Core Safety Profile

Active substance: Lisuride
Pharmaceutical form(s)/strength: Tablets, 0.2mg
P-RMS: AT/H/PSUR/0012/001
Date of FAR: 10.09.2009
4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Serious peripheral circulatory disorders and coronary insufficiency
- Caution is required in patients suffering from psychosis.
- Concomitant use with phenylpropanolamine

4.4 Special warnings and precautions for use

The clinical indication should be carefully evaluated in patients who are currently suffering from psychosis or have a history of psychosis. It is advisable to assess the risk/benefit ratio carefully, taking into particular consideration the clinical indication (dopamine agonist vs. prolactin inhibitor). A worsening or reappearance of the signs and symptoms is possible.

Hallucinations, nightmares, disorientation and confusion can occur under treatment with dopamine-agonists, more likely in elderly persons and with high dosage. At treatment initiation patients must be closely monitored for such signs, and if persistent the dose should be reduced and if still persisting treatment must be discontinued.

Caution should be advised when patients are taking medicinal products with sedative effects (e.g. benzodiazepines, antipsychotics or antidepressants) in combination with lisuride, because their sedative effects may be potentiated.

Excessive daytime somnolence was reported in patients treated with <lisuride> and sudden onset of sleep in patients treated with dopaminergic agonists, particularly in patients suffering from Parkinson disease. Patients treated with <lisuride> 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. In these patients comedication with a sedative effect can increase the risk of somnolence and should be avoided if possible (see section 4.5 Interaction with other medicinal products and other forms of interaction). Furthermore, dose reduction or treatment discontinuation should be considered.

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

Assess the indication extremely carefully when disorders of the peripheral arterial and cardiac circulation (coronary insufficiency) are present.

Patients with orthostatic hypotension may suffer sudden falls in blood pressure at the beginning of treatment. Therefore, <lisuride> should be used very cautiously in these patients. It is recommended to monitor blood pressure regulation, especially at the beginning of treatment due to the general risk of orthostatic hypotension associated with dopaminergic therapy.

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 <lisuride> to inhibit the secretion of milk. In inhibition of lactation the infant at the breast should not suck nor should the milk be extracted mechanically in order to avoid stimulation of lactation itself.
Before starting treatment of hyperprolactinaemia with <lisuride>, the cause of the disorder should be clarified (e.g. medicinal, hypothyroidism). It is particularly important to consider the presence of a large invasive adenoma of the pituitary gland. In cases where women with a hypophyseal adenoma (prolactinoma) are pregnant, any signs of resumption of tumour growth should be carefully monitored, using the most appropriate diagnostic tools.

Patients with impairment of renal function, and patients undergoing dialysis in particular, are especially sensitive to dopamine agonists. It is therefore advisable always to start treatment with prolactin inhibitors with the lowest possible dose, and to increase the dose gradually.

Lisuride is an ergot derivative. After prolonged use of ergot derivatives, including lisuride inflammatory changes of a fibrotic type have been detected with serous disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusions and retroperitoneal fibrosis. Since these changes are of insidious onset, patient should be monitored throughout the treatment, paying special attention to the appearance of signs and symptoms suggestive of an inflammatory disorder of a fibrotic or serous type. If a fibrotic disorder is suspected, the treatment should be halted and the diagnosis confirmed by performance of appropriate tests such as erythrocyte sedimentation rate, determination of serum creatinine and diagnostic imaging procedures (e.g. chest X-ray, echocardiography).

Cases of pathological gambling syndrome, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson’s disease.

Lisuride is almost completely metabolised in the liver (see section 5.2 Pharmacokinetic properties); as there is not enough verified information available concerning the use of lisuride in patients with clinically relevant liver dysfunction, it is recommended that the treatment should be started with particular caution and with low doses.

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 this medicinal product.

4.5 Interactions with other drugs and other forms of interaction

Contra-indicated association:

- *Phenylpropanolamine*: Risk of vasoconstriction and/or hypertensive crises.

Not recommended association:

- *Antipsychotic neuroleptics (except clozapine)*: mutual antagonism of dopaminergic agonist and neuroleptics
- *Alpha sympathomimetic (oral and/or nasal form) and indirect sympathomimetic*: risk of vasoconstriction and/or hypertensive crises.
- *Anticholinergic antiparkinsonians*: risk of increase of neuropsychic disorders
- *Vasconstrictive ergot alkaloids*: risk of vasoconstriction and/or hypertensive crisis.

Neuroleptics and other dopamine antagonists (haloperidol, sulpiride, metoclopramide, chlorpromazine) may reduce the effects of lisuride.

Domperidone inhibits only the peripheral, but not the central effects of lisuride, and therefore has no effect on the symptoms of Parkinson’s disease.

Sedating effects of lisuride may be enhanced by medicinal products with central nervous system depressant effects or alcohol (see section 4.4 Special warnings and precautions for use).
4.6 Pregnancy and lactation

Pregnancy
There are insufficient data from the use of lisuride in pregnant women. Animal studies with lisuride do not indicate any teratogenic effects, but reduced fertility and embryo-toxicity were observed in rats in association with pharmacodynamic activity. The potential risk for humans is unknown. Therefore, lisuride is not recommended to be used in pregnancy. If lisuride is used for the treatment of prolactin induced infertility, the treatment should be discontinued as soon as pregnancy is suspected (see section 4.4 Special warnings and precautions for use).

Breast-feeding
Small amounts of lisuride are excreted in human milk. Because lisuride decreases prolactin secretion in humans, inhibition of lactation is expected. For these reasons, lisuride should not be administered to mothers who elect to breast-feed.

4.7 Effects on ability to drive and use machines
Patients being treated with lisuride and presenting with somnolence must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injuries or death (e.g. operating machines) (see section 4.4 Special warnings and precautions for use). Lisuride can very occasionally 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 lisuride should be avoided (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.8 Undesirable effects
The following tables report the adverse effects of lisuride; the data have been obtained from clinical studies or from postmarketing reports (incidences unknown). It should be remembered that lisuride provokes adverse effects similar to those caused by other dopamine agonists. In Parkinson’s disease, lisuride is used almost exclusively in combination with other drugs. Only very limited information is available concerning the use of lisuride as monotherapy, both where clinical studies and post-marketing data are concerned. If adverse effects appear, the patient’s entire anti-Parkinson treatment regimen therefore needs to be re-assessed.

Headache, dizziness, nausea, dryness of the mouth, tiredness, sweating and, rarely, vomiting may appear at the start of the treatment if the dose is increased too rapidly or if the dose is excessive or if the tablets are not taken with a meal or with a snack.

Lisuride is associated with somnolence. Sudden onset of sleep was reported in patients treated with dopaminergic agonists, particularly in patients suffering from Parkinson disease (see section 4.4 Special warnings and precautions for use).

In isolated cases, characterised by particular individual sensitivity, unexpected falls in blood pressure (going as far as orthostatic collapse) and violent vomiting have been observed. If these serious and disproportionate intolerance reactions occur, sulpiride may be administered.

These adverse effects do not generally make it necessary to halt the treatment and they may be controlled through a reduction in the dose. Generally speaking, in the course of the treatment the adverse effects cease, even when significantly higher doses are administered.

It should also be remembered that some of the symptoms considered to be adverse effects may in reality be signs of the disease in question.
Frequency of adverse effects in accordance with the data derived from clinical studies:

The following tables give the adverse effects in accordance with the MedDRA system organ class (MedDRA SOC).
The most appropriate MedDRA term is used to describe a given reaction, its synonyms and related conditions.

Table 1: <Lisuride> in the treatment of Parkinson’s disease

Clinical trial data based on a double-blind, randomised, controlled study with L-dopa, lisuride and their “early combination” in patients with Parkinson’s disease; 30 patients per group.
The frequencies refer to 30 patients given monotherapy with lisuride.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100, &lt;1/10)</th>
<th>Uncommon (≥1/1,000, &lt;1/100)</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorders of metabolism and nutrition</td>
<td>Reduction of appetite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Hallucinations*</td>
<td>Confusion*</td>
<td></td>
<td>Paranoid reactions*, Disorientation*, Hypersexuality§, Increased libido§, Pathological gambling§</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>Nightmares*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dyskinesia</td>
<td>Dystonia</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Somnolence</td>
<td>Myoclonus</td>
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<tr>
<td></td>
<td>Vertigo</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heart disease</td>
<td></td>
<td>Palpitations</td>
<td></td>
<td>Pericarditis, Pericardial effusion,</td>
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<tr>
<td>Vascular diseases</td>
<td>Orthostatic</td>
<td>Erythromelalgia</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>hypotension. Cold</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>extremities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, chest and mediastinal disorders</td>
<td></td>
<td>Dysspnoea</td>
<td></td>
<td>Pleural effusion, Pulmonary fibrosis, Pleural fibrosis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td></td>
<td></td>
<td>Retroperitoneal fibrosis</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic disorders and conditions relating to the site of administration</td>
<td>Peripheral oedema</td>
<td>Sweating</td>
<td></td>
<td></td>
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<tr>
<td></td>
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</tbody>
</table>
Events almost exclusively seen in patients with Parkinson’s disease and are more common in elderly patients, in cases of dementia (organic cerebral syndrome), acute infections, dehydration and administration of high doses of lisuride and/or of other dopamine agonists. The symptoms can generally be controlled with a reduction in the dose.

** Seen in some patients with Parkinson’s disease. Event is generally considered to be a positive effect of the treatment.

§ Events, which were generally reversible with a reduction or withdrawal of the treatment, have been reported in patients treated with dopamine agonists, for Parkinson’s disease, especially at high dosages.

In isolated cases, after prolonged use of ergot-derived type dopamine agonists, including <lisuride>, cases of pulmonary fibrosis, pleural fibrosis, pleural effusion or retroperitoneal fibrosis have been observed. When breathing problems, a persistent urge to cough, or disorders of renal function occur in the course of treatment with <lisuride>, the origin of these symptoms must be clarified by means of appropriate diagnostic procedures.

In patients treated with ergot derivates cardiac valvulopathy (including regurgitation) has been reported (see section 4.4 Special warnings and precautions for use).

The appearance of anomalous involuntary movements (dyskinesia) is a complication of the long-term treatment of Parkinson’s disease with dopamine agonists, particularly with L-dopa. In patients with advanced Parkinson’s disease who manifest dyskinesia, the optimum dose must be carefully established and the benefits of treatment with dopamine agonists, including lisuride, re-evaluated.

In patients treated with dopamine agonists, for Parkinson’s disease, especially at high dosages, cases of pathological gambling syndrome, an increase in libido, and hypersexuality, generally reversible with a reduction or withdrawal of the treatment, have been reported.

### Table 2: <Lisuride> in the treatment of prolactin-dependent female infertility

Data based on an open uncontrolled study carried out in 1081 women with disorders of the menstrual cycle and infertility.
<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100, &lt;1/10)</th>
<th>Uncommon (≥1/1000, &lt;1/100)</th>
<th>Unknown disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system</td>
<td></td>
<td></td>
<td></td>
<td>Allergic skin or mucosa reactions</td>
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<tr>
<td>disorders</td>
<td></td>
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<td></td>
<td></td>
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</tbody>
</table>

### 4.9 Overdose

After an accidental ingestion of large quantities of tablets (e.g. 30 0.2 mg tablets of <lisuride>), serious reactions, typical of dopamine agonists, such as nausea, vomiting and vertigo, may appear. In cases of moderate overdosage, metoclopramide (domperidone in Parkinson’s disease) or sulpiride IM, up to 100 mg in serious cases, may be administered as an antidote.