows adverse reactions not listed in table 2 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, aggression, affect lability, abnormal thinking or behaviour, anger, suicidal ideation or attempt (including completed suicide), 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
Vascular disorders:	Peripheral coldness, Raynaud's phenomenon
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
Reproductive system and breast disorders:	Gynaecomastia
General disorders and administration site conditions:	Chest pain, fatigue, sudden cardiac death
Investigations:	cardiac murmur

DOSAGE AND ADMINISTRATION

Treatment should only be initiated by specialist physicians with experience in the use of the drug. Before initiating Artige treatment, patients should be assessed for pre-existing cardiovascular and psychiatric disorders and a family history of sudden death, ventricular arrhythmia and psychiatric disorders (see CONTRAINDICATIONS and PRECAUTIONS).

Dosage

The dosage of Artige should be individualised according to the patient's clinical needs and responses.

Treatment with Artige should be initiated at a low dose, with increments at weekly intervals.

ADHD

Daily dosage should not exceed 60 mg. In the treatment of ADHD, an attempt should be made to time administration of the drug to coincide with periods of greatest academic, behavioural or social difficulties for the patient.

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

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.

If therapy is interrupted for reasons other than those stated above, it should not be restarted at the dose that had been reached prior to treatment interruption, but should be re-titrated.

Children and adolescents (6 years and over):

Start with 5 mg once or twice daily (e.g. at breakfast and at lunch) with gradual increments of 5 or 10 mg weekly. The total daily dosage should be administered in divided doses.

In some children with ADHD, sleeplessness may occur as the effect of the drug wears off. On rare occasions, an additional dose at about 8.00 p.m. may help; a trial dose may help to clarify the issue in an individual case, if the symptom warrants treatment.

Narcolepsy

Adults:

Administer the tablets in divided doses 2 or 3 times daily. The average dose is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if Artige tablets are taken late in the day should take the last dose before 6 p.m.

Dosing for each patient requires titration to control symptoms. Single doses greater than 20 mg are associated with sympathomimetic side effects. Therefore, the average single dose should be less than 20 mg. A maximum total dose of 60 mg/day may be required.

Maximum daily doses

A maximum daily dose of 60 mg should not be exceeded for the treatment of narcolepsy.

Administration

The rate of absorption and, therefore, onset of action is faster when Artige tablets are taken with food. Dosage should, therefore, be standardised in relation to food to ensure consistency of effect.

Doses should be administered 1-2 hours before the maximum effect is required.

OVERDOSAGE

Symptoms:

Signs and symptoms of acute overdosage, mainly due to over-stimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: 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 and dryness of mucous membranes.

Treatment:

Treatment consists of appropriate 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 the Poisons Information Centre on 13 11 26 or current toxicological publication.

The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If the signs and symptoms are not too severe and the patient is conscious, further absorption may be limited by administration of activated charcoal. In cases of marked agitation, intravenous doses of diazepam or haloperidol should be given. Hypertension may be controlled by alpha-adrenergic blocking agents or intravenous sodium nitroprusside.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

The efficacy of peritoneal dialysis or extracorporeal haemodialysis for methylphenidate overdosage has not been established. Clinical experience with overdose is limited. Patients who have received doses higher than those recommended should be carefully monitored.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Blister pack containing 100 tablets. White, scored, marked AB, CG on reverse.

Storage

Store below 25ºC. Protect from moisture.

POISONS SCHEDULE

Controlled Drug (S8)

NAME AND ADDRESS OF SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
NORTH RYDE NSW 2113

® = Registered Trademark

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

2 June 2005

APPROVED BY THERAPEUTIC GOODS ADMINISTRATION

17 March 2008

DATE OF MOST RECENT AMENDMENT

6 April 2017

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