

Ebrantil® i.v. 25 mg

1. NAME OF THE MEDICINAL PRODUCT

Ebrantil i.v. 25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: urapidil hydrochloride

5 ml solution for injection contains:
27.35 mg Urapidil hydrochloride
(equivalent to 25 mg urapidil)

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertensive emergencies (e.g. hypertensive crises), severe to very severe forms of hypertensive illness, therapy-resistant hypertension.
Controlled reduction of blood pressure in hypertensive patients during and/or after surgery.

4.2 Posology and method of administration

Hypertensive emergencies, severe to very severe forms of hypertension and therapy-resistant hypertension

1) Intravenous injection
10-50 mg urapidil is administered as a slow intravenous injection, with continuous blood pressure monitoring. A hypotensive effect can be expected within 5 minutes after injection.

Depending on the blood pressure response, the Ebrantil i.v. 25 mg injection may be repeated.

2) Slow intravenous drip infusion or continuous infusion via infusion pump (perfusor)

The drip infusion solution for maintaining the blood pressure levels achieved with the injection is prepared as follows:

Generally, 250 mg urapidil (10 Ebrantil i.v. 25 mg ampoules) is added to 500 ml of a compatible solution for infusion, e.g. glucose solution (5% or 10%) or physiological saline solution.

When using an infusion pump (perfusor) to administer the maintenance dose, 20 ml solution for injection (= 100 mg urapidil) is drawn up into the perfusor syringe and diluted to a volume of 50 ml with a compatible solution for infusion (see above).

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

Rate of administration

The infusion rate should be based on individual blood pressure response.

Initial recommended rate

2 mg/min

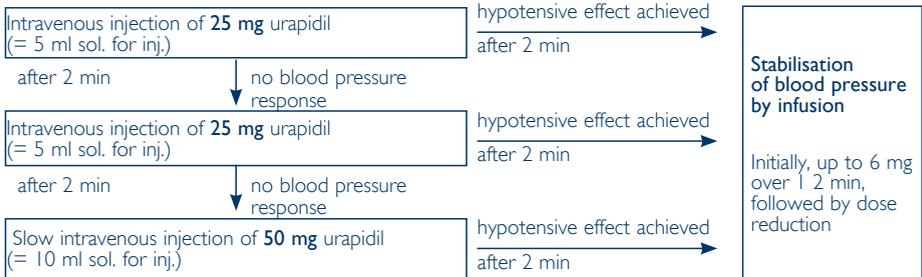
Maintenance dose

9 mg/h on average, referred to 250 mg urapidil added to 500 ml solution for infusion = 1 mg = 44 drops = 2.2 ml.

Controlled reduction of blood pressure to manage hypertensive episodes during and/or after surgery

Continuous infusion via an infusion pump (perfusor) or a slow intravenous drip is used to maintain blood pressure levels achieved with the injection.

Dosage schedule



NB:

Ebrantil i.v. 25 mg is administered intravenously as an injection or infusion to the supine patient. Single or multiple injections, as well as long-term infusions, are possible. Injections may be combined with

subsequent long-term infusions.

Overlapping with acute parenteral therapy, a switch to maintenance treatment with Ebrantil prolonged-release capsules (recommended initial dosage: 2 x 60 mg) or other orally administered antihypertensives is possible.

A treatment period of 7 days is considered to be safe



from the toxicological point of view, and it is usually not exceeded in parenteral antihypertensive therapy. Parenteral treatment may be repeated if hypertension should reoccur.

Specific patient groups

In elderly patients, antihypertensive medication must be administered with appropriate caution, with smaller doses given at the start of treatment, as sensitivity to such preparations is often increased within this patient group.

In patients with renal and/or hepatic dysfunction, the Ebrantil i.v. 25 mg dose may need to be reduced.

4.3 Contraindications

Ebrantil i.v. 25 mg must not be used in patients who are hypersensitive (allergic) to any of its ingredients.

Ebrantil i.v. 25 mg should not be used in patients with aortic isthmus stenosis and arteriovenous shunt (exception: patients with haemodynamically inactive dialysis shunt).

4.4 Special warnings and precautions for use

Particular caution is advised when using Ebrantil i.v. 25 mg in

- heart failure caused by a mechanical dysfunction, e.g. aortic or mitral valve stenosis, pulmonary embolism or impairment of cardiac function due to pericardial disease;
- children, as no studies are available;
- patients with liver dysfunction;
- patients with moderate to severe renal dysfunction;
- elderly patients;
- patients receiving concomitant cimetidine (cf. Section 4.5: "Interaction with other medicinal products and other forms of interaction").

If Ebrantil i.v. 25 mg is not the first antihypertensive agent given, sufficient time should be allowed for the previous hypotensive drug(s) to take effect. The Ebrantil i.v. 25 mg dosage should be reduced accordingly. Bradycardia or cardiac arrest may result if blood pressure drops too rapidly.

4.5 Interaction with other medicinal products and other forms of interaction

The antihypertensive effect of Ebrantil i.v. 25 mg may be potentiated by concomitant administration/use of alpha receptor blockers, vasodilators and other hypotensive agents or alcohol, as well as in volume-depleted patients (dianthoia, vomiting).

Co-administration of cimetidine causes peak serum urapidil concentrations to rise by 15%.

Since sufficient information on combination treatment with ACE inhibitors is not yet available, such treatment is at present not recommended.

4.6 Pregnancy and lactation

Ebrantil i.v. 25 mg should be administered during pregnancy only when strictly indicated, as there is no experience on the safety of use during the first and second trimesters, and only insufficient experience with its use during the third trimester. Studies in animals have not brought to light any evidence of damage to the embryo.

Ebrantil i.v. 25 mg must not be administered during lactation.

4.7 Effects on ability to drive and use machines

Because response to treatment varies between individuals, the speed of reaction can be affected to such an extent that the ability to drive, operate machinery or work without proper safeguards may be impaired. This applies particularly at the start of treatment, whenever there is a dose increase/ change of product and in combination with alcohol.

4.8 Undesirable effects

In most cases, the following undesirable effects are attributable to an excessively rapid fall in blood pressure; clinical experience has shown that such effects resolve within minutes, even during long-term infusions. Any decision to discontinue treatment must therefore be made in consideration of the severity of the adverse effects.

The assessment of undesirable effects is based on the following frequencies:

Very common (≥ 1/10)

Common (≥ 1/100 to < 1/10)

Uncommon (≥ 1/1,000 to < 1/100)

Rare (≥ 1/10,000 to < 1/1,000)

Very rare (< 1/10,000)

Not known (cannot be estimated from the available data)

Frequency Organ system	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (≤ 1/10,000)
Cardiac disorders		palpitations; tachycardia; bradycardia; sensation of pressure behind breast-bone; difficult breathing		
Gastrointestinal tract disorders	nausea	vomiting		
General disorders and administration site conditions		fatigue		

Investigations		irregular heartbeat		reduced platelet count*
Nervous system disorders	dizziness; headache			
Psychiatric disorders				restlessness
Reproductive system and breast disorders			priapism	
Respiratory, thoracic and mediastinal disorders			nasal congestion	
Skin and sub-cutaneous tissue disorders		profuse sweating	allergic reactions (itching, skin redness, exanthema)	

* In very rare isolated cases, a reduction in the platelet count has been observed in temporal association with oral administration of urapidil. However, it was not possible to demonstrate any causal link with Ebrantil therapy, e.g. by immunohaematological investigations.

If you experience any side effects not listed in this package leaflet, please tell your doctor or pharmacist.

4.9 Overdose

Signs of overdosage include

cardiovascular

dizziness, orthostatic hypotension and collapse

central nervous system

tiredness and reduced reactivity.

Treatment of overdosage:

An excessive fall in blood pressure can be improved by raising the legs and administering volume replacement therapy. If these measures prove insufficient, vasoconstrictors may be injected slowly and intravenously, with monitoring of the patient's blood pressure. In very rare cases, the administration of catecholamines is required (e.g. adrenaline 0.5 – 1.0 mg diluted to 10 ml with isotonic sodium chloride solution).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

peripherally-acting anti-adrenergic agents

ATC code: C02CA06

Urapidil brings about a reduction in systolic and diastolic blood pressure by reducing peripheral resistance.

For the most part, the heart rate remains constant.

Cardiac output remains unchanged; reduced cardiac output due to increased afterload may rise.

Mechanism of action

Urapidil has central and peripheral effects.

Peripherally, urapidil predominantly blocks postsynaptic alpha₁ receptors, thereby inhibiting the vasoconstrictive action of catecholamines.

Centrally, urapidil modulates the activity of circulatory

regulation centres, which prevents a reflexory increase in sympathetic tone or reduces sympathetic tone.

5.2 Pharmacokinetic properties

Following intravenous administration of 25 mg urapidil, a biphasic course of blood concentrations is observed (initial distribution phase, terminal elimination phase).

The distribution phase has a half-life of around 35 minutes. The volume of distribution is 0.8 (0.6-1.2) l/kg. Urapidil is predominantly metabolised in the liver. Its main metabolite is urapidil hydroxylated at position 4 of the phenyl ring; it has no appreciable antihypertensive activity. The O-demethylated urapidil metabolite has roughly the same biological activity as urapidil, but is produced only in small quantities.

In humans, renal elimination of urapidil and its metabolites is 50 - 70%, of which around 15% of the administered dose is pharmacologically active urapidil; the remainder is excreted with the faeces in the form of metabolites, primarily as non-hypotensive parahydroxylated urapidil.

The serum elimination half-life of urapidil after intravenous bolus injection is 2.7 (1.8-3.9) hours.

Plasma protein binding of urapidil (human serum) is 80% in vitro. This relatively low plasma protein binding property of urapidil might explain why there are hitherto no known interactions between urapidil and highly plasma protein bound drugs.

In patients with advanced liver and/or kidney failure, and in elderly patients, the volume of distribution and the clearance of urapidil are reduced and the elimination half-life is prolonged.

The substance crosses the blood-brain barrier and penetrates to the placenta.

5.3 Preclinical safety data

a. Acute toxicity

Acute toxicity studies with urapidil hydrochloride have been performed in mice and rats. The LD50 values (referred to urapidil base) range between 508 and 750 mg/kg body weight after oral administration, and between 140 and 260 mg/kg body weight after intravenous administration.

The predominant signs of intoxication were sedation, ptosis, reduced motility, loss of protective reflexes and hypothermia, gasping breathing, cyanosis, tremor and pre-terminal convulsions.

b. Chronic toxicity/subchronic toxicity

Chronic toxicity studies have been performed in rats with dosages of up to 250 mg/kg body weight/day, administered orally with the feed for 6 and 12 months. The following were observed: sedation, ptosis, reduced weight gain, prolongation of the oestrous cycle, and reduced uterine weight.

In the dog, chronic toxicity has been investigated in studies over 6 and 12 months, at dosages of up to 64 mg/kg body weight. Dosages of 30 mg/kg body weight/day and above caused sedation, hypersalivation and tremor. No clinical or histopathological changes were observed in the dog.

c. Mutagenic and tumorigenic potential

Urapidil showed no mutagenic properties in tests on bacteria (AMES test, host-mediated assay), human lymphocytes and in the bone marrow metaphase test in the mouse. A DNA repair test using rat hepatocytes was negative.

Carcinogenicity studies in mice and rats over 18 and 24 months have not produced evidence of any tumorigenic potential of relevance for humans. In specific mouse and rat studies, urapidil was shown to increase prolactin levels. In rodents, elevated prolactin stimulates the growth of mammary tissue. On the basis of knowledge regarding the mechanism of action of urapidil, this effect is not expected to occur in humans at therapeutic doses and could not be proven in clinical studies.

d. Reproductive toxicity

Reproductive toxicity studies in rats, mice and rabbits have not brought to light any evidence of a teratogenic effect.

Prolongation of the oestrous cycle in female rats was established in the reproduction study as well as in the chronic toxicity studies. This effect, just like the reduced uterine weight observed in the chronic study, is considered to be the result of increased prolactin levels occurring in rodents after treatment with urapidil. Female fertility was not impaired.

Because of the considerable differences between species, there is no evidence that these findings are relevant in humans. In clinical long-term studies, no effect on the female pituitary-gonad system was established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol 500 mg
Sodium dihydrogen phosphate
Disodium hydrogen phosphate
Water for injections

6.2 Incompatibilities

Ebrantil i.v. 25 mg should not be mixed with alkaline solu-

tions for injection or infusion, as clouding or flocculation may occur due to the acidic properties of the solution for injection.

6.3 Shelf life

The chemical and physical stability of the ready-to-use preparation has been demonstrated for 50 hours at 15-25°C. From a microbiological point of view, the ready-to-use preparation should be used immediately. If ready-to-use preparations are not used immediately, the user shall be responsible for the duration and conditions of storage.

Ebrantil i.v. 25 mg solution for injection is stable for 2 years.

Ebrantil i.v. 25 mg solution for injection should not be used after the expiry date.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Clear glass ampoules (type I Ph. Eur.)

Packs of five 5 ml ampoules (= 25 mg)

Hospital packs containing 50 (10x5) 5 ml ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

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Manufactured by
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D-78224 Singen

8. MARKETING AUTHORIZATION NUMBER(S)

11941.00.00

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

24. August 1988 / 03. June 2005

10. DATE OF REVISION OF THE TEXT

June 2011

11. PRESCRIPTION STATUS / LEGAL CATEGORY

Prescription-only medicine