Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benph 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg of terazosin (in the form of terazosin hydrochloride dihydrate).

Excipient(s): 110mg lactose monohydrate
0.1mg sunset yellow (E110)

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Tablets

Orange, round, flat, bevel edged, tablet imprinted “E” and “454” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Benph® tablets are indicated for:

- symptomatic treatment of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

The dose of terazosin should be managed according to each patient’s response.

An initial dose of 1.0mg daily should be given in the evening. This dose may be increased by approximately doubling the dose at weekly intervals to achieve the desired reduction in symptoms. The maintenance dose is usually 5 to 10mg once daily. At present there are insufficient data to suggest symptomatic relief with doses above 10mg.

Use with thiazide diuretics and other antihypertensive agents

The dose of terazosin should be re-titrated if a thiazide diuretic or antihypertensive agent is added to a patients medication. On initiation of the new medication hypotension may be observed.

Elderly:

In the elderly, dosage should be kept as low as possible and increments made under close supervision.

Renal dysfunction:

Pharmacokinetic studies indicate that patients with impaired renal function need no alteration in the recommended dosage. There is no evidence that terazosin aggravates renal dysfunction.

Paediatric patients:

There are no reports regarding the efficacy and safety of the drug in children, the use of terazosin is therefore not recommended for this group.

Method of administration:

Benph® tablets should be swallowed whole and not chewed and can be taken with or without food.

4.3 Contraindications

Benph tablets should not be given:

- to individuals with known hypersensitivity to terazosin, or to a structurally similar a-adrenergic antagonist, or
- to patients that are hypersensitive to quinazolines, or
- in the presence of congestive heart failure due to mechanical obstruction (e.g. aortic valve or mitral valve stenosis, pulmonary embolism, restrictive pericarditis).

4.4 Special warnings and precautions for use

As with other alpha adrenoceptor blocking agents, terazosin should not be administered to patients suffering from (or with a history of) micturition syncope.

'First dose' effect might occur after the first terazosin dose or during the initial period oftreatment. This consists of: marked reduction of blood pressure mainly as orthostatic hypotension (vertigo, unsteadiness, syncope). Volume depletion, restricted salt-intake and advanced age (i.e. 65 years or over) increase the risk of postural hypotension. It should be born in mind that this is also likely to happen when terazosin treatment is re-started after a few days break. In such case, the 1mg initial dose should be prescribed.

Syncope has been seen in one percent of patients in hypertension trials. Rapid dose increase as well as combining terazosin with a diuretic and/or another antihypertensive might result in syncope. Syncope is related to marked postural hypotension, and in some cases it is preceded by tachycardia (120-160/min). Postural hypotension is most pronounced within a short time of drug intake, while the risk of syncope is the greatest 30-90 minutes following drug administration. Dizziness, unsteadiness and syncope are most likely to be provoked by any of the following: standing up from a sitting or a supine position, long periods of standing, increased physical load, warm weather and concomitant drinking of alcoholic beverages (please also see Section 4.7 Effects on Ability to Drive and Use Machines).

Management of syncope: the patient should be kept in a supine position with elevated lower extremities. Supportive and/or symptomatic treatment might be necessary.

Special care should be taken when giving terazosin to individuals with known susceptibility to developing orthostatic hypotension or to those suffering from: ischaemic or any other heart diseases, cerebrovascular disorders, III and/or IV degree hypertensive retinopathy, insulin dependent diabetes, hepatic and/or renal failure.

In certain patients with left ventricular failure, the decrease in left ventricular filling consequent to vigorous therapy may result in a significant fall in cardiac output and systemic blood pressure after administration of terazosin. These effects should be kept in mind when introducing therapy and continuous titration of dose used.

The usual half-life of terazosin is 10-12 hours. This may be significantly prolonged in patients with congestive cardiac failure (by up to 7-8 hours), usually with reduction on clinical improvement.

Before starting terazosin therapy for BPH, carcinoma of the prostate should be excluded. The blood pressure of patients with BPH should be measured at baseline and monitored thereafter particularly at times of dose adjustment. Possible antihypertensive treatment should also be taken into consideration. Effectiveness of Terazosin in the management of BPH should be evaluated after allowing a period of 4- 6 weeks of treatment with the maintenance dose.

Since the drug is metabolised in the liver it should only be used with care in patients with existing hepatic dysfunction.

Priapism: rarely, terazosin has been associated with priapism (painful penile erection, sustained for hours and unrelieved by sexual intercourse or masturbation). Because this condition can lead to permanent impotence if not promptly treated, patients must be advised about the seriousness of that condition.

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and terazosin 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 phosphodiesterase-5-inhibitors. In addition, phosphodiesterase-5-inhibitors should be started on the lowest dose and with a time interval (e.g. 6 hours) following terazosin administration.

'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 adrenergic 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 and the ophthalmologist in advance of surgery.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and terazosin may lead to symptomatic hypotension in some patients (see section 4.4).

The drug is highly protein bound. There is a theoretical potential for interaction with such drugs as anticoagulants and nonsteroidal anti-inflammatory drugs leading to higher plasma levels of drug.

Except for angiotensin converting enzyme (ACE) inhibitors and diuretics, no clinically significant interactions have been observed with terazosin in BPH. In BPH patients the adverse events profile of patients treated concurrently with non-steroidal anti-inflammatory drugs (NSAIDs), theophylline, antianginal agents, oral hypoglycaemia agents, ACE inhibitors or diuretics was comparative to the profile in the general treated population.

In the small subset patients who were treated with terazosin and ACE inhibitors or diuretics, the percent reporting dizziness or other dizziness-related adverse events appears to be greater than in the total population of terazosin patients from double-blind placebo-controlled studies.

Caution should be observed when terazosin is administered concomitantly with other antihypertensive agents (e.g. calcium antagonists) to avoid the possibility of significant hypotension. When adding terazosin to a diuretic or other antihypertensive agent, dosing reduction and retitration of these agents may be necessary.

Laboratory tests: Laboratory findings suggestive of haemodilution (e.g. decrease in haematocrit, haemoglobin, white blood cells, total protein and albumin) have been observed in controlled clinical trials. No significant effect on prostate specific antigen (PSA) levels was reported after terazosin treatment for up to 24 months.

4.6 Fertility, pregnancy and lactation

There are no sufficient data on the use of the drug in pregnant and lactating women. Terazosin is not recommended in the treatment of pregnant women and/or breast feeding mothers unless the potential benefit is considered to outweigh the risk.

4.7 Effects on ability to drive and use machines

The drug may induce drowsiness, dizziness or light-headedness. Patients should be advised not drive a vehicle, operate machinery or perform activities with increased risk of accidents for 12 hours after starting terazosin and 12 hours after any increase in dose.
Thereafter, patients should not drive, operate machinery or perform activities with increased risk of accidents unless terazosin has been shown not to affect their physical or mental capacity.

4.8 Undesirable effects

As with other alpha adrenoceptor blocking antagonists, terazosin may cause syncope.
Syncopal episodes may occur within 30-90 minutes of the initial dose of the medicinal product. Occasionally the syncopal episode may be preceded by tachycardia with heart rates of 120 to 160 beats per minute. First-dose hypotension might occur which could lead to vertigo and in severe cases syncope. To avoid hypotension, terazosin treatment should be started with a 1mg dose at bed-time. (See section 4.4 Special Warnings and Precautions for Use).

The following adverse events have been reported:

Additional adverse reactions reported in clinical trials or reported during marketing experience but not clearly associated with the use of terazosin have been listed under the frequency heading ‘Not Known’.

	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 available data)
Blood and the lymphatic system disorders				thrombocytopenia	
Immune system disorders				anaphylactic reactions	
Psychiatric disorders					anxiety, insomnia
Nervous system disorders	nervousness, somnolence, paraesthesia	depression			
Eye disorders	blurred vision				abnormal vision, conjunctivitis, IFIS (intraoperative floppy iris syndrome) see section 4.4.
Ear and labyrinth disorders					tinnitus
Cardiac disorders	palpitations, tachycardia, chest pain			atrial fibrillation	arrhythmia
Vascular disorders	peripheral oedema				vasodilation
Respiratory, thoracic and mediastinal disorders	dyspnoea, nasal congestion, sinusitis, epistaxis				bronchitis, flu symptoms, pharyngitis, rhinitis, cold symptoms,

					increased cough
Gastrointestinal disorders	nausea, constipation, diarrhoea, vomiting				dry mouth, dyspepsia, flatulence
Skin and subcutaneous tissue disorders	pruritus, rash				facial oedema, sweating
Musculoskeletal, connective tissue and bone disorders	back pain				abdominal, neck and shoulder pain, gout, arthralgia, arthritis, joint disorders, myalgia
Renal and urinary disorders			urinary tract infection and urinary incontinence, (primarily reported in post-menopausal women)		urinary frequency
Reproductive system and breast disorders	impotence	decreased libido	priapism		
General disorders and administration site conditions	Dizziness, light-headedness, fainting (especially when standing up quickly from a lying or a sitting position - postural hypotension), asthenia, oedema, headache, pain in the extremities	weight gain, syncope			fever

4.9 Overdose

If acute hypotension occurs as a result of terazosin treatment, cardiovascular support should be of primary importance. The patient should be kept in a supine position in order to restore blood pressure and heart rate to normal. If this measure is unsuccessful then shock should be treated with volume expansion followed by administration of vasopressors. Plasma and electrolyte balance should be restored. Renal function should be monitored and general supportive measures applied as required. Terazosin is highly protein bound; therefore, dialysis may not be of benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Terazosin, the active ingredient of Benph® tablets, is a selective peripheral a1 -adrenergic blocking agent. Its antihypertensive effects may result from postsynaptic a1-adrenergic blockade, leading to vasodilatation, decreased total peripheral resistance and venous return.
Terazosin is a long-acting oral agent that is useful when given once daily to hypertensives. Long-term treatment with terazosin does not usually cause reflex tachycardia; while cardiac output, renal perfusion and glomerular filtration rate hardly become affected.

Although it has no effect on the underlying pathophysiolgic mechanism involved in BPH, terazosin has been shown to significantly increase urinary flow rates and decrease outflow obstruction. It is also effective in easing BPH-related symptoms by preventing stimulation of a1 -adrenergic receptors and consequent smooth muscle contractions in the bladder and prostatic urethra. Urodynamic improvement may help reduce urinary tract infection. The drug, however, does not affect the size of the prostate.

A significant antihypertensive effect has been observed 3 hours following oral administration of terazosin. The drug's antihypertensive effect has been reported to persist for 24 hours after oral administration.

5.2 Pharmacokinetic properties

ABSORPTION

Terazosin is rapidly and almost completely absorbed from the gastrointestinal tract, without being affected by food intake. It has a 90% bioavailability.

ONSET and DURATION

Following administration of the smallest dose, mean peak serum levels were achieved within one hour. Terazosin has a half-life of approximately 12 hours. 36 hours following drug intake, terazosin could still be traced in plasma.

DISTRIBUTION, METABOLISM and EXCRETION

Terazosin is 90-94% plasma protein-bound. It is extensively metabolised in the liver via hydrolysis, demethylation and dealkylation with five different metabolites identified. Mean elimination half-life of parent compound is 12 hours. 10% of the orally administered drug is excreted in the form of unchanged drug in the urine and 30% as inactive metabolites. Faecal elimination accounts for 55-60% of the oral dose. There are no reports on possible drug excretion in breast milk.

5.3 Preclinical safety data

Terazosin has been shown to produce tumours in male rats when administered in high doses over a long period. No such occurances were observed in female rats or in a similar study with mice. The relevance of these findings with respect to the clinical use of the drug in man is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Talc
Povidone
Pregelatinised starch
Lactose monohydrate
Sunset Yellow E.E.C. 110

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C, store in the original package.

6.5 Nature and contents of container

Benph 10mg tablets are provided in Aluminium/foil/PVC/PVDC blister strip packs.

Pack size:
Benph 10mg tablets are presented in cartons of 28, 50, 84, 98 and 100.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Limited
T/A Gerard Laboratories.
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13

8 MARKETING AUTHORISATION NUMBER

PA0577/049/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 September 2004
Date of last renewal: 31 October 2006

10 DATE OF REVISION OF THE TEXT

November 2009