1. NAME OF THE MEDICINAL PRODUCT

Neurofind 18 mg prolonged release tablets
Neurofind 27 mg prolonged release tablets
Neurofind 36 mg prolonged release tablets
Neurofind 54 mg prolonged release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.2 Qualitative and quantitative composition

One prolonged-release tablet contains 18 mg of methylphenidate hydrochloride.
Excipients with known effect:
Each tablet contains 4 mg of lactose.
Each tablet contains 24 mg of sodium chloride.
For the full list of excipients, see section 6.1.

One prolonged-release tablet contains 27 mg of methylphenidate hydrochloride.
Excipients with known effect:
Each tablet contains 3.4 mg of lactose.
Each tablet contains 24 mg of sodium chloride.
For the full list of excipients, see section 6.1.

One prolonged-release tablet contains 36 mg of methylphenidate hydrochloride.
Excipients with known effect:
Each tablet contains 6.6 mg of lactose.
Each tablet contains 48 mg of sodium chloride.
For the full list of excipients, see section 6.1.

One prolonged-release tablet contains 54 mg of methylphenidate hydrochloride.
Excipients with known effect:
Each tablet contains 6.8 mg of lactose.
Each tablet contains 48 mg of sodium chloride.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

18 mg
Round, biconvex, yellow film-coated tablets of approximately 8.5 mm of diameter with a hole in one side of the tablet.

27 mg
Round, biconvex, grey film-coated tablets of approximately 8.5 mm of diameter with a hole in one side of the tablet.

36 mg
Round, biconvex, white film-coated tablets of approximately 10 mm of diameter with a hole in one side of the tablet.

54 mg

Round, biconvex, pink film-coated tablets of approximately 10 mm of diameter with a hole in one side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention-Deficit/Hyperactivity Disorder (ADHD)
Neurofind is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of methylphenidate 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.
A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, eg, in social, academic, or occupational functioning, and be present in two or more settings, eg, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive type, at least six of the following symptoms must have persisted for at least 6 months, lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months; fidgeting/squirming; leaving seat; inappropriate running/climbing; difficult with quiet activities; “on the go;” excessive talking; blurting answers; can’t wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations

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. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the purpose of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

Methylphenidate is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child 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. 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.

Long-Term Use

The effectiveness of methylphenidate for long-term use, ie, for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use methylphenidate for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Dosage and Administration).

4.2 Posology and method of administration

Dosage

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 to 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 Table 1.

TABLE 1
Recommended Dose Conversion from Other Methylphenidate Regimens, where available, to Neurofind

Previous Methylphenidate Hydrochloride Daily Dose	Recommended Neurofind Starting Dose
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 starting 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. Daily dosages above 54 mg in children, 72 mg in adolescents have not been studied and are not recommended. Daily dosages above 72 mg in adults are not recommended.

A 27mg dosage strength is available for physicians who wish to prescribe between 18 and 36mg dosage.

Maintenance/extended treatment

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with methylphenidate. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods.

Nevertheless, the physician who elects to use methylphenidate 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. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

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.

If improvement is not observed after appropriate dosage adjustment over a one- month period, the drug should be discontinued.

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 Precautions – Information for Patients).

Neurofind may be administered with or without food (see Pharmacokinetic Properties – Food effects).

Special populations

Pediatrics (under 6 years of age)

Use of prolonged-release methylphenidate in patients under six years of age has not been studied in controlled trials. Methylphenidate should not be used in patients under six years old.

Long-term effects of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (ie 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.

Elderly (over 65 years of age)

Prolonged-release methylphenidate should not be used in the elderly. Safety and efficacy have not been established in this age group.

Renal insufficiency

There is no experience with the use of prolonged-release methylphenidate in patients with renal insufficiency (see Pharmacokinetic Properties – Special populations, Renal insufficiency).

Hepatic insufficiency

There is no experience with the use of prolonged-release methylphenidate in patients with hepatic insufficiency.

4.3 Contraindications

Prolonged-release methylphenidate is contraindicated:
• in patients known to be hypersensitive to methylphenidate or other components of the product;
• in patients with glaucoma;
• during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase (MAO) inhibitor (hypertensive crisis may result) (see Interactions);
• in patients with hyperthyroidism;
• in patients with severe angina pectoris;
• in patients with cardiac arrhythmia;
• in patients with phaeochromocytoma.

4.4 Special warnings and precautions for use

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.

Depression

Methylphenidate should not be used to treat severe depression.

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

Long-Term Suppression of Growth
Sufficient data on the safety of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (ie, 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.

Psychosis
Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.
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.
Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking or mania in patients without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant and discontinuation of treatment may be appropriate.

Suicidal Behaviour and Ideation
There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known. ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behaviour.

Therefore, it is recommended for patients treated with ADHD drugs that caregivers and physicians monitor for signs of suicide-related behaviour, including at dose initiation/optimisation and drug discontinuation. Patients should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional. Patients with emergent suicidal ideation and behaviour should be evaluated immediately. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen.

Seizures
There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and very rarely in absence of history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Potential for Gastrointestinal Obstruction
Prolonged-release methylphenidate should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel’s diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in non-deformable controlled-release formulations. Due to the controlled-release design of the tablet, prolonged-release methylphenidate should only be used in patients who are able to swallow the tablet whole (see Precautions - Information for Patients).

Hypertension and other Cardiovascular Conditions

Use cautiously in patients with hypertension. Cardiovascular status and blood pressure should be monitored at appropriate intervals in patients taking methylphenidate, especially patients with hypertension. In the laboratory classroom clinical trials in children (Studies 1 and 2), both prolonged-release methylphenidate and methylphenidate tid increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly1 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 prolonged-release methylphenidate 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 prolonged-release methylphenidate 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 increase in blood pressure or heart rate, eg. Those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.

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 (e.g., electrocardiogram and echocardiogram). 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.

Increased intraocular pressure and glaucoma

There have been reports of a transient elevation of intraocular pressure (IOP) associated with methylphenidate treatment. The use of methylphenidate in patients with glaucoma is contraindicated (See Contraindications). Patients at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) must be closely monitored.

Serious Cardiovascular Events

Children and Adolescents

Sudden death has been reported in association with central nervous system (CNS) stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden deaths, 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.

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

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 methylphenidate (see Adverse Reactions). Anxiety led to discontinuation of

methylphenidate in some patients. It is recommended to monitor patients beginning treatment with methylphenidate for the appearance of, or worsening of, aggressive behavior, marked anxiety, or agitation.

Priapism
Prolonged and painful erections requiring immediate medical attention (sometimes including surgical intervention), have been reported with methylphenidate products, including prolonged-release methylphenidate, in both pediatric and adult patients (see Adverse Reactions). Priapism can develop after some time on methylphenidate, often subsequent to an increase in dose. Priapism has also appeared during a period of methylphenidate withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained erections 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 methylphenidate (see Adverse Reactions). Consider cerebrovascular disorders as a possible diagnosis in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate 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 methylphenidate immediately. Early diagnosis may guide subsequent treatment.
In patients with pre-existing cerebrovascular disorders (e.g., aneurysm, vascular malformations/anomalies), treatment with methylphenidate is not recommended.

Drug Dependence
Methylphenidate should be given cautiously to patients with a history of drug or alcohol dependence. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. 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.

Changing from one extended-release methylphenidate product to another
The efficacy and tolerability profile of methylphenidate over the dosing period is determined by the specific release profile of the product. Other extended-release methylphenidate formulations with different release profiles may have different efficacy and tolerability profiles. If changing from one extended-release methylphenidate product to another, it is recommended that this be carried out only with additional medical supervision.

Hematologic Monitoring
Periodic hematologic monitoring (Complete Blood Count, differential, and platelet counts) is advised during prolonged therapy.

Information for patients
Patients should be informed that prolonged-release methylphenidate should 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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
In a lifetime carcinogenicity study carried out in B8C3F1 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 30 times and 4 times the maximum recommended human dose of

methylphenidate on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause increases in tumors in a lifetime carcinogenicity study carried out in F344 rats, the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of methylphenidate on a mg/kg and mg/m basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the life-time carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay.

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 80-fold and 8-fold the highest recommended human dose of methylphenidate on a mg/kg and mg/m basis, respectively.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

It is not known how methylphenidate may affect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, especially those with a narrow therapeutic window.

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

However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

Anti-hypertensive drugs

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Use with drugs that elevate blood pressure

Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in section 4.4).

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

Use with alcohol

Alcohol may exacerbate the adverse CNS effect of psychoactive medicinal products, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with serotonergic medicinal products

There have been reports of serotonin syndrome following coadministration of methylphenidate with serotonergic medicinal products. If concomitant use of methylphenidate with a serotonergic medicinal product is warranted, prompt recognition of the symptoms of serotonin syndrome is important (see section 4.4). Methylphenidate must be discontinued as soon as possible if serotonin syndrome is suspected.

Use with halogenated anaesthetics

There is a risk of sudden blood pressure increase during surgery. If surgery is planned, methylphenidate treatment should not be used on the day of surgery.

Use with centrally acting alpha-2 agonists (e.g., clonidine)

The long-term safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with dopaminergic drugs

Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extracelluar dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when coadministered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Cases of neonatal cardiorespiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports.

Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses.

Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.

Breast-feeding

Methylphenidate is excreted in human milk. Based on reports of 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.

There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There were no relevant effects observed in the non-clinical studies.

4.7 Effects on ability to drive and use machines

Methylphenidate can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision. It may have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

4.8 Undesirable effects

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

Clinical trial data

Double-blind data – adverse reactions reported at ≥ 1% frequency

Adverse reactions in either the pediatric or adult double-blind adverse reactions tables may be relevant for both patient populations.

Pediatric Patients

The safety of prolonged-release methylphenidate was evaluated in 639 pediatric patients (children and adolescents) with ADHD who participated in 4 placebo-controlled, double-blind clinical trials. Three of the studies were conducted in children aged 6-12 years of age: two were cross-over studies in which patients received prolonged-release methylphenidate (doses of either 18 mg, 36 mg or 54 mg per day), immediate release methylphenidate and placebo for each of 7 days. The third study was a parallel group comparison in which patients were randomised to prolonged-release methylphenidate (doses of either 18 mg, 36 mg or 54 mg per day), immediate release methylphenidate or placebo for 28 days. In a fourth study, adolescents aged 13-18 years, receiving prolonged-release methylphenidate doses of 18 mg, 36 mg, 54 mg or 72 mg per day were randomised into a two week placebo-controlled, double-blind phase following an open-label 4 weeks titration phase. The information presented in this section was derived from pooled data.

Adverse reactions reported by ≥1% of prolonged-release methylphenidate-treated children and adolescent patients in these trials are shown in Table 2.

Table 2. Adverse Reactions Reported by ≥1% of Prolonged-Release Methylphenidate-Treated Children and Adolescent Patients in 4 Placebo-Controlled, Double-Blind Clinical Trials		
System/Organ Class Adverse Reaction	**Prolonged-Release Methylphenidate (n=321) %**	**Placebo (n=318) %**
Infections and Infestations		
Nasopharyngitis	2.8	2.2
Psychiatric Disorders		
Insomnia*	2.8	0.3
Nervous System Disorders		
Headache	10.6	11.9
Dizziness	1.9	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.9	0.9
Oropharyngeal Pain	1.2	0.9
Gastrointestinal Disorders		
Abdominal Pain upper	6.2	3.8
Vomiting	2.8	1.6
General Disorders and Administration Site Conditions		
Pyrexia	2.2	0.9

*Terms of Initial insomnia (prolonged-release methylphenidate = 0.6%) and Insomnia (prolonged-release methylphenidate = 2.2%) are combined into Insomnia.

The majority of adverse reactions were mild to moderate in severity.

Adult Patients

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

Adverse reactions reported by ≥1% of prolonged-release methylphenidate-treated adult patients in these trials are shown in Table 3.

Table 3. Adverse Reactions Reported by ≥1% of Prolonged-Release Methylphenidate-Treated Adult Patients in 3 Placebo-Controlled, Double-Blind Clinical Trials		
System/Organ Class Adverse Reaction	**Prolonged-release Methylphenidate (n=596) %**	**Placebo (n=309) %**
Infections and Infestations		
Upper respiratory tract infection	1.7	1.0

Sinusitis	1.3	1.0
Metabolism and Nutrition Disorders		
Decreased appetite	24.8	6.1
Anorexia	4.2	0
Psychiatric Disorders		
Insomnia	13.3	7.8
Anxiety	8.4	2.9
Initial insomnia	5.7	2.6
Depressed mood	4.4	2.6
Restlessness	4.0	0
Agitation	3.2	0.6
Nervousness	2.3	0.6
Bruxism	1.5	0.6
Depression	1.6	0.6
Affect lability	1.3	0.6
Libido decreased*	1.5	0.6
Panic attack	1.3	0.3
Tension	1.3	0.3
Aggression	1.2	0.6
Confusional state	1.0	0.3
Nervous System Disorders		
Headache	24.2	18.8
Dizziness	7.4	5.5
Tremor	3.4	0.6
Paraesthesia	1.2	0
Tension headache	1.0	0.3
Eye Disorders		
Accommodation disorder	1.3	0
Vision blurred	1.3	1.0
Ear and Labyrinth Disorders		
Vertigo	2.0	0.3
Cardiac Disorders		
Tachycardia	6.0	0
Palpitations	4.5	0.6

Vascular Disorders		
Hypertension	2.2	1.6
Hot flush	1.3	0.6
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	1.5	1.3
Cough	1.2	1.0
Dyspnea	1.2	0.6
Gastrointestinal Disorders		
Dry mouth	15.1	3.6
Nausea	14.3	4.9
Dyspepsia	2.0	1.9
Vomiting	1.8	0.6
Constipation	1.5	0.6
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	5.7	1.3
Musculoskeletal and Connective Tissue Disorders		
Muscle tightness	1.3	0
Muscle spasms	1.0	0.3
Reproductive System and Breast Disorder		
Erectile dysfunction	1.0	0.3
General Disorders and Administration Site Conditions		
Irritability	5.2	2.9
Fatigue	4.7	4.2
Thirst	1.8	0.6
Asthenia	1.2	0
Investigations		
Weight decreased	8.7	3.6
Heart rate increased	3.0	1.9
Blood pressure increased	2.5	1.9
Alanine aminotransferase increased	1.0	0

*The adverse reaction Libido decreased includes the preferred term Loss of libido

The majority of adverse reactions were mild to moderate in severity.

Open-label data – Adverse reactions reported at ≥1% frequency

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

Adverse reactions reported by ≥1% of prolonged-release methylphenidate-treated patients in these trials and not listed in Tables 2 and 3 are shown in Table 4.

Table 4. Adverse Reactions Reported by ≥1% of Prolonged-Release Methylphenidate-Treated Patients in 12 Open-Label Clinical Trials	
System/Organ Class Adverse Reaction	Prolonged-release Methylphenidate **(n=3782)** **%**
Psychiatric Disorders	
Tic	2.0
Mood swings	1.1
Nervous System Disorders	
Somnolence	1.0
Gastrointestinal Disorders	
Diarrhoea	2.4
Abdominal discomfort	1.3
Abdominal pain	1.2
Skin and Subcutaneous Tissue Disorders	
Rash	1.3
General Disorders and Administration Site Conditions	
Feeling jittery	1.4

The majority of adverse reactions were mild to moderate in severity.

Double-blind and open-label data – Adverse reactions reported at <1% frequency

Additional adverse reactions that occurred in <1% of prolonged-release methylphenidate-treated pediatric and adult patients in the double-blind and open-label clinical datasets are listed in Table 5.

Table 5. Adverse Reactions Reported by <1% of Prolonged-Release Methylphenidate-Treated Pediatric and Adult Patients in Either Double-Blind or Open-Label Clinical Trials
System/Organ Class
Adverse Reaction
Blood and Lymphatic System Disorders

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

The majority of adverse reactions were mild to moderate in severity.

Postmarketing data

Adverse reactions identified during postmarketing experience with prolonged-release methylphenidate are included in Table 6. In this table, the frequencies are provided according to the following convention:

Very common	≥1/10 (≥10%)
Common	≥1/100 and <1/10 (≥1% and <10%)
Uncommon	≥1/1000 and <1/100 (≥0.1% and <1%)
Rare	≥1/10000 and <1/1,000 (≥0.01 and <0.1%)
Very rare	<1/10000 (<0.01%), including isolated reports
Not known	Cannot be estimated from the available data

Table 6. Adverse Reactions Identified During Postmarketing Experience with Prolonged-Release Methylphenidate

System/Organ Class Adverse Reaction	**Frequency Category Estimated from Clinical Trials with Prolonged-Release Methylphenidate**
Blood and Lymphatic System Disorders	
Pancytopenia	Not known
Thrombocytopenia swings	Not known
Thrombocytopenic purpura	Not known
Immune System Disorders	
Hypersensitivity reactions such	Uncommon

as Angioedema, Uncommon Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions and Exanthemas NEC	
Psychiatric Disorders	
Disorientation	Rare
Hallucination	Not known
Hallucination auditory	Rare
Hallucination visual	Not known
Mania	Uncommon
Logorrhea	Uncommon
Libido disorder*	Not known
Nervous System Disorders	
Convulsion	Not known
Grand mal convulsion	Not known
Cerebrovascular disorder (including cerebral, vasculitis, cerebral haemorrhage, cerebral arteritis, cerebral vascular occlusion)	Not known
Dyskinesia	Uncommon
Eye Disorders	
Diplopia	Rare
Mydriasis	Rare
Visual impairment	Rare
Cardiac Disorders	
Angina pectoris	Rare
Bradycardia	Not known
Extrasystoles	Rare
Supraventricular tachycardia	Not known

Ventricular extrasystoles	Rare
Vascular Disorders	
Raynaud's phenomenon	Not known
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Rare
Hepatobiliary Disorders	
Blood alkaline phosphatase increased	Not known
Blood bilirubin increased	Uncommon
Hepatic enzyme increased	Uncommon
Hepatocellular injury	Not known
Acute hepatic failure	Not known
Skin and Subcutaneous Tissue Disorders	
Alopecia	Uncommon
Erythema	Rare
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	Common
Myalgia	Common
Muscle twitching	Uncommon
Reproductive System and Breast Disorders	
Priapism	Not known
Gynecomastia	
General Disorders and Administration Site Conditions	
Therapeutic response decreased	Not known
Chest pain	Uncommon
Chest discomfort	Uncommon
Drug effect decreased	Uncommon
Hyperpyrexia	Not known
Investigations	
Platelet count decreased	Not known
White blood cell count abnormal	Not known

NEC Not elsewhere classified

*The adverse reaction Libido disorder includes terms apart from those associated with decreases in libido

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

When treating patients with overdose, allowances must be made for the delayed release of methylphenidate from formulations with extended durations of action.

Signs and Symptoms

Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems, may result in vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Treatment

There is no specific antidote to methylphenidate overdosage.

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 hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for overdose of methylphenidate has not been established.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: centrally acting sympathomimetics: ATC code: N06BA04

Mechanism of action

Methylphenidate HCl is a mild central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of noradrenaline and dopamine into the presynaptic neurone 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.

Clinical efficacy and safety

Prolonged-release methylphenidate was demonstrated to be effective in the treatment of ADHD in 4 randomized, double-blind, placebo-controlled studies in children and adolescents and 2 double-blind

placebo-controlled studies in adults who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD.

Children

The controlled studies compared prolonged-release methylphenidate given qd (18, 36, or 54 mg) over 12 hours (15, 30, or 45 mg total daily dose), and placebo in two single-center, 3-week crossover studies (Studies 1 and 2) and in a multicenter, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was prolonged-release methylphenidate versus placebo.

Symptoms of ADHD were evaluated by community school teachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale. Statistically significant reduction in the Inattention/Overactivity subscale versus placebo was shown consistently across all three controlled studies for prolonged-release methylphenidate qd.

In two controlled studies (Studies 1 and 2), symptoms of ADHD were evaluated by laboratory school teachers using the SKAMP* laboratory school rating scale. The combined results from these two studies demonstrated significant improvements in attention and behavior in patients treated with prolonged-release methylphenidate versus placebo that were maintained through 12 hours after dosing.

*Swanson, Koikin, Agler, M-Fynn and Pelham

Adolescents

In a randomized, double blind, multi-center, placebo-controlled trial (Study 4) involving 177 patients, prolonged-release methylphenidate was demonstrated to be effective in the treatment of ADHD in adolescents aged 13 to 18 and weighing 34.1 – 128.9 kg (mean [SD] = 66.0 [17.1] kg) at doses up to 72 mg/day (1.4mg/kg/day). Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum of 72 mg/day) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness with acceptable tolerability. Patients who met these criteria were then randomized to receive either their individualized dose of prolonged-release methylphenidate (18 – 72 mg/day, n=87) or placebo (n=90) during a two-week double-blind phase. At the end of this phase, mean scores for the investigator rating on the ADHD Rating Scale demonstrated that prolonged-release methylphenidate was significantly superior to placebo.

Adults

Two double-blind, placebo-controlled studies were conducted in 627 adults aged 18 to 65 years. The controlled studies compared prolonged-release methylphenidate administered once daily and placebo in a multicenter, parallel group, 7-week dose-titration study (Study 5) (36 to 108 mg/day) and in a multicenter, parallel group 5-week, fixed-dose study (Study 6) (18, 36, and 72 mg/day).

Study 5 demonstrated the effectiveness of prolonged-release methylphenidate in the treatment of ADHD in adults aged 18 to 65 years at doses from 36 mg/day to 108 mg/day based on the change from baseline to final study visit on the Adult ADHD Investigator Rating Scale (AISRS). Of 226 patients who entered the 7-week trial, 110 were randomized to prolonged-release methylphenidate and 116 were randomized to placebo. Treatment was initiated at 36 mg/day and patients continued with incremental increases of 18 mg/day (36 to 108 mg/day) based on meeting specific improvement criteria with acceptable tolerability. At the final study visit, mean change scores (LS Mean, SEM) for the investigator rating on the AISRS demonstrated that prolonged-release methylphenidate was statistically significantly superior to placebo.

Study 6 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-response study (5-week duration) with 3 fixed dose groups (18, 36, and 72 mg). Patients were randomized to receive prolonged-release methylphenidate administered at doses of 18 mg (n=101), 36 mg (n=102), 72 mg/day (n=102), or placebo (n=96). All three doses of prolonged-release methylphenidate were statistically significantly more effective than placebo in improving the CAARS (Conners' Adult ADHD Rating Scale) total scores at double blind end point in adult patients with ADHD.

5.2 Pharmacokinetic properties

Absorption

Methylphenidate is readily absorbed. Following oral administration of prolonged-release methylphenidate to adults the drug overcoat dissolves, providing an initial maximum drug concentration at about 1 to 2 hours. The methylphenidate contained in the two internal drug layers is gradually released over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours, after which plasma levels of methylphenidate gradually decrease. Prolonged-release methylphenidate taken once daily minimises the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily. The extent of absorption of Methylphenidate once daily is generally comparable to conventional immediate release preparations.

Following the administration of prolonged-release methylphenidate 18 mg once daily in 36 adults, the mean pharmacokinetic parameters were: C_{max} 3.7 ± 1.0 (ng/mL), T_{max} 6.8 ± 1.8 (h), AUC_{inf} 41.8 ± 13.9 (ng.h/mL), and $t_{½}$ 3.5 ± 0.4 (h).

No differences in the pharmacokinetics of prolonged-release methylphenidate 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 prolonged-release methylphenidate18 mg.

Following administration of prolonged-release methylphenidate in single doses of 18, 36, and 54 mg/day to adults, C_{max} and AUC_{inf} of methylphenidate were proportional to dose, whereas 1-methylphenidate Cmax and AUCinf increased disproportionately with respect to dose. Following administration of prolonged-release methylphenidate, 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 prolonged-release methylphenidate doses from 54 to 144 mg/day resulted in linear and dose proportional increases in Cmax and AUCinf 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 prolonged-release methylphenidate, mean Cmax 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

prolonged-release methylphenidate was approximately 3.5 h. The rate of protein binding of methylphenidate and of its metabolites is approximately 15%. The apparent volume of distribution of methylphenidate is approximately 13 litres/kg.

Biotransformation

In humans, methylphenidate is metabolised primarily by de-esterification to alpha-phenyl-piperidine acetic acid (PPA, approximately 50-fold the level of the unchanged substance) which has little or no pharmacologic activity. In adults the metabolism of prolonged-release methylphenidate once daily as evaluated by metabolism to PPA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once daily doses of prolonged-release methylphenidate is similar.

Elimination

The elimination half-life of methylphenidate in adults following administration of prolonged-release methylphenidate was approximately 3.5 hours. After oral administration, about 90% of the dose is excreted in urine and 1 to 3% in faeces, as metabolites within 48 to 96 hours. Small quantities of unchanged methylphenidate are recovered in urine (less than 1%). The main urinary metabolite is alpha-phenylpiperidine acetic acid (60-90%).

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

Food Effects

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of prolonged-release methylphenidate when administered after a high fat breakfast on an empty stomach.

Special Populations

Gender

In healthy adults, the mean dose-adjusted AUC_{inf} values for prolonged-release methylphenidate 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 healthy adults receiving prolonged-release methylphenidate, 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 prolonged-release methylphenidate has not been studied in children younger than 6 years of age. In children 7-12 years of age, the pharmacokinetics of prolonged-release methylphenidate after 18, 36 and 54 mg were (mean±SD): C_{max} 6.0 ± 1.3, 11.3 ± 2.6, and 15.0 ± 3.8 ng/mL, respectively, T_{max} 9.4 ± 0.02, 8.1 ± 1.1, 9.1 ± 2.5 h, respectively, and $AUC_{0-11.5}$ 50.4 ± 7.8, 87.7 ± 18.2, 121.5 ± 37.3 ng.h/mL, respectively.

Renal Insufficiency

There is no experience with the use of prolonged-release methylphenidate in patients with renal insufficiency. After oral administration of radiolabelled methylphenidate in humans, methylphenidate was extensively metabolised and approximately 80% of the radioactivity was excreted in the urine in the form of PPA. Since renal clearance is not an important route of

methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of prolonged-release methylphenidate.

Hepatic Insufficiency

There is no experience with the use of prolonged-release methylphenidate in patients with hepatic insufficiency.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Macrogol
Succinic Acid
Magnesium Stearate
Sodium Chloride
Silica colloidal, anhydrous
Black Iron Oxide

Film coating
Cellulose Acetate
Macrogol

Clear coating
Hypromellose
Macrogol/Polyethylene Glycol
Phosphoric Acid

Color coating
Lactose Monohydrate
Hypromellose
Titanium dioxide
Triacetin
Yellow Iron Oxide (18 mg tablet)
Red Iron Oxide (18 mg, 27 mg and 54 mg tablet)
Black Iron Oxide (27 mg tablet)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Refer to outer carton.
In use: 30 days

6.4 Special precautions for storage

Refer to outer carton. Keep the bottle tightly closed to protect from moisture.

6.5 Nature and contents of container

The product would be packaged in HDPE bottle including 2 canisters with HDPE child resistant cap. Each canister consists of silica gel and carbon.

Pack size: 30 prolonged release tablets.

6.6 Special precautions for disposal

No special requirements for disposal

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

7. MANUFACTURER

Laboratorios LICONSA S.A.
Av. De Miralcampo 7
19200 Azuqueca de Henares
Guadalajara, SPAIN

8. DATE OF REVISION OF THE TEXT

11/2023