# ART025136P
## METHYLPHENIDATE MY ALL STRENGTH PIL

lotus PHARMACEUTICAL

### GENERAL INFORMATION

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### REGULATORY APPROVAL

Package Insert

# Neurofind Prolonged Release Tablets 18mg, 27mg, 36mg

METHYLPHENIDATE HYDROCHLORIDE

## 1. NAME OF THE MEDICINAL PRODUCT

Neurofind Prolonged Release Tablets 18mg
Neurofind Prolonged Release Tablets 27mg
Neurofind Prolonged Release Tablets 36mg

FOR SPECIALIST'S USE ONLY

## 2. QUALITATIVE AND QUANTITVATIVE COMPOSITION

Each tablet contains 18 mg of methylphenidate hydrochloride
Each tablet contains 27 mg of methylphenidate hydrochloride
Each tablet contains 36 mg of methylphenidate hydrochloride
For excipients, see *List of Excipients*

## 3. PHARMACEUTICAL FORM

Prolonged-release tablets
Neurofind Prolonged Release Tablets 18mg
Round, biconvex, yellow and homogeneous aspect film-coated tablets of approximately 8.5 mm of diameter with a hole in one side of the tablet
Neurofind Prolonged Release Tablets 27mg
Round, biconvex, grey and homogeneous aspect film-coated tablets of approximately 8.5 mm of diameter with a hole in one side of the tablet
Neurofind Prolonged Release Tablets 36mg
Round, biconvex, white and homogeneous aspect film-coated tablets of approximately 10 mm of diameter with a hole in one side of the tablet

## 4. CLINICAL PARTICULARS

### 4.1 Indications

Neurofind is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).
The efficacy of Neurofind in the treatment of ADHD was established in controlled trials of children and adolescents aged 6 to 17 and adults aged 18 to 65 who met DSM-IV criteria for ADHD.
Neurofind should be used as a part of a comprehensive treatment program where remedial measures alone prove insufficient. A comprehensive treatment program for the treatment of ADHD may include other measures (psychological, educational, social) for patients with this disorder. Diagnosis must be made according to the current DSM criteria or ICD guidelines.
Neurofind treatment is not indicated in all patients with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity of the patient's symptoms. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis.
Appropriate educational placement is essential, and psychosocial intervention is often helpful.
Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and special psychological, educational, and social resources. Learning may or may not be impaired.

### 4.2 Posology and Administration

**Posology**

**Patients new to methylphenidate**

The recommended starting dosage of Neurofind for patients who are not currently taking methylphenidate or stimulants other than methylphenidate is 18 mg once daily for children and adolescents and 18 or 36 mg once daily for adults.

**Patients currently using methylphenidate**

The recommended dosage of Neurofind for patients who are currently taking methylphenidate twice daily or three times daily, at dosages of 10 to 60 mg/day, is provided in the following table:

**Recommended Dosage Conversion from Methylphenidate Regimens to Neurofind**

| Previous Methylphenidate Daily Dose | Recommended Neurofind Starting Dosage |
|---|---|
| 5 mg Methylphenidate twice daily or three times daily | 18 mg every morning |
| 10 mg Methylphenidate twice daily or three times daily | 36 mg every morning |
| 15 mg Methylphenidate twice daily or three times daily | 54 mg every morning |
| 20 mg Methylphenidate twice daily or three times daily | 72 mg every morning |

Clinical judgment should be used when selecting the dose for patients currently taking methylphenidate in other regimens.

**Dose titration**

The dosage should be individualized according to the needs and responses of the patient. Doses may be increased in 18 mg increments at weekly intervals. The maximum daily dosage of Neurofind is 54 mg in children and 72 mg in adolescents and adults.

**Maintenance/extended treatment**

The long-term use of methylphenidate has not been systematically evaluated in controlled trials. The physician who elects to use Neurofind for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy.

**Dose reduction and discontinuation**

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

**Special populations**

***Pediatrics (under 6 years of age)***

Use of Neurofind in patients under six years of age has not been studied in controlled trials. Neurofind should not be used in patients under six years old.

***Elderly (over 65 years of age)***

Use of Neurofind in elderly patients over 65 years of age has not been studied in controlled trials.

***Renal insufficiency***

There is no experience with the use of Neurofind in patients with renal insufficiency (see *Pharmacokinetic properties - Special populations, Renal insufficiency*).

***Hepatic insufficiency***

There is no experience with the use of Neurofind in patients with hepatic insufficiency.

**Administration**

Neurofind is administered orally once daily. As the effect has been shown to be present 12 hours after dosing, the product should be taken once daily in the morning.
Neurofind must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed (see *Warnings and Precautions - Dose administration*).
Neurofind may be administered with or without food (see *Pharmacokinetic properties - Food effects*).

### 4.3 Contraindications

Neurofind is contraindicated:

- in patients known to be hypersensitive to methylphenidate or other components of the product
- during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO inhibitor (hypertensive crises may result)

### 4.4 Warnings and Precautions

Structural cardiac abnormalities
Although a causal relationship has not been established, sudden death has been reported in patients with structural cardiac abnormalities treated with ADHD drugs with stimulant effects. These treatments should be used with caution in patients with structural cardiac abnormalities.

Patients under six years old
Neurofind should not be used in patients under six years old. Sufficient data on the safety of long-term use of methylphenidate is not yet available.

Motor and verbal tics, and worsening of Tourette's syndrome
Central nervous system (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. It is recommended that the family history be assessed, and that the patient is clinically evaluated for tics or Tourette's syndrome before initiating methylphenidate. Regular monitoring for the emergence or worsening of tics or Tourette's syndrome during treatment with methylphenidate is recommended at every dose adjustment and every visit, and treatment discontinued if clinically appropriate.

Long-term use
Although a causal relationship has not been established, suppression of growth (i.e. weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Increased intraocular pressure and glaucoma
There have been reports of an elevation of intraocular pressure (IOP) associated with methylphenidate treatment.
Prescribe Neurofind to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor Neurofind-treated patients with a history of abnormally increased IOP or open angle glaucoma.

Acute angle closure glaucoma
There have been rare reports of angle closure glaucoma associated with methylphenidate treatment. Although the mechanism is not clear, Neurofind-treated patients considered at risk for acute angle closure glaucoma (e.g. patients with significant hyperopia) should be evaluated by an ophthalmologist.

Dose administration
Neurofind must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a non-absorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet. Because the Neurofind tablet is non-deformable and does not appreciably change in shape in the GI tract, Neurofind should ordinarily not be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Due to the controlled-release design of the tablet, Neurofind should only be used in patients who are able to swallow the tablet whole.

Use in other indications
Neurofind should not be used to treat severe depression and/or for the prevention or treatment of normal fatigue states.

Psychotic or manic symptoms
Psychotic (e.g. hallucinations) or manic symptoms have been reported in patients without a prior history of psychotic illness or mania during treatment with Neurofind at usual doses. If such symptoms occur, consideration should be given to a possible causal role of Neurofind and discontinuation of treatment may be appropriate (see *Undesirable effects*).

Aggression, anxiety and agitation
Aggressive behavior, marked anxiety, or agitation are often observed in patients with ADHD, and have been reported in patients treated with Neurofind. Anxiety led to discontinuation of Neurofind in some patients. It is recommended to monitor patients beginning treatment with Neurofind for the appearance of, or worsening of, aggressive behavior, marked anxiety, or agitation.

Priapism
Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric 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 during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Cerebrovascular disorders
Cerebrovascular disorders (including cerebral vasculitis and cerebral hemorrhage) have been reported with the use of Neurofind (see *Undesirable effects*). Consider cerebrovascular disorders as a possible diagnosis in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during Neurofind therapy. These symptoms could include severe headache, unilateral weakness or paralysis, and impairment of coordination, vision, speech, language, or memory. If a cerebrovascular disorder is suspected during treatment, discontinue Neurofind immediately. Early diagnosis may guide subsequent treatment.
In patients with pre-existing cerebrovascular disorders (e.g. aneurysm, vascular malformations/anomalies), treatment with Neurofind is not recommended.

Conditions requiring caution
Neurofind should be given with caution in the following conditions:
*Psychotic patients*
Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

*Underlying medical conditions that might be compromised by increases in blood pressure or heart rate*
In the laboratory classroom clinical trials in children, both Neurofind and methylphenidate three times daily increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1 to 4 mm Hg during the day, relative to placebo. In placebo-controlled studies in adults, mean increases in resting pulse rate of approximately 4 to 6 bpm were observed with Neurofind at endpoint vs. a mean change of roughly -2 to 3 bpm with placebo. Mean changes in blood pressure at endpoint ranged from about -1 to 1 mm Hg (systolic) and 0 to 1 mm Hg (diastolic) for Neurofind and from -1 to 1 mm Hg (systolic) and -2 to 0 mm Hg (diastolic) for placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. Blood pressure (especially for patients with hypertension) and heart rate should be monitored at appropriate intervals in patients taking Neurofind.

*History of drug dependence or alcoholism*
Neurofind 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 behavior. 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.

Hematologic monitoring
Periodic hematologic monitoring (complete blood count, differential, and platelet counts) is advised during prolonged therapy.

### 4.5 Interactions

Neurofind should not be used in patients being treated (currently or within the preceding 2 weeks) with MAO inhibitors.
Because of possible increases in blood pressure, Neurofind should be used cautiously with vasopressor agents.
Neurofind may decrease the effectiveness of drugs used to treat hypertension. It is recommended to monitor blood pressure and adjust the dosage of the antihypertensive drug as needed.
Concomitant use of halogenated anesthetics and Neurofind may increase the risk of sudden blood pressure and heart rate increase during surgery. It is recommended to avoid use of Neurofind in patients being treated with anesthetics on the day of surgery.
There have been reports of serotonin syndrome following coadministration of methylphenidate with serotonergic drugs. If concomitant use of Neurofind with a serotonergic drug is warranted, prompt recognition of the symptoms of serotonin syndrome is important. Neurofind must be discontinued as soon as possible if serotonin syndrome is suspected.
Because a predominant action of methylphenidate is to increase extracellular dopamine levels, Neurofind may be associated with pharmacodynamic interactions when co-administered with some antipsychotics. Caution is warranted in patients receiving both Neurofind and an antipsychotic, as extrapyramidal symptoms could emerge when these drugs are administered concomitantly or when adjusting the dosage of one or both drugs.
Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

### 4.6 Pregnancy, Lactation and Fertility

Pregnancy
The safety of methylphenidate for use during human pregnancy has not been established. No studies are available on the use of Neurofind in pregnant women. Neurofind should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Methylphenidate hydrochloride has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m$^2$ basis, respectively.
Teratogenic effects were not seen in rats at methylphenidate hydrochloride doses up to 30 mg/kg/day, resulting in a systemic exposure to methylphenidate of approximately seven times that seen in trials in adult and adolescent volunteers and patients receiving daily dose of 72 mg of Neurofind, based on pharmacokinetic data.
Lactation
Methylphenidate has been detected in human milk. Based on breast milk sampling from five mothers, methylphenidate concentrations in human milk resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage, and a milk to maternal plasma ratio ranging between 1.1 and 2.7. Caution should be exercised if Neurofind is administered to a breast-feeding woman.
Fertility
Methylphenidate did not impair fertility in mice that received up to 160 mg/kg/day methylphenidate hydrochloride in an 18-week Continuous Breeding study.

### 4.7 Effects on ability to drive and use machines

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that Neurofind does not adversely affect their ability to engage in such activities.

### 4.8 Undesirable effects

Adverse drug reactions observed during clinical trials and post-marketing experience are presented in the table below. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

| System Organ Class | Frequency | Preferred Term |
|---|---|---|
| Infections and infestations | Common | : Nasopharyngitis, upper respiratory tract infection[1], sinusitis[1] |
| Blood and lymphatic system disorders | Very rare | : Anaemia[2], leucopenia[2], thrombocytopenia, thrombocytopenic purpura |
| | Not known | : Pancytopenia |
| Immune system disorders | Uncommon | : Hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritus, rashes, eruptions |
| Metabolism and nutrition disorders* | Common | : Anorexia, decreased appetite[2], moderately reduced weight and height gain during prolonged use in children* |
| Psychiatric disorders* | Very common | : Insomnia, nervousness |
| | Common | : Affected lability, aggression*, agitation*, anxiety[2], depression*[1], irritability, abnormal behaviour, mood swings, tics*, initial insomnia[1], depressed mood[1], libido decreased[1], tension[1], bruxism[3], panic attack[1] |
| | Uncommon | : Psychotic disorders*, auditory, visual and tactile hallucination*, anger, suicidal ideation*, mood altered, restlessness[2], tearfulness, worsening of pre-existing tics of Tourette's syndrome*, logorrhoea, hypervigilance, sleep disorder |
| | Rare | : Mania*[2], disorientation, libido disorder, confusional state[2], obsessive-compulsive disorders and symptoms (including trichotillomania, compulsive thoughts, compulsions) |
| | Very rare | : Suicidal attempt (including completed suicide)*[2], transient depressed mood*, abnormal thinking, apathy[2] |
| | Not known | : Delusions*[2], thought disturbances*, dependence (cases of abuse and dependence have been described, more often with immediate release formulations) |

| | | |
|---|---|---|
| Nervous system disorders | Very common | : Headache |
| | Common | : Dizziness, dyskinesia, psychomotor hyperactivity, somnolence, paresthaesia[1], tension headache[1] |
| | Uncommon | : Sedation, tremor[2], lethargy[1] |
| | Very rare | : Convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit, neuroleptic malignant syndrome (reports were poorly documented and, in most cases, patients were also receiving other drugs, so the role of methylphenidate is unclear) |
| | Not known | : Cerebrovascular disorders*[2] (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsion*, migraine[2], dysphemia |
| Eye disorders | Common | : Accommodation disorder[1] |
| | Uncommon | : Blurred vision[2], dry eye[1] |
| | Rare | : Difficulties in visual accommodation, visual impairment, diplopia |
| | Not known | : Mydriasis |
| Ear and labyrinth disorders | Common | : Vertigo[1] |
| Cardiac disorders* | Common | : Palpitations, arrhythmia, tachycardia |
| | Uncommon | : Chest pain |
| | Rare | : Angina pectoris |
| | Very rare | : Cardiac arrest, myocardial infarction |
| | Not known | : Supraventricular tachycardia, bradycardia, ventricular extrasystoles[2], extrasystoles[2] |
| Vascular disorders* | Common | : Hypertension |
| | Uncommon | : Hot flush[1] |
| | Very rare | : Cerebral arteritis and/or occlusion, peripheral coldness[2], Raynaud's phenomenon |
| Respiratory, thoracic and mediastinal disorders | Common | : Cough, pharyngolaryngeeal pain |
| | Uncommon | : Dyspnoea[2] |
| | Not known | : Epistaxis |
| Gastrointestinal disorders | Common | : Abdominal pain upper, diarrhoea, nausea[2], abdominal discomfort, vomiting, dry mouth[2], dyspepsia[1] |
| | Uncommon | : Constipation[2] |
| Hepatobiliary disorders | Common | : Alanine aminotransferase increased[1] |
| | Uncommon | : Hepatic enzyme increased |
| | Very rare | : Abnormal liver function, including acute hepatic failure and hepatic coma, blood alkaline phosphatase increased, blood bilirubin increased[2] |
| Skin and subcutaneous tissue disorders | Common | : Alopecia, pruritis, rash, urticaria, hyperhidrosis[2] |
| | Uncommon | : Angioneurotic oedema, bullous conditions, exfoliative conditions |
| | Rare | : Macular rash, erythema |
| | Very rare | : Erythema multiforme, exfoliative dermatitis, fixed drug eruption |
| Musculoskeletal and connective tissue disorders | Common | : Arthralgia, muscle tightness [1], muscle spasms[1] |
| | Uncommon | : Myalgia[2], muscle twitching |
| | Very rare | : Muscle cramps |
| | Not known | : Trismus[3] |
| Renal and urinary disorders | Uncommon | : Haematuria, pollakiuria |
| | Not known | : Incontinence |
| Reproductive system and breast disorders | Common | : Erectile dysfunction[1] |
| | Rare | : Gynaecomastia |
| | Not known | : Priapism*, erection increased* and prolonged erection* |
| General disorders and administration site conditions | Common | : Pyrexia, growth retardation during prolonged use in children*, fatigue[2], irritability[1], feeling jittery[1], asthenia[1], thirst[1] |
| | Uncommon | : Chest pain |
| | Very rare | : Sudden cardiac death* |
| | Not known | : Chest discomfort[2], hyperpyrexia |
| Investigations | Common | : Changes in blood pressure and heart rate (usually an increase)*, weight decreased* |
| | Uncommon | : Cardiac murmur* |
| | Very rare | : Platelet count decreased, white blood cell count abnormal |

* see Section 4.4
[1] Frequency derived from adult clinical trials and not on data from trials in children and adolescents; may also be relevant for children and adolescents
[2] Adverse drug reaction from clinical trials in adult patients that were reported with a higher frequency than in children and adolescents
[3] Based on the frequency calculated in adult ADHD studies (no cases were reported in the paediatric studies)

**4.9 Overdose**

Symptoms and signs

Signs and symptoms of Neurofind overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, muscle twitching, convulsion, grand mal convulsion, confusional state, hallucination (auditory and/or visual), hyperhidrosis, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus arrhythmia, hypertension, mydriasis, and dry mouth.

Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present.

The efficacy of activated charcoal has not been established. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for pyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Neurofind overdosage has not been established.

The prolonged release of methylphenidate from Neurofind should be considered when treating patients with overdose.

## 5. PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamics properties**

Pharmacotherapeutic group: Centrally acting sympathomimetics, ATC code: N06BA04

Mechanism of action

Methylphenidate hydrochloride is a CNS stimulant. The mode of therapeutic action in ADHD is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

**5.2 Pharmacokinetic properties**

Absorption

Methylphenidate is readily absorbed. Following oral administration of methylphenidate hydrochloride to adults, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 to 2 hours, then increase gradually over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours after which a gradual decrease in plasma levels of methylphenidate begins. Methylphenidate hydrochloride once daily minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily. The relative bioavailability of methylphenidate hydrochloride once daily and methylphenidate three times daily in adults is comparable.

The mean pharmacokinetic parameters in 36 adults following the administration of methylphenidate hydrochloride 18 mg once daily and methylphenidate hydrochloride 5 mg three times daily are summarized in table below.

| Mean ± SD Pharmacokinetic Parameters | | |
|---|---|---|
| **Parameters** | **Methylphenidate hydrochloride 18 mg once daily (n = 36)** | **Methylphenidate hydrochloride 5 mg three times daily (n = 35)** |
| $C_{max}$ (ng/mL) | 3.7 ± 1.0 | 4.2 ± 1.0 |
| $T_{max}$ (h) | 6.8 ± 1.8 | 6.5 ± 1.8 |
| $AUC_{inf}$ (ng.h/mL) | 41.8 ± 13.9 | 38.0 ± 11.0 |
| $t_{1/2}$ (h) | 3.5 ± 0.4 | 3.0 ± 0.5 |

No differences in the pharmacokinetics of methylphenidate hydrochloride were noted following single and repeated once daily dosing indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once daily dosing are similar to those following the first dose of methylphenidate hydrochloride.

Dose proportionality

Following administration of methylphenidate hydrochloride in single doses of 18, 36, and 54 mg/day to healthy adults, $C_{max}$ and $AUC_{inf}$ of d-methylphenidate were proportional to dose, whereas l-methylphenidate $C_{max}$ and $AUC_{inf}$ increased disproportionately with respect to dose. Following administration of methylphenidate hydrochloride, plasma concentrations of the l-isomer were approximately 1/40$^{th}$ the plasma concentrations of the d-isomer.

In healthy adults, single and multiple dosing of once daily methylphenidate hydrochloride doses from 54 to 144 mg/day resulted in linear and dose proportional increases in $C_{max}$ and $AUC_{inf}$ for total methylphenidate (MPH) and its major metabolite, (alpha)-phenyl-piperidine acetic acid (PPAA). The single dose and steady state (Day 4) clearance and half-life parameters were similar, indicating that there was no time dependency in the pharmacokinetics of methylphenidate. The ratio of metabolite (PPAA) to parent drug (MPH) was constant across doses from 54 to 144 mg/day, both after single dose and upon multiple dosing.

In a multiple-dose study in adolescent ADHD patients aged 13 to 16 years administered 18 to 72 mg/day of methylphenidate hydrochloride, mean $C_{max}$ and AUC during a dosing interval of the d-isomer and total methylphenidate increased proportionally with respect to dose.

Distribution

Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The half-life of methylphenidate in adults following oral administration of methylphenidate hydrochloride was approximately 3.5 hours.

Metabolism

In humans, methylphenidate is metabolized primarily by de-esterification to PPAA, which has little or no pharmacologic activity. In adults, the metabolism of methylphenidate hydrochloride once daily as evaluated by metabolism to PPAA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once daily doses of methylphenidate hydrochloride is similar.

Elimination

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.

Food effects

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of methylphenidate hydrochloride when administered after a high fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Alcohol effect

An *in vitro* study was conducted to explore the effect of alcohol on the release characteristics of methylphenidate from the methylphenidate hydrochloride 18 mg tablet dosage form. At an alcohol concentration up to 40% there was no increased release of methylphenidate in the first hour. The results with the 18 mg tablet strength are considered representative of the other available tablet strengths.

**Special populations**

Gender

In healthy adults, the mean dose-adjusted $AUC_{inf}$ values for methylphenidate hydrochloride were 36.7 ng·h/mL in men and 37.1 ng·h/mL in women, with no differences noted between the two groups.

Race

In adults receiving methylphenidate hydrochloride, dose-adjusted $AUC_{inf}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age

The pharmacokinetics of methylphenidate hydrochloride has not been studied in children less than 6 years of age.

Renal insufficiency

There is no experience with the use of methylphenidate hydrochloride in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of methylphenidate hydrochloride.

Hepatic insufficiency

There is no experience with the use of methylphenidate hydrochloride in patients with hepatic insufficiency.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Tablet content

Hypromellose, Polyethylene oxide, Succinic acid, Magnesium stearate, Sodium chloride, silica colloidal anhydrous, Black iron oxide, Cellulose acetate, Polyethylene glycol, Acetone, Phosphoric acid

Film-coating 18 mg

Lactose monohydrate, Hypromellose, Titanium dioxide, Triacetin, Yellow iron oxide, Red iron oxide

Film-coating 27 mg

Lactose monohydrate, Hypromellose, Titanium dioxide, Triacetin, Black iron oxide, Red iron oxide

Film-coating 36 mg

Lactose monohydrate, Hypromellose, Titanium dioxide, Triacetin

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

Please refer to outer carton

**6.4 Storage condition**

Store below 30ºC
Keep the bottle tightly closed to protect from moisture.

**6.5 Nature and contents of container**

HDPE bottle with a child-resistant HDPE cap and two desiccants (silica gel and activated carbon). Each bottle contains 30 tablets and is packed in an outer carton along with an insert

**6.6 Special precautions for disposal**

No special requirements

## 7. MANUFACTURER

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## 8. PRODUCT REGISTRATION HOLDER

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## 9. DATE OF REVISION OF THE TEXT

15/07/2026