SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Urapidil Stragen i.v. 25 mg solution for injection
Urapidil Stragen i.v. 50 mg solution for injection
Urapidil Stragen i.v. 100 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 5 mg urapidil.

5 ml ampoule contains 25 mg urapidil.
10 ml ampoule contains 50 mg urapidil.
20 ml ampoule contains 100 mg urapidil.

For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

25 mg/ 50 mg: Solution for injection, which could also be diluted for infusion purposes.
100 mg: Concentrate for solution for infusion.

Clear, colourless solution with a pH of 5.6 to 6.6.
Free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertensive emergencies (e.g. a critical rise in blood pressure), severe and very severe forms of hypertensive disease, hypertension resistant to treatment.

Controlled lowering of blood pressure in hypertensive patients during and/or after surgery.

4.2 Posology and method of administration

For hypertensive emergencies, severe and very severe forms of hypertension, and treatment resistant hypertension

Intravenous injection
10-50 mg urapidil is slowly administered by intravenous injection - while constantly monitoring the blood pressure. A fall in blood pressure can be expected within 5 min. of administering the injection. The injection of 10-50 mg urapidil can be repeated depending how the blood pressure reacts.

Intravenous infusion or syringe pump are used to maintain the level of blood pressure achieved by the injection.
For instructions on dilution of the medicinal product before administration, see section 6.6.

The maximum quantity compatible is 4 mg urapidil per ml of solution for infusion.

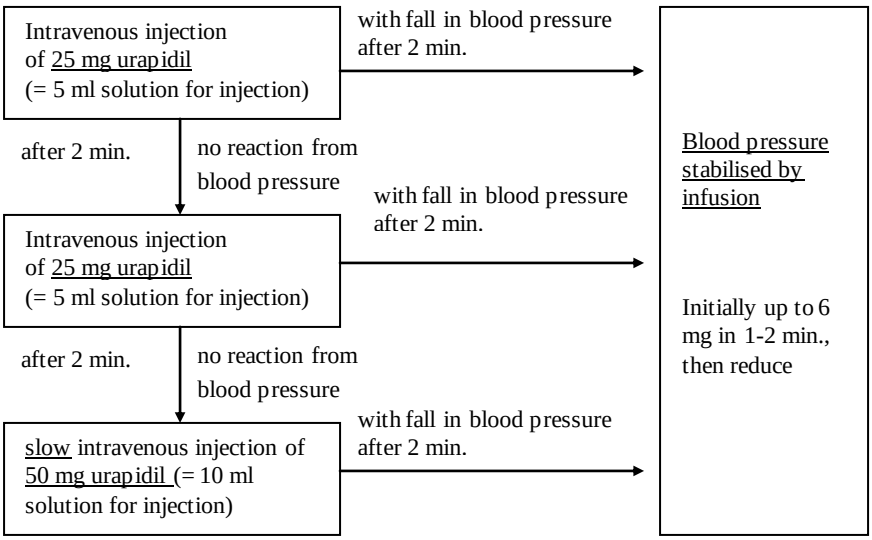
Speed of administration: The infusion rate is determined from the individual blood pressure situation. Initial recommended maximum infusion rate: 2 mg/min.

Maintenance dose: On average 9 mg/h, referring to 250 mg urapidil added to 500 ml solution for infusion corresponding to 1 mg = 44 drops = 2.2 ml.

Controlled lowering of blood pressure when blood pressure is raised during and/or after surgery

Intravenous infusion or syringe pump is used to maintain the level of blood pressure achieved by the injection.

Dosage regimen



Note
Urapidil Stragen i.v. is administered intravenously as an injection or infusion to supine patients. The dose may be administered as one or several injections or as slow intravenous infusion. Injections can be combined with subsequent slow infusion.

Elderly
In elderly patients antihypertensive agents must be administered with appropriate care and at the beginning in small doses, as in these patients sensitivity to these kinds of preparations is often modified.

Patients with kidney and/or liver function disorders
In patients with kidney and/or liver function disorders it may be necessary to reduce the dose of urapidil.

Paediatric population
Safety and efficacy of intravenous urapidil in children aged 0-18 years have not been established. No recommendation on a posology can be made.

Duration of treatment
A period of treatment of 7 days has been found to be safe from a toxicological point of view; with parenteral antihypertensive drugs this period should also not, in general, be exceeded. Renewed parenteral treatment is possible if the blood pressure rises again.
It is possible to overlap acute parenteral therapy with changing to continuous treatment with oral

agents that lower blood pressure.

4.3 Contraindications

Urapidil Stragen i.v. should not be used if there is hypersensitivity (allergy) to the active substance or to any of the ingredients. Urapidil Stragen i.v. should not be used in cases of aortic isthmus stenosis and arteriovenous shunt (except where the dialysis shunt is not haemodynamically active).

4.4 Special warnings and precautions for use

Precautions for use

- In cardiac insufficiency caused by mechanical function impairment, such as stenosis of the aortic or mitral valves, pulmonary embolism or limited cardiac action due to pericardial disease;

- In patients with liver function disorders;
- In patients with moderate to severe kidney function disorders;
- In elderly patients;
- In patients who are receiving cimetidine concomitantly (see section 4.5 Interaction with other medicinal products and other forms of interaction).

If urapidil is not being administered as the first-line antihypertensive agent, a sufficiently long time must be allowed to pass for the effect of the previously administered antihypertensive drug(s) to be observed. The dose of urapidil chosen should be correspondingly lower.
A too rapid fall in blood pressure can lead to bradycardia or cardiac arrest.

Due to the presence of propylene glycol, symptoms similar those of alcohol may be observed when administering Urapidil Stragen i.v.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction

The antihypertensive action of urapidil can be exacerbated by concomitant administration of alpha-receptor blockers including those given for urological conditions, vasodilators and other blood pressure lowering drugs, and in conditions involving hypovolaemia (diarrhoea, vomiting) and alcohol.

The combination of urapidil with baclofen should be considered cautiously, as baclofen can increase the antihypertensive effect.

Cimetidine administered concomitantly inhibits the metabolism of urapidil. Urapidil serum concentration is likely to increase by 15%, so that dosage reduction should be considered

Consideration should be given to the following concomitant administration:
- imipramine (antihypertensive effect and risk of orthostatic hypotension);
- neuroleptics (antihypertensive effect and risk of orthostatic hypotension) and
- corticoids (decrease in the antihypertensive effect by hydro sodium retention).

As no adequate experience yet exists of combining treatment with ACE inhibitors, this is not at the moment recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
Urapidil Stragen i.v. during pregnancy is not recommended. There is no adequate data from the use of urapidil in pregnant women.
Studies in animals have shown reproductive toxicity without teratogenicity (section 5.3). Because of the limitations of the studies, the potential risk for humans is unknown.

Breastfeeding
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

This medicinal product has minor influence on the ability to drive and use machines.
The response to treatment may vary from one patient to another. This applies most particularly at the start of treatment, after changes to treatment, or in the event of concomitant alcohol intake.

4.8 Undesirable effects

In the majority of cases the following undesirable effects can be attributed to too rapid a fall in blood pressure; however, experience shows that they disappear within minutes, even during slow infusion, so that interrupting the treatment must be decided depending on the degree of severity of the undesirable effect.

Frequency / System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,1000	Very rare (<1/10,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders					Thrombocytope-nia	
Cardiac disorders			Palpitations; Tachycardia; Bradycardia; Chest pressure sensation; Respiratory distress; Cardiac dysrhythmias			
Gastrointestinal disorders		Nausea	Vomiting			
General disorders and administration site conditions			Fatigue		Asthenia,	
Nervous system disorders		Dizziness, Headaches				

Psychiatric disorders					Restlessness	
Reproductive system and breast disorders				Priapism		
Respiratory, thoracic and mediastinal disorders				Nasal congestion		
Skin and subcutaneous tissue disorders			Sweating	Symptoms of cutaneous allergic reactions (pruritus, rashes, exanthema)		

4.9 Overdose

Symptoms
Symptoms of overdose are dizziness, orthostatic hypotension and collapse as well as fatigue and decreased reactivity.

Treatment of overdose
An excessive fall in blood pressure can be corrected by raising the legs and performing volume replacement. If these measures are not sufficient, vasoconstricting preparations can be slowly injected intravenously while monitoring the blood pressure. In very rare cases the administration of catecholamines (e.g. adrenaline, 0.5-1.0 mg diluted to 10 ml with isotonic sodium chloride solution) is necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING, Alpha-adrenoreceptor antigonists
ATC code: C02CA06

Urapidil results in a drop in the systolic and diastolic blood pressure through a reduction in the peripheral resistance.
Heart rate remains largely constant.
Cardiac output is not modified; cardiac output reduced as a result of increased afterload may increase.

Mechanism of action
Urapidil has both central and peripheral effects.

- Peripheral: Urapidil predominantly blocks postsynaptic alpha-receptors and consequently inhibits the vasoconstrictor effect of catecholamines.

- Central: Urapidil has also a central effect. It modulated the activity of the cerebral centers which control the circulatory system. Thus, a reactive increase in sympathetic tone is inhibited or the sympathetic tone is reduced.

5.2 Pharmacokinetic properties

Following intravenous administration of 25 mg urapidil, the serum concentration (initial distribution phase, terminal elimination phase) is biphasic. The distribution phase has a half-life of approx. 35 min. The volume of distribution is 0.8 (0.6-1.2) l/kg.
Urapidil is predominantly metabolised in the liver. The principal metabolite is urapidil hydroxylated in the 4 position on the phenyl nucleus, which has no notable antihypertensive action. The metabolite of O-demethylated urapidil has roughly the same biological activity as urapidil, but arises to a much lesser extent.
50-70% of urapidil and its metabolites are eliminated in humans via the kidneys, including about 15% of the dose administered as pharmacologically active urapidil; the remainder is excreted in the faeces as metabolites, primarily as para-hydroxylated urapidil which does not lower the blood pressure.
After intravenous bolus injection, the elimination half-life from the serum has been found to be 2.7 (1.8-3.9) h. Plasma protein binding of urapidil (human serum) is 80% in vitro. This relatively low plasma protein binding of urapidil could explain why to date no interactions are known between urapidil and drugs bound strongly to plasma protein.
In advanced hepatic and/or renal insufficiency and in elderly patients, the volume of distribution and clearance of urapidil is reduced, and the elimination half-life extended.
Urapidil penetrates the blood-brain barrier and passes through the placenta.

5.3 Preclinical safety data

Acute toxicity
Studies with urapidil hydrochloride have been performed in mice and rats to test acute toxicity. The LD_{50} (referring to urapidil base) following oral administration is between 508 and 750 mg/kg BW and following intravenous administration, between 140 and 260 mg/kg BW.
Toxicity was observed predominantly as sedation, ptosis, reduced motility, loss of the protective reflex and hypothermia, gasping for breath, cyanosis, tremor and convulsions before death.

Chronic toxicity /Sub-chronic toxicity
Studies on chronic toxicity have been performed in rats after oral administration with food over 6 and 12 months, using doses up to 250 mg/kg BW/day. Sedation, ptosis, reduced increase in body weight, lengthening of the oestrus cycle and reduced uterus weight were observed.
Chronic toxicity was investigated in the dog in studies over 6 and 12 months with doses up to 64 mg/kg BW. Doses from 30 mg/kg BW/day caused sedation, hypersalivation and tremor. No clinical or histopathological changes were found in the dog.

Mutagenic and tumour inducing potential
In bacterial studies (the AMES test, the host-mediated assay), investigations on human lymphocytes and the bone marrow metaphase test on the mouse, urapidil exhibited no mutagenic characteristics. A test of DNA repair on rat hepatocytes was negative.

Carcinogenic studies in mice and rats over 18 and 24 months produced no indications relevant to humans of tumour inducing potential. In special studies in rats and mice urapidil was found to raise the prolactin level. In the rodent a raised prolactin level leads to stimulation of the growth of mammary tissue. In view of what is known of the mechanism of action, this effect is not expected to occur in humans receiving therapeutic doses, and could not be established in clinical trials.

Reproductive toxicity
Studies on reproduction toxicity in the rat, mouse and rabbit produced no indication of a teratogenic effect.
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.

The reproduction study established that the oestrus cycle of female rats was lengthened, as the study

for chronic toxicity had also established. This effect, like the decreased weight of the uterus in the chronic test, is considered a result of the raised prolactin level occurring in rodents after treatment with urapidil. The fertility of the females was not impaired.

Owing to the considerable differences between the species however, these results cannot be considered as applicable to humans. In long-term clinical studies no influence on the pituitary gonad axis in the woman could be established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol,
sodium dihydrogen phosphate dihydrate,
hydrochloric acid (37 % w/w),
disodium phosphate dihydrate,
hydrochloric acid (3.7 % w/w),
sodium hydroxide (4 % w/w),
water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
The following active substance(s) [or solution for reconstitution/dilution] should not be administered simultaneously:
alkaline injection and infusion solutions
This may cause turbidity or flocculation.

6.3 Shelf life

3 years.

After first opening/dilution:
Chemical and physical in use stability has been demonstrated for 50 hours at 15-25 °C.
From the microbiological point of view, the product should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8° C, unless reconstitution/dilution has been taken place in controlled and validated conditions.

6.4 Special precautions for storage

Do not store above 30°C.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of the container

Ampoules of clear glass (type I Ph. Eur.)
Pack size: 5 ampoules

6.6 Special precautions for disposal

The 100 mg ampoule can only be used for stabilisation of blood pressure by infusion.
For the initial treatment ampoules containing 25 mg and 50 mg urapidil are available. These dosage strengths can also be used for intravenous infusion after dilution.

The dilution is made under aseptic conditions.

The solution should be expected visually for particulate matter and discoloration prior to administration. Only clear and colourless solution should be used.

Preparation of diluted solution:
- Intravenous infusion:
Add 250 mg urapidil (2 ampoules of 100 mg urapidil + 1 ampoule of 50 mg urapidil) to 500 ml of one of the compatible solvents.

- Syringe pump:
100 mg urapidil is drawn up into a syringe pump and diluted to a volume of 50 ml with one of the compatible solvents.

Compatible solvents for dilution:
- Sodium chloride 9 mg/ml (0.9%) solution for infusion
- Glucose 50 mg/ml (5%)
- Glucose 100 mg/ml (10%)

For single use only.
Any unused solution and the "bags/sachets" should be adequately disposed of, in accordance with local requirements".

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}>
<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<[To be completed nationally]>