SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

CONTRAMYL XR 18 mg (prolonged release tablets)

CONTRAMYL XR 27 mg (prolonged release tablets)

CONTRAMYL XR 36 mg (prolonged release tablets)

CONTRAMYL XR 54 mg (prolonged release tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each prolonged release tablets contains 18 mg, 27 mg, 36 mg or 54 mg of methylphenidate hydrochloride respectively.

Excipient with known effect

Contains sugar:

Each CONTRAMYL XR 18 mg tablet contains: sucrose 10,013 mg

Each CONTRAMYL XR 27 mg tablet contains: sucrose 15,024 mg

Each CONTRAMYL XR 36 mg tablet contains: sucrose 20,027 mg

Each CONTRAMYL XR 54 mg tablet contains: sucrose 30,040 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablets.

CONTRAMYL XR 18 mg:

Yellowish to yellow, round, biconvex, film-coated tablets.

CONTRAMYL XR 27 mg:

Yellow, oblong, biconvex, film-coated tablets with break scores on both sides.

CONTRAMYL XR 36 mg:

White to off-white, oblong, biconvex, film-coated tablets with break scores on both sides.

CONTRAMYL XR 54 mg:

Reddish to red, oblong, biconvex, film-coated tablets with break scores on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CONTRAMYL XR is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children, adolescents aged 6 to 17, and adults aged 18 to 65 who meet DSM-IV criteria for ADHD.

4.2 Posology and method of administration

Posology

Patients new to methylphenidate:

- The recommended starting dose of CONTRAMYL XR for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily for children (6 years and older) and adolescents; and 18 or 36 mg once daily for adults.

Patients currently using methylphenidate:

- The recommended dose of CONTRAMYL XR for patients who are currently taking methylphenidate three times daily at doses of 15 to 60 mg/day is provided in table 1.
- Dosing recommendations are based on current dose regimen and clinical judgement.

Table 1: Recommended dose conversion from other methylphenidate regimens to CONTRAMYL XR

Previous methylphenidate daily dose	**Recommended CONTRAMYL XR dose**
5 mg methylphenidate hydrochloride twice daily or three times daily	18 mg once daily
10 mg methylphenidate hydrochloride twice daily or three times daily	36 mg once daily
15 mg methylphenidate hydrochloride twice daily or three times daily	54 mg once daily
20 mg methylphenidate hydrochloride twice daily or three times daily	72 mg once daily

- Clinical judgement should be used when selecting the dose for patients currently taking methylphenidate in other regimens.
- Dosage may be adjusted in 18 mg increments to a maximum of 54 mg/day for children aged between 6 – 12 years and to a maximum of 72 mg for adolescents aged between 13 – 18

years and 108 mg in adults. In general, dosage adjustment may proceed at approximately weekly intervals.

- Daily dosage above 54 mg is not recommended for children aged between 6 – 12 years.
- Daily dosage above 72 mg is not recommended for adolescents aged between 13 – 18 years.
- Daily dosage above 108 mg is not recommended in adults.

Maintenance/Extended treatment:

- The long-term use of CONTRAMYL XR has not been systemically evaluated in controlled clinical trials.
- The medical practitioner who elects to use CONTRAMYL XR for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness for the individual patient with trials off medicine to assess the patient's functioning without pharmacotherapy.

Changing from one prolonged release methylphenidate medicine to another

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

Dose reduction and discontinuation:

- If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, CONTRAMYL XR should be discontinued (*see section 4.4*).

Special populations

Elderly population:

Use of CONTRAMYL XR in elderly patients over 65 years has not been studied in controlled trials.

Hepatic impairment

Methylphenidate has not been studied in patients with hepatic impairment.

Renal impairment

Methylphenidate has not been studied in patients with renal impairment.

Paediatric population

CONTRAMYL XR should not be used in patients under six years old.

Method of administration

- For oral use.
- CONTRAMYL XR is administered orally once daily.
- As the effect has been shown to be present 12 hours after dosing, it should be taken in the morning.
- CONTRAMYL XR must be swallowed whole with adequate amounts of liquids and must not be chewed, divided or crushed.
- Even though the tablets have a score line, it is not intended as a break line and the tablets should not be divided and taken at different intervals.
- CONTRAMYL XR may be administered with or without food.

- Dosage should be individualised according to the needs and responses of the patients.

4.3 Contraindications

- Hypersensitivity to methylphenidate or to any of the excipients of CONTRAMYL XR (listed in section 6.1).
- Glaucoma.
- Phaeochromocytoma.
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those medicines, due to the risk of hypertensive crisis (*see section 4.5*).
- Hyperthyroidism or thyrotoxicosis.
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder.
- Diagnosis or history of severe and episodic (Type I) bipolar (affective) disorder (that is not well controlled).
- Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, ischaemic heart disease, potentially life-threatening dysrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).
- Pre-existing cerebrovascular disorders: cerebral aneurysm, vascular abnormalities including vasculitis or stroke.
- Family history or diagnosis of Tourette’s syndrome.
- Impaired liver and renal function.
- CONTRAMYL XR should not be used in children under six years old (*see section 5.2 (Special populations) and section 4.4*).
- Pregnancy and lactation *(see section 4.6).*

4.4 Special warnings and precautions for use

CONTRAMYL XR treatment is not indicated in all children with ADHD and the decision to use it must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age.

Long-term use (more than 12 months) in children and adolescents:

The safety and efficacy of long-term use of methylphenidate, as in CONTRAMYL XR, has not been systematically evaluated in controlled trials. CONTRAMYL XR treatment should not and need not, be indefinite. CONTRAMYL XR treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in *sections 4.2 and 4.4* for cardiovascular status, growth, weight, appetite, development of *de novo* or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The medical practitioner who elects to use CONTRAMYL XR for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of CONTRAMYL XR for the individual patient with trial periods off medicine to assess the patient's functioning without pharmacotherapy. It is recommended that CONTRAMYL XR is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when CONTRAMYL XR is either temporarily or permanently discontinued.

Use in adults:

Safety and efficacy have not been established for the initiation of treatment in adults or the routine continuation of treatment beyond 18 years of age. If treatment withdrawal has not been successful when an adolescent has reached 18 years of age continued treatment into adulthood may be necessary. The need for further treatment of these adults should be reviewed regularly and undertaken annually.

Use in the elderly:

CONTRAMYL XR should not be used in the elderly. Safety and efficacy has not been established in this age group. CONTRAMYL XR has not been studied in ADHD in patients older than 65 years.

Use in children under 6 years of age:

CONTRAMYL XR should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established (*see section 4.3*).

Cardiovascular status:

Patients who are being considered for treatment with stimulant medicines should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant dysrhythmia) and physical exam to assess for the presence of cardiac disease and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during CONTRAMYL XR treatment should undergo a prompt specialist cardiac evaluation.

Analyses of data from clinical trials of methylphenidate, as contained in CONTRAMYL XR, in children and adolescents with ADHD showed that patients using methylphenidate may experience changes in diastolic and systolic blood pressure of over 10 mmHg relative to controls. The short- and long-term clinical consequences of these cardiovascular effects in children and adolescents are not known. The possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data especially when treatment during childhood/adolescence is continued into adulthood.

Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. See *section 4.3* for conditions in which CONTRAMYL XR treatment is contraindicated.

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.

Methylphenidate as contained in CONTRAMYL XR should be discontinued in patients under treatment with repeated measures of tachycardia, dysrhythmia or increased systolic blood pressure (> 95th percentile) and referral to a doctor e.g. cardiologist should be considered.

The use of CONTRAMYL XR is contraindicated in certain pre-existing cardiovascular disorders **unless specialist cardiac advice has been obtained** (*see section 4.3*).

Sudden death and pre-existing structural cardiac abnormalities or other serious cardiac disorders:

Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had structural cardiac abnormalities or other serious

heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant medicines (such as CONTRAMYL XR) are not recommended in children or adolescents with known 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 medicine.

Adults: Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant medicines at usual doses for ADHD. Although the role of stimulants in these adult cases is 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 medicines.

Misuse and cardiovascular events:

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

Cerebrovascular disorders:

See *section 4.3* for cerebrovascular conditions in which CONTRAMYL XR treatment is contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant medicines that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with CONTRAMYL XR.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate, as in CONTRAMYL XR exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of CONTRAMYL XR and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischaemia during CONTRAMYL XR therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of co-ordination, vision, speech, language or memory.

Treatment with CONTRAMYL XR is not contraindicated in patients with hemiplegic cerebral palsy.

Psychiatric disorders:

Co-morbidity of psychiatric disorders in ADHD is frequent and should be taken into account when prescribing stimulant medicines, such as CONTRAMYL XR.

Before the start of treatment with methylphenidate, the patient should be examined for any existing psychiatric disorders and a family history with regard to psychiatric disorders should be obtained. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, CONTRAMYL XR should not be given unless the benefits outweigh the risks to the patient.

Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate.

Exacerbation of pre-existing psychotic or manic symptoms:

In psychotic patients, administration of CONTRAMYL XR may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms:

Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by CONTRAMYL XR at usual doses (*see section 4.8*). If manic or psychotic symptoms occur, consideration should be given to a possible causal role for CONTRAMYL XR, and discontinuation of treatment may be appropriate.

Aggressive or hostile behavior:

The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Aggression has been reported in patients treated with methylphenidate as contained in CONTRAMYL XR (*see section 4.8*). Patients treated with CONTRAMYL XR should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Medical practitioners should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency:

Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their medical practitioner. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of CONTRAMYL XR treatment.

Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of CONTRAMYL XR.

Tics:

CONTRAMYL XR is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of CONTRAMYL XR. Patients should be regularly monitored for the emergence or worsening of tics during treatment with CONTRAMYL XR.

Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

Anxiety, agitation or tension:

Anxiety, agitation and tension have been reported in patients treated with methylphenidate (*see section 4.8*). CONTRAMYL XR is associated with the worsening of pre-existing anxiety, agitation or tension. Anxiety has led to discontinuation of methylphenidate in some patients. Clinical evaluation for anxiety, agitation or tension should precede use of CONTRAMYL XR and patients should be **regularly monitored for the emergence or worsening of these symptoms during treatment, at every adjustment of dose and then at least every 6 months or every visit.**

Forms of bipolar disorder:

Particular care should be taken in using CONTRAMYL XR to treat ADHD in patients with co-morbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with CONTRAMYL XR, patients with co-morbid depressive symptoms should be

adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Close ongoing monitoring is essential in these patients (*see above 'Psychiatric Disorders'*). Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.

Growth:

Moderately reduced weight gain and growth retardation have been reported with the long-term use of CONTRAMYL XR in children. Weight decrease has been reported with methylphenidate treatment in adults (*see section 4.8*).

The effects of methylphenidate, as contained in CONTRAMYL XR on final height and final weight are unknown.

Growth should be monitored during CONTRAMYL XR treatment: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. In adults, weight should be regularly monitored.

Seizures:

CONTRAMYL XR should be used with caution in patients with epilepsy. CONTRAMYL XR may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and rarely in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, CONTRAMYL XR should be discontinued.

Abuse, misuse and diversion:

Patients should be carefully monitored for the risk of diversion, misuse and abuse of CONTRAMYL XR.

CONTRAMYL XR should be used with caution in patients with known substance or alcohol dependency because of a potential for abuse, misuse or diversion.

Chronic abuse of CONTRAMYL XR can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse.

Patient age, the presence of risk factors for substance use disorder (such as co- morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of substance or alcohol dependence, because such patients may increase the dosage on their own initiative.

For some high-risk substance abuse patients, CONTRAMYL XR or other stimulants may not be suitable and non-stimulant treatment should be considered.

Withdrawal:

Careful supervision is required during CONTRAMYL XR withdrawal since this may unmask depression as well as chronic over-activity. Some patients may require long-term follow up.

Careful supervision is required during withdrawal from abusive use since severe depression may occur.

Fatigue:

CONTRAMYL XR should not be used to treat severe depression and/or for the prevention or treatment of normal fatigue states.

Renal or hepatic insufficiency:

There is no experience with the use of CONTRAMYL XR in patients with renal or hepatic insufficiency (*see section 4.3*).

Haematological effects:

The long-term safety of treatment with methylphenidate, as contained in CONTRAMYL XR, is not fully known. Periodic haematologic monitoring (complete blood count, differential, and platelet counts) is advised during prolonged therapy. In the event of leukopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Potential for gastrointestinal obstruction:

Because the CONTRAMYL XR tablet is non-deformable and does not appreciably change in shape in the gastrointestinal (GI) tract, it should not ordinarily be administered to patients with pre-existing severe GI narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been reports of obstructive symptoms in patients with known strictures in association with the ingestion of medicines in non-deformable prolonged release formulations.

Due to the prolonged release design of the tablet, CONTRAMYL XR should only be used in patients who are able to swallow the tablet whole. Even though the tablets have a score line, it is not intended as a break line and the tablets should not be divided and taken at different intervals. Patients should be informed that CONTRAMYL XR must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medicine is contained within a non-absorbable shell designed to release it at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Choice of methylphenidate (as in* CONTRAMYL XR*) formulation:

The choice of formulation of a methylphenidate-containing medicine (as in CONTRAMYL XR) will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effect.

Substance screening:

CONTRAMYL XR contains methylphenidate, which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

Priapism:

Prolonged and painful erections requiring immediate medical attention (sometimes including surgical intervention), have been reported with methylphenidate medicines, including CONTRAMYL XR, in both paediatric and adult patients (*see section 4.8*). 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.

Use with serotonergic medicines:

Serotonin syndrome has been reported following co-administration of CONTRAMYL XR with serotonergic medicines (*see section 4.5*). If concomitant use of CONTRAMYL XR with a serotonergic medicine is warranted, prompt recognition of the symptoms of serotonin syndrome is important. These symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyper reflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). CONTRAMYL XR must be discontinued as soon as possible if serotonin syndrome is suspected.

Information about some of the ingredients of CONTRAMYL XR:

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of Interaction

Pharmacokinetic interaction

It is not known how methylphenidate may affect plasma concentrations of concomitantly administered medicines. Therefore, caution is recommended at combining methylphenidate, as contained in CONTRAMYL XR with other medicines, 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, as contained in CONTRAMYL XR pharmacokinetics. Conversely, the d- and l- enantiomers of methylphenidate as contained in CONTRAMYL XR do not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2El or 3A.

Because of possible effects on blood pressure, CONTRAMYL XR should be used cautiously with pressor medicines.

Human pharmacological studies have shown that methylphenidate may inhibit the metabolism of warfarin anticoagulants, anticonvulsants (e.g. phenobarbitone, phenytoin, primidone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustments of these medicines may be required when given concomitantly with CONTRAMYL XR. It may be necessary to adjust the dosage and monitor plasma medicine concentrations (or, in the case of warfarin, coagulation times/INR), when initiating or discontinuing concomitant use of CONTRAMYL XR.

Because of possible hypertensive crisis, methylphenidate, as contained in CONTRAMYL XR, is contraindicated in patients being treated (currently or within the preceding 2 weeks) with MAO (monoamine oxidase)-inhibitors (*see section 4.3*).

Pharmacodynamic interactions

Anti-hypertensive medicines:

- CONTRAMYL XR may decrease the effectiveness of medicines used to treat hypertension.

Use with medicines that elevate blood pressure:

- Caution is advised in patients being treated with CONTRAMYL XR with any other medicine that can also elevate blood pressure *(see also sections under sub-headers 'Cardiovascular status' and 'Cerebrovascular disorders' in section 4.4*).

- Because of possible hypertensive crisis, CONTRAMYL XR 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 effects of CONTRAMYL XR. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with serotonergic medicines:

- There have been reports of serotonin syndrome following co-administration of CONTRAMYL XR with serotonergic medicines.
  If concomitant use of CONTRAMYL XR with a serotonergic medicine is warranted, prompt recognition of the symptoms of serotonin syndrome is important (*see section 4.4*).
  CONTRAMYL XR must be discontinued as soon as possible if serotonin syndrome is suspected.

Use with halogenated anaesthetics:

- There is a risk of sudden blood pressure and heart rate increase during surgery. If surgery is planned, CONTRAMYL XR treatment should not be used 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 of methylphenidate and clonidine. The long-term safety of using CONTRAMYL XR in

combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with dopaminergic medicines:

- Caution is recommended when administering CONTRAMYL XR with dopaminergic medicines, including antipsychotics. Because a predominant action of methylphenidate, as contained in CONTRAMYL XR, is to increase extracellular dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists, including antipsychotics.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of CONTRAMYL XR in pregnant women.

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

Studies in animals have shown evidence of reproductive toxicity at maternally toxic doses.

CONTRAMYL XR is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy (*see section 4.3*).

Breastfeeding

Methylphenidate, as contained in CONTRAMYL XR, is excreted in breast milk (*see section 4.3*).

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, as contained in CONTRAMYL XR. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from CONTRAMYL XR therapy taking into account the benefit of breastfeeding 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 (*see section 4.8*). It may have a moderate influence on the ability to drive and use potentially hazardous machines.

Patients should be cautioned accordingly until they are reasonably certain that CONTRAMYL XR does not adversely affect their ability to engage in such activities.

4.8 Undesirable effects

Tabulated list of adverse reactions

Body System	**Undesirable effect**

	Frequent	***Less frequent***	***Frequency not known***
Infections and infestations	Nasopharyngitis, upper respiratory tract infection, sinusitis		
Blood and lymphatic system disorders		Anaemia, leucopenia, thrombocytopenia, thrombocytopenic purpura	Pancytopenia
Immune system disorders		Hypersensitivity reactions such as angioedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritus, rashes and eruptions	
Metabolism and nutritional disorders	Anorexia, decreased appetite, moderately		

	reduced weight and height gain during prolonged use in children		
Psychiatric disorders	Insomnia, nervousness, affect lability, aggression, agitation, anxiety, depression, irritability, abnormal behaviour, mood swings, tics, initial insomnia, depressed mood, libido decreased, tension, bruxism, panic attack	Psychotic disorders, auditory, visual and tactile hallucination, anger, suicidal ideation, mood altered, restlessness, tearfulness, worsening of pre-existing tics of Tourette's syndrome, logorrhoea, hypervigilance, sleep disorder, mania, disorientation, libido disorder, confusional state**,** suicidal attempt (including	Delusion, thought disturbance, abuse and dependence

		completed suicide), transient depressed mood, abnormal thinking, apathy, repetitive behaviours, over-focussing	
Nervous system disorders	Headache, dizziness, dyskinesia, psychomotor hyperactivity, somnolence, paraesthesia, tension headache	Sedation, tremor, lethargy**,** convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit, neuroleptic malignant syndrome	Cerebrovascular disorders (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsion, migraine, dysphemia
Eye disorders	Accommodation disorder	Blurred vision, dry eye, difficulties in visual accommodation, visual impairment, diplopia	Mydriasis
Ear and labyrinth disorders	Vertigo		

Cardiac disorders	Dysrhythmia, arrhythmia, tachycardia, palpitations	Chest pain, angina pectoris, cardiac arrest, myocardial infarction	Supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles
Vascular disorders	Hypertension	Hot flush, cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders	Cough, oropharyngeal pain	Dyspnoea	
Gastrointestinal disorders	Abdominal pain upper, diarrhoea, nausea, abdominal discomfort, vomiting, dry mouth, dyspepsia	Constipation	
Hepatobiliary disorders		Hepatic enzyme elevations, abnormal liver	Hepatocellular injury, acute hepatic failure

		function, including hepatic coma	
Skin and subcutaneous tissue disorders	Alopecia, pruritus, rash, urticaria	Bullous conditions, exfoliative conditions, hyperhidrosis, macular rash, erythema, Erythema multiforme, exfoliative dermatitis, fixed medicine eruption, angioneurotic oedema,	
Musculoskeletal and connective tissue disorders	Arthralgia, muscle tightness, muscle spasms	Myalgia, muscle twitching, muscle cramps	Trismus
Renal and urinary disorders		Haematuria, pollakiuria	Incontinence
Reproductive system and breast disorders	Erectile dysfunction	Gynaecomastia	Priapism, erection increased and prolonged erection (*see section 4.4*)

General disorders and administration site conditions	Pyrexia, growth retardation during prolonged use in children, fatigue, irritability, feeling jittery, asthenia, thirst	Sudden cardiac death	Chest discomfort, chest pain, hyperpyrexia, decreased therapeutic response, decreased medicine effect
Investigations	Changes in blood pressure and heart rate (usually an increase), decreased weight, increased alanine aminotransferase	Cardiac murmur, increased hepatic enzyme, increased blood alkaline phosphatase, increased blood bilirubin, decreased platelet count, abnormal white blood cell count	

Description of post-marketing adverse reactions

- Risk of epistaxis (nosebleed).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested

to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

Signs and symptoms of acute methylphenidate overdosage, as contained in CONTRAMYL XR, resulting principally from overstimulation of the CNS (central nervous system) and excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyper reflexia, muscle twitching, convulsions, coma, grand mal convulsion, euphoria, confusional state, confusion, hallucinations (auditory and/or visual), hyperhidrosis, flushing, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus dysrhythmias, hypertension, mydriasis, and dry mouth.

Treatment consists of appropriate supportive measures. The patients must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Measures to detoxify the gut include administration of activated charcoal and a cathartic.

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 haemodialysis for methylphenidate, as in CONTRAMYL XR, overdosage has not been established.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A.1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group and ATC code:

Pharmacotherapeutic group: Centrally Acting Sympathomimetics: ATC code: N06BA04

Methylphenidate HCl is a 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 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 well absorbed. Following oral administration of prolonged release methylphenidate to adults, plasma methylphenidate concentrations increase 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. Prolonged release methylphenidate once daily reduces the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily.

The mean pharmacokinetic parameters in 36 adults following the administration of prolonged release methylphenidate 18 mg once daily are summarised in Table 2 below.

Table 2: Mean ± SD pharmacokinetic parameters	
Parameters	**Prolonged release methylphenidate (18 mg once daily) (n = 36)**
C_{max} (ng/ml)	3,7 ± 1,0
T_{max} (h)	6,8 ± 1,8
AUC_{inf} (ng-h/ml)	41,8 ±13,9
$t_{½}$ (h)	3,5 ± 0,4

No differences in the pharmacokinetics of prolonged release methylphenidate were noted following single and repeated once daily dosing indicating no significant accumulation. The AUC and $t_{½}$ following repeated once daily dosing are similar to those following the first dose of prolonged release methylphenidate.

Dose proportionality:

Following administration of prolonged release methylphenidate in single doses of 18, 36 and 54 mg/day to healthy adults, C_{max} and $AUC_{(0-\infty)}$ of d-methylphenidate were proportional to dose, whereas l methylphenidate C_{max} and $AUC_{(0-\infty)}$ 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 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 compound (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 adolescents ADHD patients aged 13 – 16 administered their prescribed dose (18 to 72 mg/day) of prolonged release methylphenidate, mean C_{max} and AUC_{TAU} of methylphenidate increased proportionally with respect to the dose.

Distribution:

Plasma methylphenidate concentrations in adults decline bi-exponentially following oral administration. The half-life of methylphenidate in adults following oral administration of prolonged release methylphenidate was approximately 3,5 hours. 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 (PPAA) which has little or no pharmacologic activity. In adults, the metabolism of prolonged release methylphenidate 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 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)-phenyl-piperidine acetic acid (60-90 %).

After oral dosing of radio labelled 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 prolonged release methylphenidate when administered after a high fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Special populations:

Gender:

In healthy adults, the mean dose-adjusted $AUC_{(0\text{-}inf)}$ values for prolonged release methylphenidate were 36,7 ng.h/mL in men and 37,1 ng.h/mL in women, with no difference noted between the two groups.

Age:

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

Renal insufficiency:

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

- *Active pellets:*

Hypromellose; sugar spheres; talc

- *EC pellet coating:*

Ethylcellulose; hydroxypropylcellulose; talc; triethyl citrate

- *HPMC/AS pellet coating:*

Hypromellose acetate succinate

- *Final blending:*

Carmellose sodium; cellulose; microcrystalline; magnesium stearate; silica, colloidal anhydrous

- *Tablet coating (API):*

Opadry® II white (Macrogol 3350; polyvinyl alcohol; talc, titanium dioxide);

Opadry® II yellow (Iron oxide yellow; macrogol 3350; polyvinyl alcohol; talc);

Opadry® II red (Iron oxide red; macrogol 3350; polyvinyl alcohol; talc)

Tablet coating colour 18 mg: Opadry® II white; Opadry® II yellow

Tablet coating colour 27 mg: Opadry® II yellow

Tablet coating colour 36 mg: Opadry® II white

Tablet coating colour 54 mg: Opadry® II white; Opadry® II red

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the container tightly closed.

6.5 Nature and contents of container

CONTRAMYL XR tablets are available in white high-density polyethylene (HDPE) bottles with round, white, child-resistant, tamper-evident screw caps with three break-points on the tamper-evident ring made of polypropylene and aperture for desiccant insert.

Packs of 30's.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street

Isando, Johannesburg,

1609

8 REGISTRATION NUMBER(S)

CONTRAMYL XR 18 mg: 49/1.2/1137

CONTRAMYL XR 27 mg: 49/1.2/1138

CONTRAMYL XR 36 mg: 49/1.2/1139

CONTRAMYL XR 54 mg: 49/1.2/1140

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 September 2017

10 DATE OF REVISION OF TEXT

25 March 2025