

## Data Sheet

### DOPERGIN<sup>®</sup>

Lisuride Hydrogen Maleate 0.2 mg Tablet

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## Presentation

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Each v-shaped, scored white tablet contains 0.2 mg lisuride hydrogen maleate.

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## Uses

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### *Actions*

DOPERGIN displays dopaminergic and, associated with this, prolactin-reducing properties. The active substance lisuride has a pronounced affinity for dopamine receptors in the striatum and pituitary.

- Parkinsonism

In parkinsonism, DOPERGIN replaces the missing dopamine effect. It improves or eliminates the reduced locomotion (hypokinesia, bradykinesia, akinesia), rigor and tremor. The combination of DOPERGIN with L-dopa-containing preparations is particularly effective and allows low dosages of both active substances. The two substances complement each other in their mechanism of action, since L-dopa requires intact dopamine neurons to be effective, while DOPERGIN directly stimulates postsynaptic dopamine receptors. By combining L-dopa-containing preparations with DOPERGIN, fluctuations of locomotion and dyskinesia, which occur frequently in long-term L-dopa therapy, are favourably influenced or their occurrence retarded.

- Endocrine Indications

Mammary gland function is controlled essentially by prolactin. The prolactin inhibitor DOPERGIN is therefore suitable for suppressing the normal production and flow of milk (primary ab lactation) and for improving pathological states of the mammary gland (galactorrhea).

An elevated prolactin level also inhibits the function of the gonads. Amenorrhea and infertility in women resulting from these conditions can therefore be treated with DOPERGIN if they are based on an elevated prolactin level. The corresponding symptoms in men are disorders of libido and potency.

The above-mentioned disorders can be caused by prolactin-producing pituitary tumours. In macroadenomas, DOPERGIN not only leads to an improvement of the clinical symptoms, but frequently also to a marked diminution in the size of the tumour.

In acromegaly, the over-production of growth hormone can be favourably influenced in some patients. Consequently, DOPERGIN can be employed here when other forms of therapy are not feasible or are inadequate.

### **Pharmacokinetics**

Following oral ingestion of DOPERGIN, the active ingredient lisuride is rapidly (half-life of 1.2 hours) and completely absorbed.

Maximum medicine plasma levels of about 200 pg/mL are reached after 1.1 - 1.3 hours. The post maximum decrease of medicine plasma levels is characterised by a (terminal) half-life of 1 - 3 hours. During absorption and the first passage through the liver, lisuride is intensively metabolised. The absolute bioavailability was estimated to be 21% of a 0.2 mg dose (range: 0 - 56%) in young volunteers and 14% (range: 1.3 - 50%) in healthy elderly subjects. In accordance with this high "first-pass" metabolism, the metabolic clearance rate of parentally administered lisuride was found to range between 11 - 14 mL/min/kg. Lisuride is mainly metabolised by oxidation pathways including N'-desalkylation of ethyl groups, hydroxylation of the benzene ring, mono-oxygenation and oxidation of double bonds. Conjugation of metabolites is of minor importance. The main metabolite in urine is the 2-keto-3-hydroxy derivative of lisuride. Pharmacologically active metabolites are not known. Metabolites of lisuride are eliminated from plasma with a half-life of 10 hours. Besides this (main) excretion phase, small parts of the dose are excreted with a half-life of about 23 hours. Unchanged medicine is almost not found in urine (0.1% of the dose). Nearly the same parts of the dose are excreted as metabolites via the kidney and the liver.

Lisuride widely distributes into the body. The apparent volume of distribution is 2.3 L/kg. The plasma protein binding is non-specific (albumin) and accounts for 66%. Due to the extensive "first-pass" metabolism and inter-individual differences in metabolic clearance rates, the pharmacokinetic parameters of lisuride in man are at high variance, and individual dosing should be guided more by clinical symptoms of dopaminergic effects than by a pre-fixed dose. Indeed, individually titrated doses are effective and exert the same medicine plasma levels during long-term administration. Thus, the intra-individual variation of lisuride pharmacokinetics is much lower than the variations between patients. Coefficients of variation in AUC of various studies ranged from 2 - 27% within patients and from 22 - 77% between individuals. Following three or even four administrations per day, no medicine accumulation in plasma occurs over days because of the short half-life of the terminal medicine disposition from plasma.

There are no indications for any age or sex dependency in lisuride pharmacokinetics of volunteers or patients suffering from parkinsonism. The chronic use of DOPERGIN does not lead to an induction of liver enzymes of the P450 family as followed by renal 6 $\beta$ -hydroxycortisol excretion. *In vitro* results with single liver enzymes showed that lisuride is metabolized by human liver cytochromes P450 2 D6 and 3A4. There is an indication that the systemic availability of lisuride *in vivo* is greatly enhanced in "slow metabolisers" of the P450 2 D6 type. *In vivo*, no medicine-medicine interaction was found with erythromycin. No medicine-medicine interaction is expected at the level of protein binding. The therapeutic medicine plasma levels in the treatment of parkinsonism are dependent upon the individual sensitivity but generally should range between 0.2 - 2.0 ng/mL.

The concomitant intake of food and medicines leads to a reduced maximum medicine plasma level, while the bioavailability remains unchanged. Because actual medicine plasma or serum levels are closely correlated with a particular undesired

side-effect, i.e. nausea, DOPERGIN tablets should always be taken together with a snack or meal.

The absolute bioavailability of lisuride is highly variable after oral ingestion. On average, it was found to be 10 - 20% of the dose in various studies.

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## Indications

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### As a Dopamine Agonist in:

- Parkinson's disease, postencephalitic parkinsonism, parkinsonism of other origin (with the exception of the medicine-induced form)

### As a Prolactin Inhibitor in:

- Prevention of the onset of lactation in the puerperium (primary ab lactation) only for clearly defined medical reasons
- Galactorrhea; prolactin-induced amenorrhea; prolactin-induced infertility in women; prolactinomas
- Acromegaly

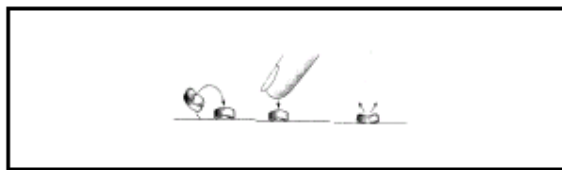
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## Dosage and Administration

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The tablets must always be taken with a meal or snack. Tolerance can generally be improved by starting the treatment gradually (exception: primary ab lactation) and, if possible, in the evening. This applies in particular to higher dosages.

To halve a 0.2 mg tablet, place the tablet on a hard surface with the scored side facing down, then press on the tablet with one finger.



The following guidelines apply:

- Parkinsonism

The dose must be adapted to the individual requirements.

The treatment begins with half of a 0.2 mg DOPERGIN tablet (0.1 mg) in the evening and should be increased by 0.1 mg weekly until a clinical effect becomes apparent.

Treatment week	Number of DOPERGIN 0.2 mg tablets		
	morning	midday	evening
1	–	–	½
2	½	–	½
3	½	½	½
4	½	½	1
5	1	½	1
6	1	1	1
7	further weekly increases by ½ tablet, if necessary		

The daily dose depends on tolerance and effectiveness and on the severity of the disease and generally lies between 0.6 and 2 mg, although higher doses may be necessary in individual cases. It is usually divided into 3 to 4 smaller doses which can be taken together with levodopa and/or other anti-parkinsonism medicines. In cases of marked fluctuation, it is advisable to divide the daily dose into even smaller portions.

The dose should be low in early phases of parkinsonism and should only be increased slowly. The dose of the levodopa preparation can be reduced as the dose of DOPERGIN is increased. This merits particular attention in cases where the MAO-B inhibitor selegiline, which increases and prolongs the availability of dopamine at the receptors, is administered concomitantly with levodopa. Monotherapy with DOPERGIN is also possible in individual cases.

After every dose increase, the effect and tolerance should be observed for at least one week before the dose is increased again.

Under no circumstances should the dose be increased any further if side-effects occur. Tolerance usually develops towards some of the side-effects (nausea, headaches, tiredness and dizziness), so that the dose can, if necessary, be increased further after the side-effects have disappeared. The more the total daily dose is divided into smaller doses, the better the tolerance of DOPERGIN.

In advanced cases of parkinsonism, the dose may sometimes be increased more quickly depending on tolerance and effectiveness.

If the patient's clinical condition makes a rapid onset of the effect of DOPERGIN appear desirable, then the aforementioned side-effects can be eliminated by the concurrent administration of domperidone and the dosage increased further as required. This should, however, be the exception. The need for continued domperidone medication should be checked after 4 weeks at the most by withdrawing it. A temporary reduction of the dose of DOPERGIN is recommended in the case of pronounced side-effects.

Treatment discontinuation should be tapered, because symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy.

- Endocrine Indications

Primary ab lactation (where medically indicated)

Treatment should be initiated, if possible, immediately after delivery or abortion, but certainly within the first 24 hours. One DOPERGIN 0.2 mg tablet should be taken 2 to 3 times daily for 14 days. Renewed but slight milk secretion may occur in rare cases after discontinuation of DOPERGIN treatment, but this can be arrested with another week's therapy.

Galactorrhoea; prolactin-induced amenorrhoea and prolactin-induced infertility in women

Day of treatment	Number of tablets (0.2 mg)		
	morning	midday	evening
1st	-	-	½
2nd	-	½	½
from 3rd	½	½	½

The treatment of galactorrhoea must be continued until the milk flow has been completely arrested. In the case of amenorrhoea, it must be continued (without stopping for several months) until normal cycles with regular menstrual periods are restored.

Depending on how high the prolactin level is elevated, or its effect, the daily dose of DOPERGIN may need to be increased. In this case, in order to achieve better tolerance, the dose increase should start no earlier than the 3<sup>rd</sup> or 4<sup>th</sup> day of treatment, and should be divided into several single doses.

Acromegaly

Dosage as for galactorrhea (see above). Depending on the tolerance and effect on the growth hormone levels, the dose may also be increased further to a maximum of 2 mg per day.

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## Contraindications

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Hypersensitivity to lisuride and other ergot derivatives

Serious peripheral arterial disorders and coronary insufficiency

Concomitant use with phenylpropanolamine

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## Warnings and Precautions

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In patients with past or present psychoses, the clinical indication must be carefully reviewed and the benefits weighed against the risks, since deterioration or recurrence of the symptoms is possible.

The indication must be considered very carefully in severe disorders of arterial circulation in the periphery and heart (coronary failure).

Hypertension, myocardial infarction, convulsive seizures and stroke (well-known symptoms of post-partum cerebral angiopathy) have been observed rarely in combination with the use of ergot-derived dopamine agonists as inhibitors of milk secretion in the puerperium. If these events occur and a causal relationship with lisuride is suspected, it is advisable to halt the treatment immediately to prevent the development of hypertension, persistent headache or other signs of impairment of the central nervous system in women who take DOPERGIN to inhibit the secretion of milk.

Excessive daytime somnolence was reported in patients treated with DOPERGIN and sudden onset of sleep in patients treated with dopaminergic agonists, particularly in patients suffering from Parkinson's disease.

Patients treated with DOPERGIN must be informed of this and advised to exercise caution while driving or operating machines. The patients who have experienced somnolence must refrain from driving or operating machines. Furthermore, dose reduction or treatment discontinuation should be considered.

Caution should be advised when patients are taking medicinal products with sedative effects in combination with DOPERGIN, because their sedative effects may be potentiated (see "Interactions").

Lisuride is an ergot derivative. After prolonged use of ergot derivatives, including lisuride, inflammatory changes of a fibrotic type have been detected (see "Adverse Effects"). Since these changes are of insidious onset, patients should be monitored.

If a fibrotic disorder is suspected, the treatment should be halted and the diagnosis confirmed.

In ab lactation, the baby should not be put to the breast nor should the milk be pumped off in order to avoid the stimulus to lactation. In its early stage, mastitis can usually be managed simply by restricting the production of milk by means of DOPERGIN, after which the baby can often be breast-fed again.

Additional therapeutic measures (e.g. administration of antibiotics etc.) are required in pre-existing bacterial superinfection, persistent fever or abscess formation.

Before starting treatment of hyperprolactinaemia with DOPERGIN, the cause of the disorder must be clarified (e.g. medicines, hypothyroidism). Of particular importance is the question of whether there is an invasive, large adenoma of the pituitary gland. In the case of visual field defects or if the sella is significantly enlarged, either surgery (with or without additional DOPERGIN therapy) or DOPERGIN treatment alone can be applied.

If pregnancy occurs in women who have a pituitary adenoma (prolactinoma), signs of renewed tumour growth (severe and sustained headaches, disturbed vision) must be very closely observed by adequate diagnostic measures.

Persons with impaired renal function, and especially dialysis patients, are particularly sensitive to dopamine agonists. Treatment with prolactin inhibitors should therefore always be initiated with the lowest possible dose and the dose should then be slowly increased.

Lisuride is almost completely metabolised in the liver (see "*Pharmacokinetics*") and since insufficient controlled data are available with the use of lisuride in patients with clinically relevant disturbances of liver function, treatment should be initiated with special care and with low doses.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease including lisuride. Healthcare professionals should advise their patients to seek appropriate help and inform their doctor if they, their family or their carer notice that their behaviour is unusual.

The development of cardiac fibrosis, pulmonary fibrosis, pleural fibrosis, pleural effusion or retroperitoneal fibrosis has been observed in isolated cases after long-term use of ergot-type dopamine agonists, including DOPERGIN. Shortness of breath, a persistent urge to cough or disturbances of kidney function occurring under treatment with DOPERGIN must be clarified by appropriate diagnostic procedures; if necessary DOPERGIN should be withdrawn.

Symptoms suggestive of neuroleptic malignant syndrome have been reported with the abrupt withdrawal of dopaminergic therapy, therefore treatment discontinuation should be tapered.

Patients who receive lisuride may suffer from sudden falls in blood pressure (orthostatic hypotension), especially at the beginning of treatment.

The medicinal product contains lactose and therefore patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take DOPERGIN.

### **Use in Pregnancy**

DOPERGIN should not be used during pregnancy. When used for the treatment of prolactin-induced infertility, DOPERGIN should be discontinued as soon as pregnancy is suspected. As long as no pregnancy is desired, some form of contraception must be used.

Animal experiments into the influence on fertility, embryonal development, delivery and lactation as well as on development and reproductive capacity of the offspring did not indicate undesirable effects, in particular teratogenic effects, to be expected in humans.

### **Use in Lactation**

Lisuride may be excreted into breast milk. In the absence of studies, breast feeding under the treatment with lisuride is not recommended.

## Effects on Ability to Drive and Use Machines

Patients being treated with DOPERGIN and presenting with somnolence must be warned not to drive or engage in activities where impaired alertness may put themselves or others at risk of serious injuries or death (e.g. operating machines) (see “Warnings and Precautions”).

Lisuride can lead to a sudden fall in blood pressure and, hence, affect the reactions to such an extent that the ability to participate in road traffic or to operate machines is impaired.

The consumption of alcohol during treatment with DOPERGIN should be avoided (see “Interactions”).

## Preclinical Safety Data

Studies on toxicity after repeated oral administration showed that at doses  $\geq$  0.1 mg/kg body weight, exaggerated dopamine-agonistic reactions might occur as a sign of overdose, but even then toxic organ damage is not to be expected.

Studies on genotoxic effects *in vitro* and *in vivo* did not indicate a mutagenic potential for somatic or germ cells in humans.

In tumorigenicity studies no indication of a tumorigenic effect of the product was observed. Due to its dopaminergic effect the rate of pituitary prolactinomas was reduced.

A slight contact-sensitising potential was noted in guinea pigs. Since the medicinal product is used orally in humans, this finding indicates at most a low risk of allergic skin reactions.

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## Adverse Effects

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The following tables list adverse reactions of DOPERGIN and are compiled from data obtained in clinical studies. It should be considered that DOPERGIN exhibits similar adverse reactions as other dopaminergics. In parkinsonism, DOPERGIN is almost exclusively used in combination with other drugs. Only very limited experience is available from monotherapy with DOPERGIN, both in clinical studies and from postmarketing data. Reconsideration of a patient’s entire anti-Parkinsonian regimen is therefore required in the event of undesirable treatment effects.

### Frequency of Adverse Reactions from Clinical Trial Data:

#### Table 1: DOPERGIN for the treatment of Parkinson’s Disease

Data are based on a randomised, controlled, double-blind trial of levodopa, lisuride and their “early combination” in patients with Parkinson’s disease, with 30 patients per group. The frequencies refer to 30 patients receiving lisuride as monotherapy. Adverse Drug Reactions (ADR) identified during post-marketing surveillance, and for which a frequency could not be estimated, are listed under “Frequency not known”

<b>System/Organ Class</b>	<b>Very common (≥ 1/10)</b>	<b>Common (≥ 1/100 to &lt;1/10)</b>	<b>Uncommon (≥ 1/1,000 to &lt;1/100)</b>	<b>Frequency not known</b>
<b>Metabolism and Nutrition Disorders</b>	Decreased appetite			
<b>Psychiatric Disorders</b>	Hallucination, anxiety	Confusion, nightmares, insomnia		Paranoid reactions, disorientation, hypersexuality, increased libido, pathological gambling
<b>Nervous System Disorders</b>	Dyskinesia, somnolence, vertigo, headache	Dystonia, myoclonus		
<b>Cardiac Disorders</b>		Palpitation		Pericarditis, pericardial effusion
<b>Vascular Disorders</b>	Orthostatic hypotension, cold extremities	Erythromelalgia		
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		Dyspnoea		Pleural effusion, pulmonary fibrosis, pleural fibrosis
<b>Gastrointestinal Disorders</b>	Nausea, dry mouth, obstipation	Vomiting		Retroperitoneal fibrosis
<b>General Disorders and Administration Site Conditions</b>	Peripheral oedema, sweating			
<b>Immune system disorders</b>				Allergic skin or mucosa reactions
<b>Investigations</b>				Weight gain

**Table 2: DOPERGIN in the Indication of Menstrual Cycle Disorders and Hyperprolactinemia-induced Infertility**

Based on an open-label, uncontrolled study in 1081 women with menstrual cycle disorders and infertility. ADRs identified during post-marketing surveillance, and for which a frequency could not be estimated, are listed under “Frequency not known”

<b>System/Organ Class</b>	<b>Very common (≥ 1/10)</b>	<b>Common (≥ 1/100 to &lt;1/10)</b>	<b>Uncommon (≥ 1/1,000 to &lt;1/100)</b>	<b>Frequency not known</b>
<b>Metabolism and Nutrition Disorders</b>		Appetite loss		
<b>Nervous System Disorders</b>			Dizziness, headache	
<b>Cardiac Disorders</b>			Tachycardia, palpitation	
<b>Vascular Disorders</b>			Orthostatic hypotension, increased blood pressure	
<b>Gastrointestinal Disorders</b>			Nausea, abdominal discomfort	
<b>Immune system disorders</b>				Allergic skin or mucosa reactions

Headaches, dizziness, nausea, dry mouth, tiredness, sweating and rarely vomiting may occur particularly at the beginning of treatment, if the dose is increased too quickly or if the dosage is too high, and if the tablets are not taken together with a meal or snack.

Sudden drops in blood pressure (ranging to orthostatic collapse) and violent vomiting have been observed in individual cases of particular individual sensitivity. Sulpiride (up to 100 mg) can be given i.m. in the event of such disproportionately severe intolerance reactions.

These adverse effects usually do not necessitate termination of the treatment and can be controlled by dose reduction. In the course of treatment, adverse effects generally cease to occur even with markedly higher doses.

Nightmares, hallucinations, paranoid reactions, disorientation and confusion may occur, almost exclusively, in patients with parkinsonism. These are more frequent in elderly patients, concurrent dementia (organic brain syndrome), acute infections, dehydration and a high dosage of DOPERGIN and other dopaminergic medicines. The symptoms can usually be managed by dose reduction

Weight gain has been reported in some patients with parkinsonism. Usually this is considered a positive treatment effect.

The development of pulmonary fibrosis, pleural fibrosis, pleural effusion, pleuritis, pericarditis, pericardial effusions and retroperitoneal fibrosis has been observed in isolated cases after long-term use of ergot-type dopamine agonists, including DOPERGIN (see "Warnings and Precautions"). Shortness of breath, a persistent

urge to cough or disturbances of kidney function occurring under the treatment with DOPERGIN must be clarified by appropriate diagnostic procedures.

In patients treated with ergot derivatives cardiac valvulopathy (including regurgitation) has been reported.

Dyskinesia is a complication of long-term treatment of parkinsonism with dopaminergic agents, particularly levodopa. Careful dose finding and benefit evaluation is required for optimum dosage of dopaminergic drugs including DOPERGIN in advanced Parkinson's disease patients who exhibit dyskinesia.

Patients treated with dopamine agonists for treatment of Parkinson's disease, including lisuride, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

It should also be noted that some of the symptoms rated as undesirable effects may be signs of the underlying disease.

Lisuride is associated with somnolence. Sudden onset of sleep was reported in patients treated with dopaminergic agonists, particularly in patients suffering from Parkinson's disease (see "Warnings and Precautions").

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## Interactions

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### **Concomitant use contra-indicated:**

- *Phenylpropanolamine*: Risk of vasoconstriction and/or hypertensive crises (see "Contraindications")

### **Concomitant use not recommended:**

- *Neuroleptics and other dopamine antagonists (e.g. haloperidol, sulpiride, metoclopramide, chlorpromazine)*: may attenuate the effect of lisuride. Domperidone inhibits only the peripheral but not the central effects of lisuride and thus has no influence on the symptoms of parkinsonism.
- *Medicinal products with central nervous system depressant effects (e.g. benzodiazepines, antipsychotics or antidepressants) or alcohol*: sedating effects of lisuride may be enhanced (see "Warnings and Precautions").
- *Antipsychotic neuroleptics (except clozapine)*: mutual antagonism of dopaminergic agonists and neuroleptics with risk of reduced efficacy
- *Alpha sympathomimetics (oral and nasal form) and indirect sympathomimetics*: risk of vasoconstriction and/or hypertensive crises
- *Vasoconstrictive ergot alkaloids*: risk of vasoconstriction and/or hypertensive crisis
- *Other ergot alkaloids (e.g. methyl ergometrin)*: Lisuride should not be used together with other ergot alkaloids after delivery and in the puerperal period, although no interactions have so far been reported.
- *Anticholinergic antiparkinsonians*: risk of increase of neuropsychic disorders

- *Antihypertensives*: special caution should be exercised when prescribing DOPERGIN for women who have taken or are taking drugs for blood pressure control.

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## Overdosage

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### *Symptoms of Overdosage*

After single intake of large amounts of tablets (e.g. 30 tablets of 0.2 mg DOPERGIN) severe dopamine-agonistic reactions, such as nausea, vomiting and vertigo, may occur.

### *Treatment of Overdosage*

In the event of milder cases of overdosage, metoclopramide oral drops may be given as an antidote if necessary (in parkinsonism: domperidone) and in severe cases up to 100 mg sulphiride i.m.

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## Pharmaceutical Precautions

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**Special Precautions for Storage:** Store below 25 °C. Protect from light.

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## Medicine Classification

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Prescription Medicine

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## Package Quantities

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Glass jar with a desiccant stopper containing 30 tablets

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## Further Information

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### **List of Excipients**

Lactose monohydrate, microcrystalline cellulose, magnesium stearate, tartaric acid, sodium calcium edetate.

Store all medicines properly and keep them out of reach of children.

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## **Name and Address**

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Bayer New Zealand Limited  
3 Argus Place,  
Hillcrest  
North Shore  
AUCKLAND 0627  
Free phone 0800 233 988

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## **Date of Preparation**

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22 March 2011