SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hypovase 0.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Prazosin hydrochloride equivalent to 500 micrograms prazosin base, based on potency of 93.1 % base activity.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

White and round marked “Pfizer” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension: Hypovase is indicated in the treatment of all grades of essential (primary) hypertension and all grades of secondary hypertension of varied aetiology. It can be used as the initial and sole agent or it may be employed in a treatment regimen in conjunction with a diuretic and/or other antihypertensive drug as needed for proper patient response.

Congestive heart failure: Hypovase may be used alone or added to the therapeutic regimen in those patients with congestive heart failure who are resistant or refractory to conventional therapy with diuretics and/or cardiac glycosides.

Raynaud’s phenomenon and Raynaud’s disease: Hypovase is indicated for the symptomatic treatment of patients with Raynaud’s phenomenon and Raynaud’s disease.

Benign prostatic hyperplasia: Hypovase is indicated as an adjunct in the symptomatic treatment of urinary obstruction caused by benign prostatic hyperplasia (BPH). It may therefore be of value in patients awaiting prostatic surgery.

4.2 Posology and method of administration

Posology

Hypertension: The dosage range is from 500 micrograms – 20 mg daily. It is recommended that therapy be initiated at the lowest dose, 500 micrograms, twice or

three times daily for three to seven days, with the starting dose administered in the evening. This dose should be increased to 1 mg twice or three times daily for a further three to seven days. Thereafter, the daily dose should be increased gradually as determined by the patient's response to the blood pressure lowering effect. Most patients are likely to be maintained on a dosage regimen of Hypovase alone of up to 15 mg daily in divided doses. Maximum recommended daily dosage: 20 mg in divided doses.

Patients receiving other antihypertensive therapy but with inadequate control: The dosage of the other drug should be reduced to a maintenance level and Hypovase initiated at 500 micrograms in the evening, then continuing with 500 micrograms twice or three times daily. Subsequent dosage increases should be made gradually depending upon the patient's response.

There is evidence that adding Hypovase to angiotensin converting enzyme inhibitor, beta-adrenergic antagonist or calcium antagonist therapy may bring about a substantial reduction in blood pressure. Therefore, the low initial dosage regimen is recommended.

Congestive cardiac failure: The recommended starting dose is 500 micrograms two, three or four times daily, increasing to 4 mg in divided doses. Dosage should be adjusted according to the patient's clinical response, based on careful monitoring of cardiopulmonary signs and symptoms, and when indicated, haemodynamic studies. Dosage may be adjusted as often as every two to three days in patients under close medical supervision. In severely ill, decompensated patients, rapid dosage adjustment over one to two days may be indicated and is best done when haemodynamic monitoring is available. In clinical studies the therapeutic dosages ranged from 4 mg to 20 mg daily in divided doses. Adjustment of dosage may be required in the course of Hypovase therapy in some patients to maintain optimal clinical improvement.

Usual daily maintenance dosage: 4 mg to 20 mg in divided doses.

Raynaud's phenomenon and Raynaud's disease: The recommended starting dosage is 500 micrograms twice daily given for a period of three to seven days and should be adjusted according to the patient's clinical response. Usual maintenance dosage is 1 mg or 2 mg twice daily.

Benign prostatic hyperplasia: The recommended dosage is 500 micrograms twice daily for a period of 3 to 7 days, with the initial dose administered in the evening. The dosage should then be adjusted according to clinical response. The usual maintenance dosage is 2 mg twice daily. This dose should not be exceeded unless the patient requires Hypovase as antihypertensive therapy. Patients with benign prostatic hyperplasia receiving hypertensive therapy, should be administered Hypovase only under the supervision of the practitioner responsible for treating the patient's hypertension.

Patients with moderate to severe grades of renal impairment

Evidence to date shows that Hypovase does not further compromise renal function when used in patients with renal impairment. As some patients in this category have responded to small doses of Hypovase, it is recommended that therapy be initiated at 500 micrograms daily and that dosage increases be instituted cautiously.

Patients with hepatic dysfunction: No information is available on the use of Hypovase in this patient group, however, since Hypovase normally undergoes substantial first

pass metabolism and subsequent metabolism and excretion by the liver, it is recommended that therapy be initiated at 500 micrograms daily and that dosage increases be instituted cautiously.

Paediatric population: Hypovase is not recommended for the treatment of children under the age of 12 years since safe conditions for its use have not been established.

Elderly: Since the elderly may be more susceptible to hypotension, therapy should be initiated with the lowest possible dose.

Method of administration
Hypovase tablets are for oral administration only.

4.3 Contraindications

Hypersensitivity to the active substance, other quinazolines, prazosin or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In patients with benign prostatic hyperplasia: Hypovase is not recommended for patients with a history of micturition syncope.

Hypovase decreases peripheral vascular resistance and since many patients with this disorder are elderly, careful monitoring of blood pressure during initial administration and during adjustment of dosage is recommended. The possibility of postural hypotension, or rarely, loss of consciousness, as reported in other patient groups should be borne in mind. Close observation is especially recommended. For patients taking medications that are known to lower blood pressure, Hypovase may augment the efficacy of antihypertensive therapy, consequently, close observation is especially recommended for patients taking medications that are known to lower blood pressure. Hypovase should not normally be administered to patients already receiving another alpha-1-antagonist.

In patients with congestive cardiac failure: Hypovase is not recommended in the treatment of congestive cardiac failure due to mechanical obstruction such as aortic valve stenosis, mitral valve stenosis, pulmonary embolism and restrictive pericardial disease. Adequate data are not yet available to establish efficacy in patients with heart failure due to recent myocardial infarction.

When Hypovase is initially administered to patients with congestive cardiac failure who have undergone vigorous diuretic or other vasodilator treatment, particularly in higher than the recommended starting dose, the resultant decrease in left ventricular filling pressure may be associated with a significant fall in cardiac output and systemic blood pressure. In such patients, observance of the recommended starting dose of Hypovase followed by gradual dosage increase is particularly important.

The clinical efficacy of Hypovase in congestive cardiac failure has been reported to diminish after several months of treatment, in a proportion of patients. In these patients there is usually evidence of weight gain or peripheral oedema indicating fluid retention. Since spontaneous deterioration may occur in such severely ill patients, a causal relationship to prazosin therapy has not been established. Thus, as with all patients with congestive cardiac failure, careful

adjustment of diuretic dosage according to the patient's clinical condition is required to prevent excessive fluid retention and consequent relief of symptoms.

In those patients without evidence of fluid retention, when clinical improvement has diminished, an increase in the dosage of Hypovase will usually restore clinical efficacy.

In patients with hypertension: A very small percentage of patients may respond in an abrupt and exaggerated manner to the initial dose of Hypovase. Postural hypotension evidenced by dizziness and weakness, or rarely loss of consciousness, has been reported, particularly with the commencement of therapy, but this effect is readily avoided by initiating treatment with a low dose of Hypovase and with small increases in dosage during the first one to two weeks of therapy. The effect when observed is not related to the severity of hypertension, is self-limiting and in most patients does not recur after the initial period of therapy or during subsequent titration steps.

Raynaud's phenomenon and Raynaud's disease: Because Hypovase decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and during subsequent dosage increments of Hypovase is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure.

Use with Phosphodiesterase type-5 Inhibitors: Concomitant use of phosphodiesterase type-5 (PDE-5) inhibitors (e.g. sildenafil, tadalafil, vardenafil) and prazosin hydrochloride may lead to symptomatic hypotension in some patients. In order to minimise the risk for developing postural hypotension the patient should be stable on the alpha-blocker therapy before initiating use of PDE-5 inhibitors.

Priapism: Prolonged erections and priapism have been reported with alpha-1 blockers including prazosin in post marketing experience. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

Cataract surgery: The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin. Isolated reports have also been received with other alpha-1 blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during the cataract operation current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

4.5 Interaction with other medicinal products and other forms of interaction

Hypovase has been administered without any adverse drug interaction in clinical experience to date with the following:

Cardiac glycosides: digitalis and digoxin.
Hypoglycaemic agents: insulin, chlorpropamide, phenformin, tolazamide and tolbutamide.
Tranquillizers and sedatives: chlordiazapoxide, diazepam and phenobarbital.
Agents for treatment of gout: allopurinol, colchicine and probenecid.
Anti-arrhythmic agents: procainamide and quinidine.
Analgesic, antipyretic and anti-inflammatory agents: dextropropoxyphene, aspirin, indomethacin and phenylbutazone.

There is evidence that adding Hypovase to beta-adrenergic antagonist or calcium antagonist therapy may produce a substantial reduction in blood pressure. Therefore the low initial dosage regimen is recommended.

PDE-5 Inhibitors: Concomitant use of PDE-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) and prazosin hydrochloride may lead to symptomatic hypotension in some patients (see section 4.4).

Drug/Laboratory Test Interactions: False positive results may occur in screening tests for phaeochromocytoma urinary vanillylmandelic acid (VMA) and methoxyhydroxyphenyl glycol (MHPG) metabolites of norepinephrine (noradrenaline) in patients who are being treated with Hypovase**.**

4.6 Fertility, pregnancy and lactation

Fertility
A decrease in fertility in male and female rats treated with prazosin hydrochloride was observed at high non-clinically relevant doses (225 times the usual maximum recommended human dose). However no adverse effects were observed at doses up to 75 times the usual maximum recommended human dose.

Pregnancy
Prazosin hydrochloride was not teratogenic in rats and rabbits.

Although no teratogenic effects were seen in animal testing, the safety of Hypovase during pregnancy has not yet been established. The use of Hypovase and a beta-blocker for the control of severe hypertension in 44 pregnant women revealed no drug-related foetal abnormalities or adverse effects. Therapy with Hypovase was continued for as long as 14 weeks. No foetal or neonatal abnormalities have been reported with the use of prazosin hydrochloride.

Hypovase has also been used alone or in combination with other hypotensive agents in severe hypertension of pregnancy.

Hypovase should be used only when, in the opinion of the physician, potential benefit outweighs potential risk

Breast-feeding
Hypovase has been shown to be excreted in small amounts in human milk. Caution should be exercised when Hypovase is administered to nursing mothers.

4.7 Effects on ability to drive and use machines

When instituting therapy with any effective antihypertensive agent, the patient should be advised on how to avoid symptoms resulting from postural hypotension and what measures to take should they develop. The patient should be cautioned to avoid situations where injury could result should dizziness or weakness occur during the initiation of Hypovase therapy (i.e. driving or operating machinery).

4.8 Undesirable effects

The following side-effects have been associated with Hypovase therapy:
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: 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) and not known (frequency cannot be estimated from the available data).

MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Immune System Disorders	Rare	Allergic reaction
Psychiatric Disorders	Common Uncommon Rare	Depression, nervousness Insomnia Hallucinations
Nervous System Disorders	Common Uncommon Rare	Dizziness, drowsiness, headache, faintness, syncope Paraesthesia Worsening of pre-existing narcolepsy
Eye Disorders	Common Uncommon	Blurred vision Eye pain, reddened sclera
Ear and Labyrinth Disorders	Common Uncommon	Vertigo Tinnitus
Cardiac Disorders	Common Uncommon Rare	Palpitations Angina pectoris, tachycardia, Bradycardia
Vascular Disorders	Rare	Flushing, hypotension, orthostatic hypotension, vasculitis
Respiratory, Thoracic and Mediastinal Disorders	Common Uncommon	Dyspnoea, nasal congestion Epistaxis
Gastrointestinal Disorders	Common Uncommon	Constipation, diarrhoea, dry mouth, nausea, vomiting Abdominal discomfort and/or pain
	Rare	Pancreatitis
Hepato-biliary Disorders	Rare	Liver function abnormalities
Skin and Subcutaneous Tissue Disorders	Common Uncommon Rare	Rash Diaphoresis, pruritis, urticaria Alopecia, lichen planus
Musculoskeletal and Connective Tissue Disorders	Uncommon	Arthralgia
Renal and Urinary Disorders	Common Rare	Urinary frequency Incontinence
Reproductive System and Breast Disorders	Uncommon Rare	Impotence Gynaecomastia, priapism
General Disorders and Administration Site	Common	Oedema, lack of energy, weakness

Conditions	Rare	Fever, pain
Investigations	Rare	Positive ANA titer

The frequency of side-effects observed in patients being managed for left ventricular failure with Hypovase when used in conjunction with cardiac glycosides and diuretics is shown below:

MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Nervous System Disorders	Common Uncommon Rare	Dizziness Headache Drowsiness
Eye Disorders	Common	Blurred vision
Cardiac Disorders	Rare	Palpitations
Vascular Disorders	Common	Postural hypotension
Respiratory, Thoracic and Mediastinal Disorders	Rare	Nasal congestion
Gastrointestinal Disorders	Common	Dry mouth, nausea
	Uncommon	Diarrhoea
Reproductive System and Breast Disorders	Common	Impotence
General Disorders and Administration Site Conditions	Rare	Oedema

In most instances these occurrences have been mild to moderate in severity and have resolved with continued therapy or have been tolerated with no decrease in drug dosage.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Should over-dosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary vasopressors including angiotensin should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate Hypovase is not dialysable because it is protein bound.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists, ATC code: C02CA01

Hypovase causes a decrease in total peripheral vascular resistance through selective inhibition of postsynaptic alpha-1-adrenoreceptors in vascular smooth muscle. The results of forearm plethysmographic studies in humans demonstrate that the resultant peripheral vasodilatation is a balanced effect on both resistance vessels (arterioles) and capacitance vessels (veins).

In hypertensive patients, blood pressure is lowered in both the supine and standing positions; this effect is more pronounced on the diastolic blood pressure. Tolerance to the antihypertensive effect has not been observed in long-term clinical use; relatively little tachycardia or change in renin levels has been noted. Rebound elevation of blood pressure does not occur following abrupt cessation of Hypovase therapy.

The therapeutic efficacy of Hypovase in patients with congestive heart failure is ascribed to a reduction in left ventricular filling pressure, reduction in cardiac impedance and an augmentation of cardiac output. The use of Hypovase in congestive heart failure does not provoke a reflex tachycardia and blood pressure reduction is minimal in normotensive patients.

Hypovase has been found to successfully reduce the severity of the signs, symptoms, frequency and duration of attacks, in patients with Raynaud's disease.

In low dosage, antagonism of alpha-1-receptors on prostatic and urethral smooth muscle has been shown to improve the urinary pressure profile in men and to improve symptoms of benign prostatic hypertrophy.

Clinical studies have shown that Hypovase therapy is not associated with adverse changes in the serum lipid profile.

5.2 Pharmacokinetic properties

Following oral administration in normal volunteers and hypertensive patients plasma concentrations of prazosin reach a peak in one to two hours with a plasma half-life of two to three hours. Pharmacokinetic data in a limited number of patients with congestive heart failure, most of whom showed evidence of hepatic congestion, indicates that peak plasma concentrations are reached in 2.5 hours and plasma half life is approximately 7 hours. Hypovase is highly bound to plasma protein. Studies indicate that Hypovase is extensively metabolised, primarily by demethylation and conjugation, and excreted mainly via bile and faeces.

Renal blood flow and glomerular filtration rate are not impaired by long term oral administration and thus Hypovase can be used with safety in hypertensive patients with impaired renal function.

5.3 Preclinical safety data

Prazosin hydrochloride was not mutagenic in genetic toxicology testing, and was not carcinogenic in rats. In chronic studies (> 1 year) conducted with prazosin hydrochloride in rats and dogs, testicular changes consisting of atrophy and necrosis occurred at 25 mg/kg/day (75 times the usual maximum recommended human dose), while no such changes were observed in either species at a dose of 10 mg/kg/day (30 times the usual maximum recommended human dose).

Fertility in rats was decreased at high nonclinically relevant doses (225 times the usual maximum recommended human dose). Prazosin hydrochloride was not teratogenic at doses up to 75 mg/kg/day (225 times the maximum recommended human dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium phosphate dibasic anhydrous
Maize starch
Microcrystalline cellulose
Magnesium stearate
Sodium lauryl sulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC/Aluminium blisters in cartons of 60 tablets (blister strips of 4 x 15 tablets).

6.6 Special precautions for disposal

No special requirements for disposal. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PL0057/0149R

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 October 1988
Date of last renewal: 22 November 2004

10 DATE OF REVISION OF THE TEXT

07/06/2017