1. **NAME OF THE MEDICINAL PRODUCT**

URAPIDIL NORDIC PHARMA 25 mg/5 ml, solution for injection
URAPIDIL NORDIC PHARMA 50 mg/10 ml, solution for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Urapidil (as urapidil hydrochloride)……………………………………………………………………………………………………… 5 mg
For 1 ml of solution for injection

One 5 ml ampoule contains 25 mg urapidil.
One 10 ml ampoule contains 50 mg urapidil.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection.

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic indications**

Severe hypertension:
- Associated with short term life threatening or internal end organ damage (hypertensive emergency)
- During and/or after surgery

4.2. **Posology and method of administration**

**Adults**

**Preparation of the solutions:**
- Intravenous infusions: add 5 x 50 mg ampoules of urapidil to 500 ml of solution
- Syringe pump: 2 x 50 mg ampoules of urapidil to 50 ml of solution

**Recommended dosage for treating a hypertensive emergency**

**Initiation of treatment**
- Intravenous injection:
  
  One ampoule of urapidil 25 mg is to be injected in bolus. In case of sufficient reduction after 5 minutes, the treatment will be administered at the maintenance dose. If there is not sufficient reduction, the treatment will be repeated (injection of one 25 mg ampoule in 20 seconds). In case of sufficient reduction after 5 minutes, the treatment will be administered at the maintenance dose.

  If there is still not sufficient reduction 5 minutes after, one 50 mg ampoule of urapidil will be injected in bolus. If there is sufficient reduction in blood pressure after 5 minutes, the treatment will be administered at the maintenance dose.
Intravenous infusion or syringe pump:

By intravenous infusion:
The rate of infusion should be 2 mg/min (88 drips: 4.4 ml/min). If there is sufficient reduction in blood pressure, change to the maintenance dose.

By syringe pump:
The administration flow-rate should be 2 mg/min (1 ml/min). If there is sufficient reduction in blood pressure, change to the maintenance dose.

In the treatment of hypertensive emergency, the dose should be adjusted such that the drop in blood pressure does not exceed 25% of the initial level in the hour following the initiation of the treatment by injection; as too sudden a fall in blood pressure may result in myocardial, cerebral or renal ischemia.

Maintenance treatment (when the blood pressure has been sufficiently reduced):

- Administration by intravenous infusion:
  A flow rate of 9 to 30 mg/h (an average of 15), i.e. 7 to 22 drips/h (an average of 11).

- Administration by syringe pump:
  A flow rate of 9 to 30 mg/h (an average of 15), i.e. 4.5 to 15 ml/h (an average of 7.5).

Recommended doses for treatment of severe hypertension during and/or after surgery:

Initiation of treatment:

- Intravenous injection:
  One ampoule of urapidil 25 mg is to be injected over 20 seconds. In case of sufficient reduction after 2 minutes the treatment will be administered at the maintenance dose. If there is still not sufficient reduction after 5 minutes, repeat the treatment (one 25 mg ampoule injected over 20 seconds).

  If there is sufficient reduction after 2 minutes, the treatment should be administered at the maintenance dose; if there is still not sufficient reduction after 5 minutes one 50 mg ampoule of urapidil should be injected over 20 seconds. If there is sufficient reduction in blood pressure after 2 minutes, the treatment will be administered at the maintenance dose.

- Intravenous infusion:
  The rate of infusion should be 6 mg/min (264 drips: 13.2 ml/min).

- Administration by syringe pump:
  The flow-rate for administration should be 6 mg/min (3 ml/min).

Maintenance treatment (when the response by blood pressure has been sufficient):

- Administration by intravenous infusion:
  The flow-rate should be from 60 to 180 mg/h [an average of 120, i.e. 44 to 132 drips/h (an average of 88)].

- Administration by syringe pump:
  The flow-rate should be 60 to 180 mg/h [an average of 120, i.e. 30 to 90 ml/h (an average of 60)].
Summary of Product Characteristics
Urapidil Nordic Pharma 5 mg/ml

Use in patients with renal impairment
No initial dosage adjustment is necessary in patients with mild to moderate renal impairment. In patients with severe renal impairment, monitoring of haemodynamic changes might be necessary (see section 4.4).

Use in patients with hepatic impairment
No initial dosage adjustment is necessary in patients with mild to moderate hepatic impairment. Urapidil should be used with caution in patients with severe hepatic impairment (see section 4.4).

Use in the elderly
In elderly, a reduction of the dose might be necessary (see section 4.4)

Use in children and adolescents (< 18 years):
The experience in children is limited.
- Initiation of the treatment: 2 mg/kg/h
- Maintenance of the treatment: 0.8 mg/kg/h

Considering the duration of the toxicological studies available, intravenous urapidil should be used for a maximum of 7 days.

4.3. Contra-indications
- Known allergy to urapidil or any of the constituents.
- Stenosis of the aortic isthmus or an arterio-venous shunt (with the exception of arterio-venous shunts for haemodialyses).

4.4. Special warnings and precautions for use

Warnings
Hypertension during pregnancy: due to the risk to the foetus including foetal death, the drop in blood pressure must be gradual and always controlled.

The rise in hypertension which may often accompany a cerebrovascular accident is not an indication for emergency antihypertensive treatment. The decision should be taken in the light of any short term life-threatening internal organ complications.

Precautions for use
Because of the additive effect of antihypertensive treatments, it is recommended to use them considering their half-life to avoid a too rapid reduction in blood pressure which may cause bradycardia or cardiac arrest.

Caution must be exercised using antihypertensive treatments in the elderly and the starting dose should be lower as the elderly are more sensitive to this type of treatments.

In case of volume depletion (diarrhoea, vomiting), risk of increased antihypertensive effect of urapidil. In patients with renal insufficiency, monitoring of haemodynamic changes may be necessary.

Considering the studies performed with the oral formulation, it is preferable to reduce the dosage in patients with severe hepatic insufficiency.

Urapidil may be administered to children.

Due to the presence of propylene glycol, urapidil may cause symptoms similar to those of alcohol.
4.5. Interactions with other medicinal products and other forms of interaction

**Combinations not recommended:**
- Alpha-blockers given for urological purposes
  Increase in the hypotensive effect. Risk of severe orthostatic hypotension.

**Combinations that are part of precautions for use:**
- Baclofen
  Increase in the antihypertensive effect.
  Monitoring of blood pressure and adjustment of the antihypertensive agent dosage if necessary.

**Combinations to take into consideration:**
- Amifostine
  Increase in hypertension due to the addition of undesirable effects.
- Imipramine antidepressants
  Antihypertensive effect and risk of orthostatic hypotension are increased (additive effect).
- Neuroleptics
  Antihypertensive effect and risk of orthostatic hypotension are increased (additive effect).
- Antihypertensive agents except alpha-blockers
  Increase in the hypotensive effect. Increased risk of orthostatic hypotension.
- Corticoids
  Decrease in the antihypertensive effect (hydro sodium retention of corticoids)

Drinking alcohol can increase the vasodilatation.

4.6. Pregnancy and lactation

**Pregnancy**
The use of Urapidil during pregnancy is not recommended (see section 4.4). There are no adequate data from the use of urapidil in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

**Lactation**
In the absence of data on excretion into mother’s milk, breast-feeding is not recommended in case of treatment with urapidil.

4.7. Effects on ability to drive and use machines

The response to treatment may vary from one patient to another. Urapidil may impair the ability to drive or to use machinery, particularly at the start of treatment, in the event of changes to the treatment, or in the event of concomitant alcohol intake.

4.8. Undesirable effects

Undesirable effects are most often due to a rapid lowering of blood pressure, but they usually disappear in a few minutes or indeed even in the course of injection.

Depending on how serious the undesirable effects are, the possibility of stopping the treatment must be envisaged.
Summary of Product Characteristics
Urapidil Nordic Pharma 5 mg/ml

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Uncommon (≥1/1,000 to ≤1/100)</th>
<th>Very rare (≤1/10,000)</th>
<th>Not known*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Thrombopenia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td>Agitation</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td>Headache; dizziness</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td>Tachycardia; palpitations; bradycardia; feelings of tightness in chest and of dyspnea</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td>Nasal congestion</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea; vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin reactions of the allergic type such as pruritus, erythema and rashes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td>Priapism</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td>Asthenia; sweating</td>
</tr>
</tbody>
</table>

*Cannot be estimated from the available data

4.9. Overdose

Symptoms of intoxication:
The clinical manifestations are of circulatory and neurological type:
- circulatory system: dizziness, orthostatic hypotension, circulatory collapse,
- central nervous system: fatigue, reduction in the speed of reaction.

Treatment of intoxication:
Lay the patient down and initiate a standard treatment for arterial hypotension (restoration of blood volume, catecholamines if necessary).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Antihypertensive, peripherally acting adrenolytic agent/alpha-blocker
ATC code: C02CA06

Urapidil acts as an antihypertensive agent. This vasodilating action is caused by blocking the postsynaptic peripheral alpha 1-adrenergic receptors. The reduction in blood pressure is secondary to the reduction in the total peripheral resistances.

Urapidil has also a central effect. The exact mechanism in humans is not established, but animal studies show a stimulation of the 5HT 1A serotonin receptors. Probably due to this central effect no
reflex tachycardia is seen. Normally the cardiac output stays the same, except for patient with cardiac failure, where a reduced peripheral resistance (afterload) can cause an increase in cardiac output.

After intravenous injection an effect is seen within minutes. A duration of the effect of a few hours can be expected based on the pharmacokinetics.

When there is an increase in pulmonary resistance, for an equal dose of urapidil, the fall in pulmonary resistance is greater than the fall in total peripheral resistances.

No potentiation of a bronchospasm has been found. There is no increase in the secretion of renin and aldosterone. No first-dose effect has been observed, nor tachyphylaxis, nor rebound phenomenon.

In clinical studies, urapidil had no effect on the fluid and electrolyte balance, the lipid metabolism, the tolerability to carbohydrate, hepatic and renal functions and (or) haematological parameters.

In patients suffering from pulmonary disease with chronic respiratory insufficiency (hypoxia and hypercapnia) and secondary pulmonary arterial hypertension, several studies have shown that urapidil has a vasodilatory effect on pulmonary circulation; it does not have any adverse effect on ventilatory function, on bronchoreactivity or on gas exchange.

Studies made in the field of neurosurgery have shown that there is no increase in intracranial pressure and that the intracranial haemodynamic parameters are maintained when urapidil is administered intravenously.

5.2. Pharmacokinetic properties

After intravenous administration, the plasma concentration decreases for 10 minutes and then remains level for about 1 hour. The mean serum half-life of elimination is 2.7 hours. The distribution volume is 0.77 l/kg. The plasma protein binding is 80%.

Urapidil is metabolised principally at the hepatic level, into three metabolites, the main one of which in human is the parahydroxylated derivative (M1), which is inactive.

50-70 % of the dose administered is eliminated in the form of metabolites in the urine, together with 15-50 % of the original product unchanged.

No dose adjustment is necessary in patients with renal impairment. Due to its metabolism, Urapidil might be used with caution in patients with severe hepatic impairment. In elderly patients, the dose might be reduced due to the decreased clearance.

5.3. Preclinical safety data

No data derived from conventional studies of genotoxicity and carcinogenicity are available.

No teratogenic effects of urapidil after oral administration in rats or rabbits were observed, nor were adverse effects observed on the development of the offspring.

Studies in rats and rabbits have shown reproductive toxicity of urapidil. The adverse effects consisted of decreased pregnancy rate in rats; reduced body weight gain and food and water intake in pregnant rabbits; a decreased rate of live rabbit foetuses; and a decreased perinatal survival rate and body weight gain of newborn rats. Because of the limitations of the studies, the potential risk for humans is unknown.
6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Propylene glycol, dihydrated monosodium phosphate, dihydrated disodium phosphate, diluted hydrochloric acid, sodium hydroxide, water for injections.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

No special storage precautions.

6.5. Nature and content of outer packaging

25 mg: 5 ml ampoules (type I glass). Boxes of 1 or 5 ampoules.
50 mg: 10 ml ampoules (type I glass). Boxes of 1 or 5 ampoules.

Not all pack sizes may be marketed.

6.6. Instructions for use, handling and disposal

Like all products for parenteral use, the solution must be checked visually to see that it is free of particles and of any change of colour and to check the integrity of the packaging before use.

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

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/OF RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF TEXT