# SUMMARY OF PRODUCT CHARATERISTICS

## HYPERIUM

## I.N.N. : Rilmenidine

## 1. DENOMINATION

HYPERIUM 1 mg, tablets

## 2. COMPOSITION

Rilmenidine (I.N.N.) dihydrogenphosphate ….1.544 mg
amount equivalent to rilmenidine base……1 mg
Excipients q.s. for one tablet.

## 3. PHARMACEUTICAL FORM

Tablet

## 4. CLINICAL DATA

### 4.1. THERAPEUTIC INDICATIONS

Hypertension.

### 4.2. DOSAGE AND METHOD OF ADMINISTRATION

The recommended dosage is 1 tablet per day as a single morning administration.
If results are not adequate after one month of treatment, the dosage may be increased to 2 tablets per day, given in divided doses (1 tablet morning and evening) before meals.

As a result of its good clinical and biological acceptability, HYPERIUM may be administered to both elderly and diabetic hypertensive patients.

In patients with renal insufficiency, no dosage adjustment is necessary in principle when the creatinine clearance is greater than 15 ml/min.
Treatment may be continued indefinitely.

### 4.3. CONTRA-INDICATIONS

This medicine MUST NEVER BE used in the following cases:

- hypersensitivity to one of the ingredients
- severe depression,
- severe renal insufficiency (creatinine clearance < 15 ml/min),
- in combination with sultopride.

This medicine SHOULD NOT GENERALLY be used in the following cases:
in combination with:

- alcohol,
- beta-blockers used in heart failure (bisoprolol, carvedilol, metoprolol) (See Section 4.5 Interactions with other medicinal products and other forms of interactions).

## 4.4. WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Therapy should never be interrupted suddenly, the dosage should be reduced gradually.
As with all antihypertensive agents, regular medical monitoring is required when HYPERIUM is administered to patients with a recent history of cardiovascular disease (stroke, myocardial infarction).
Alcohol consumption should be avoided during treatment.
In patients with renal insufficiency, no dosage adjustment is necessary if creatinine clearance is greater than 15 ml/min.
In the absence of documented experiments in this area, HYPERIUM is not recommended for prescription to children.

## 4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

***Contraindicated associations***

+ **Sultopride**
  Increased risk of ventricular arrhythmias, particularly torsades de pointes.

***Inadvisable associations***

+ **Alcohol**
  Alcohol increases the sedative effect of these substances. Impaired vigilance may render driving of vehicles and use of machinery dangerous. Alcoholic beverages and medicines containing alcohol should be avoided.

+ **Beta-blockers used in heart failure (bisoprolol, carvedilol, metoprolol)**
  Central reduction of sympathetic tone and vasodilator effect of centrally acting antihypertensive agents that may be harmful in patients with heart failure undergoing treatment with beta-blockers and vasodilators.

***Combinations requiring cautions for use***

+ **Baclofen**
  Increased antihypertensive effect; blood pressure must be monitored and the dosage of the antihypertensive agent adjusted if necessary.

+ **Beta-blockers**
  Marked increase in blood pressure in the event of abrupt discontinuation of treatment with the central antihypertensive agent.

Avoid abrupt discontinuation of the central antihypertensive agent. Clinical monitoring is required.

+ **Medicines that induce torsades de pointes (except sultopride):**
  - **class Ia antiarrhythmic agents (quinidine, hydroquinidine, disopyramide);**
  - **class III antiarrhythmic agents (amiodarone, dofetilide, ibutilide, sotalol);**
  - **certain neuroleptics: phenothiazines (chlorpromazine, levomepromazine, thioridazine), benzamides (amisulpride, sulpiride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide);**
  - **other drugs: bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, moxifloxacin, pentamidine, spiramycin IV, vincamine IV.**

  Increased risk of ventricular arrhythmias, particularly torsades de pointes.
  Clinical and electrocardiographic monitoring.

***Combinations to be taken into consideration***

+ **Alpha-blockers**
  Potentiation of hypotensive effect. Increased risk of orthostatic hypotension.

+ **Amifostine**
  Increased antihypertensive effect.

+ **Corticosteroids, tetracosactide (systemic route) (except hydrocortisone used as replacement therapy in Addison's disease)**
  Reduced antihypertensive effect (water/sodium retention through corticosteroids)

+ **Neuroleptics, imipramine antidepressants**
  Increased antihypertensive effect and risk of orthostatic hypotension (cumulative effect).

+ **Other CNS depressants: morphine derivatives (analgesics, antitussive agents and replacement treatments), benzodiazepines, anxiolytics other than benzodiazepines, hypnotics, neuroleptics, sedative $H_1$ histamine antagonists, sedative antidepressants (amitriptyline, doxepine, mianserine, mirtazapine, trimipramine), other centrally acting antihypertensive agents, baclofen, thalidomide, pizotifen, indoramin.**

  Increased central depression. Impaired vigilance may render driving vehicles and operation of machinery dangerous.

## 4.6. PREGNANCY AND BREAST-FEEDING

- Pregnancy : as with all new molecules, administration of HYPERIUM should be avoided in pregnant women, although no teratogenic or embryotoxic effects have been observed in animal studies.
- Lactation **:** HYPERIUM is excreted in breast milk, its use is therefore not recommended during lactation.

## 4.7. EFFECTS ON THE ABILITY TO DRIVE MOTOR VEHICLES OR OPERATE MACHINERY

Double-blind placebo controlled studies have not shown HYPERIUM to have any effect on alertness at therapeutic doses (1or 2 daily administrations of 1 mg). If these doses are exceeded or if HYPERIUM is associated with other drugs capable of reducing alertness, vehicle drivers or machine operators should be warned of the possibility of drowsiness.

## 4.8. SIDE-EFFECTS

At the dose of 1 mg in a single daily administration, during controlled studies, the incidence of undesirable effects was comparable to that observed with placebo.

At a dose of 2 mg of HYPERIUM daily, the controlled comparative studies versus clonidine at a dose of 0.15 to 0.30 mg/day or alphamethyldopa at a dose of 500 to 1000 mg/day showed that the incidence of undesirable effects was significantly lower than that observed with clonidine or alphamethyldopa.

Incidence estimate: Very common: (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1 000, <1/100), Rare (≥1/10 000, <1/1 000), Very Rare: (< 1/10 0000)

Cardiac disorders
Common: palpitations

Nervous system disorders
Common: drowsiness.

Skin and subcutaneous tissue disorders
Common: pruritus, rash

Reproductive system and breast disorders
Common: sexual dysfunction

Gastrointestinal disorders
Common: gastralgia, dry mouth, diarrhoea, constipation
Uncommon: nausea

Musculoskeletal disorders
Common: muscle cramps

Psychiatric disorders
Common: anxiety, depression, insomnia

Vascular disorders
Common: cold in the extremities, oedema
Uncommon: hot flushes, orthostatic hypotension

General disorders

Common: asthenia, fatigue on effort

## 4.9. OVERDOSAGE

No cases of massive absorption have been reported. Likely symptoms in such an eventuality would be marked hypotension and lowered alertness. In addition to gastric lavage, sympathomimetic agents may also be required. HYPERIUM is only slightly dialysable.

## 5. PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

- HYPERIUM, an oxazoline compound with anti-hypertensive properties acts on both medullary and peripheral vasomotor structures. HYPERIUM shows greater selectivity for "imidazoline" receptors than for cerebral alpha-2-adrenergic receptors, distinguishing it from reference alpha-2-agonists.

- HYPERIUM exerts dose-dependent antihypertensive effect in the congenitally hypertensive rat. Its effects are not associated with the central neuropharmacological effects usually seen with alpha 2 agonists, except at doses higher than the antihypertensive dose in animals. In particular, the sedative effect appears to be considerably less marked.

- This dissociation between the antihypertensive activity and neuropharmacological effects has been confirmed in man.
  HYPERIUM exerts a dose-dependent antihypertensive activity on the systolic and diastolic blood pressure in both the erect and supine positions. At therapeutic doses (1mg per day as a single administration or 2 mg per day in divided doses), double- blind studies versus placebo and reference product have demonstrated the antihypertensive efficacy of HYPERIUM in mild to moderate hypertension. This efficacy is maintained throughout the 24-hour period and on exercise. These results have been confirmed over the long-term, without the development of tolerance.
  With the dose of 1 mg per day, double-blind placebo controlled studies have shown that HYPERIUM does not affect tests of alertness. The incidence of side-effects (drowsiness, dryness of the mouth, constipation) was no different than that seen with placebo.
  With the dose of 2 mg per day, double-blind studies versus a reference alpha-2-agonist administered at an equihypotensive dose demonstrated that the incidence of side-effects, and the severity of these effects were significantly lower with HYPERIUM.

- At therapeutic doses, HYPERIUM has no effect on cardiac function, does not cause salt and water retention and does not disturb metabolic equilibrium :

  - HYPERIUM continues to exert significant antihypertensive activity 24 hours after administration, with a reduction in total peripheral resistance, but no change in cardiac output. Indices of contractility and cardiac electrophysiology are not affected.

  - HYPERIUM does not cause postural hypotension (particularly in the elderly) and does not interfere with the physiological increase in heart rate on exercise.

  - HYPERIUM does not induce any changes in renal blood flow, glomerular filtration rate or filtration fraction, and does not affect kidney function.

  - HYPERIUM spares glucose metabolism (including that of diabetic subjects, whether insulin or non-insulin dependent), and does not affect lipid metabolism.

## 5.2. PHARMACOKINETICS PROPERTIES

**Absorption :**
- is rapid : the peak plasma concentration (3.5 ng/ml) is reached 1.5 to 2 hours following absorption of a single dose of 1 mg of HYPERIUM ;
- is complete : the absolute bioavailability is 100 %, there is no hepatic first-pass effect ;
- is consistent : interindividual variation is not marked, and concomitant food consumption does not affect the bioavailability. There is no variation in absorption levels at the recommended therapeutic doses.

**Distribution** : protein binding is less than 10%. The volume of distribution is 5 l/kg.

**Metabolism** : HYPERIUM is only very slightly metabolised. The metabolites are found in trace amounts in the urine and result from the hydrolysis or oxidation of the oxazoline ring. These metabolites are devoid of alpha 2 agonist activity.

**Elimination** : HYPERIUM is essentially eliminated by the kidney : 65 % of the dose administered is excreted unchanged in the urine. Renal clearance represents two thirds of total clearance.
The elimination half-life is 8 hours. This is not affected by the dose administered nor by repeated administration. The pharmacological duration of action is longer, significant antihypertensive activity being maintained to 24 h after administration in hypertensive patients treated with a dose of 1 mg per day.

Repeated administration : Steady state is attained at 3 days ; study of plasma levels has shown that they remain stable over 10 days.

Long-term monitoring of plasma levels in hypertensive patients (treatment for 2 years) has established that plasma levels of HYPERIUM remain stable.

In elderly subjects : pharmacokinetic studies in elderly patients (over 70 years old) have demonstrated an elimination half-life of 12 hours.

In subjects with hepatic insufficiency : the elimination half-life is 11 hours.

In subjects with renal insufficiency : as a result of the essentially renal elimination of the drug, a reduction in the rate of elimination is observed proportional to the severity of the renal insufficiency. In patients with severe renal insufficiency (creatinine clearance less than 15 ml/min), the elimination half-life is approximately 35 hours.

## 5.3 PRECLINICAL SAFETY DATA

Not applicable

# 6. PHARMACEUTICAL DATA

## 6.1 INCOMPATIBILITIES

Not applicable

## 6.2 SHELF-LIFE

3 years

## 6.3 SPECIAL STORAGE PRECAUTIONS

Store up to 30°C.