

DILATED CARDIOMYOPATHY AND TREATMENT OF CHRONIC HEART FAILURE

Dilated cardiomyopathy of unknown cause is one of the leading causes of heart failure in Africa.

KAREN SLIWA

MD, PhD, FESC, DTM&H

Associate Professor

Soweto Cardiovascular Research Unit
Department of Cardiology
Chris Hani Baragwanath Hospital and
University of the Witwatersrand

For the past 10 years Karen Silwa's research has focused mainly on immune activation in heart failure, and idiopathic and peripartum cardiomyopathy. In recent years she has established research collabo-

rations with various national and international centres. She is a founding member of the new World Heart Failure Society, a working group member of the international campaign to revitalise academic medicine (ICRAM), and on the editorial board of The Lancet.

OLAF FÖRSTER

MD

Medical Officer

Soweto Cardiovascular Research Unit
Department of Cardiology

Chris Hani Baragwanath Hospital and
University of the Witwatersrand

Olaf Förster's research focuses on peripartum cardiomyopathy – an autoimmune disease, the topic of his PhD. Dr Förster completed a doctoral thesis at the Freie Universitaet Berlin, Germany, on pharmacotherapy in the traditional medicine of Eastern Africa. He is the founder and chairman of Medical Assistance in Africa, an organisation that provides primary health care in a rural area of Kenya.

EPIDEMIOLOGY

Dilated cardiomyopathy (DCM) of unknown cause vies with rheumatic heart disease and hypertension as one of the leading causes of heart failure in Africa. Whereas the incidence and prevalence of DCM in the USA is reported to be 36.5 per 100 000 individuals, there are no population-based data on the burden of DCM in Africa. The prevalence of idiopathic DCM as a cause of heart failure in hospitalised cases is higher in Africa than in Europe and North America, where cardiomyopathy is rare. This apparent difference in prevalence may be related to a greater preponderance of nutritional and inflammatory heart diseases in Africa.

DCM occurs at any age, but is common in the third and fourth decades of life. Men are affected twice as commonly as women. The majority of patients with DCM, especially those over 55 years of age, die within 5 years of their first symptoms. Chetty and Mitha reported 65% mortality over a 3-year period in a small study of 20 black patients with DCM. About 25% improve spontaneously. The most common causes of death are progression of congestive heart failure or arrhythmias. A persistently low arterial pressure and mitral and/or tricuspid incompetence carry a poor prognosis.

AETIOLOGY

Although the causes of idiopathic DCM are largely unknown, manifestation of the disease probably represents a final common expression of myocardial damage that could be provoked by multiple insults, including haemodynamic, infective, immunological, toxic, nutritional and genetic factors. Possible aetiological factors that have been examined in Africa include burnt-out, untreated hypertension, alcohol, thiamine deficiency, pregnancy and childbirth, viral myocarditis and HIV, iron overload and other metabolic causes, genetic factors, and immune mechanisms.

METHODS FOR DIAGNOSIS OF DCM AND HEART FAILURE IN CLINICAL PRACTICE

Heart failure should never be the only diagnosis! Symptoms and signs are important as they alert the observer to the possibility that heart failure exists. The clinical suspicion of DCM and heart failure must be confirmed by objective tests with the aim of documenting the degree of left ventricular dilatation and dysfunction (Fig. 1 – modified ESC Guidelines, 2005).



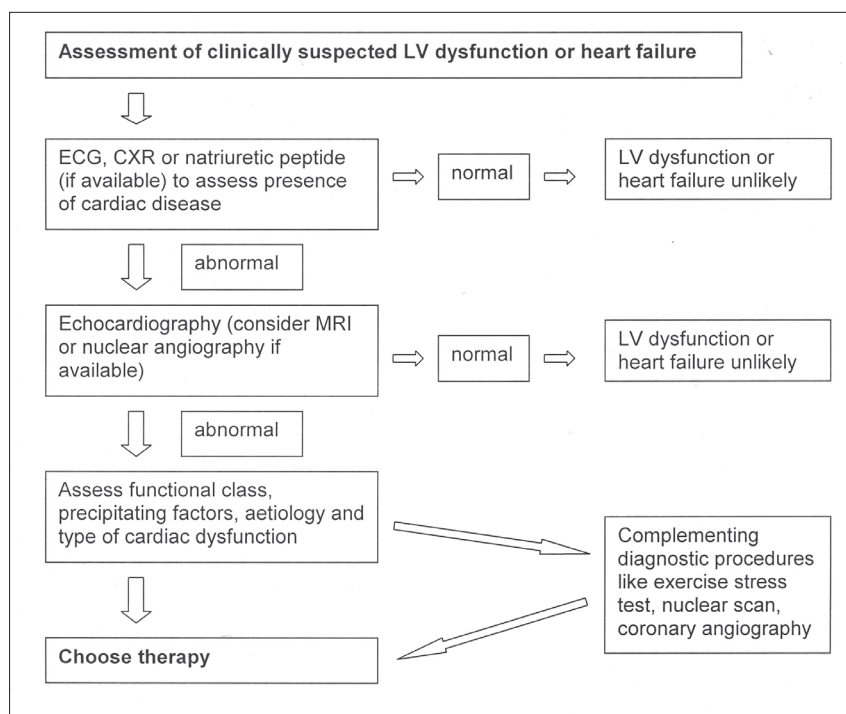


Fig. 1. Algorithm for the diagnosis of left ventricular dysfunction or heart failure.

There is poor correlation between the symptoms and the severity of cardiac dysfunction. However, symptoms are related to prognosis, particularly if persistent after therapy.

TREATMENT OF CHRONIC HEART FAILURE

Aims

The aims in treating heart failure are the following:

- prevention
- controlling the diseases leading to cardiac dysfunction
- preventing the progression to heart failure once dysfunction has been diagnosed
- improvement of symptoms
- improving survival.

Prevention of heart failure should always be the primary objective. When left ventricular systolic dysfunction is already present the most important objective is to correct, where possible, the underlying cause of ventricular dysfunction (e.g. alcohol, drugs, ischaemia, thyroid disease) (Table I).

Table I. Recommendations for patients at high risk of developing heart failure

- Control of systolic and diastolic hypertension
- Treatment of lipid disorders in accordance with recommended guidelines
- Avoidance of patient behaviours that may increase the risk of heart failure (e.g. smoking, alcohol abuse)
- ACE inhibition in patients with a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension and associated cardiovascular risk factors
- Control of ventricular rate in patients with supraventricular tachyarrhythmias
- Periodic evaluation for signs and symptoms of heart failure

ACC/AHA Guideline for Evaluation and Management of Heart Failure (*J Am Coll Cardiol* 2001; **38**: 2101-2113).

MANAGEMENT OF CHRONIC HEART FAILURE

Heart failure is a complex syndrome and the stepwise therapeutic approach includes general advice and non-pharmacological measures, pharmacological therapy and insertion of mechanical devices.

Non-pharmacological management

Heart failure patients and their relatives should receive general advice. Patients should weigh

themselves regularly at a fixed time (e.g. in the morning) and carefully monitor weight gain. In the case of unexpected weight gain of > 2 kg in 3 days, the patient should alert a doctor or adjust his/her diuretic dose accordingly. Fluid restriction to 1.5 - 2 l/day oral intake is advised in advanced heart failure. The treatment of heart failure includes weight reduction in obese patients. However, 50% of patients with severe heart failure develop clinical or subclinical malnutrition that is called cardiac cachexia, an important predictor of reduced survival.

In acute heart failure physical rest or bed rest is recommended. However, stable patients (New York Heart Association Functional Class (NYHA FC) II - III) should be encouraged to exercise and advised on how to carry out daily physical activities that do

not induce symptoms. Standardised recommendations for exercise training in heart failure patients have been published by the European Society of Cardiology Working Group on Cardiac Rehabilitation.

Pharmacological therapy

Surveys of prescribing patterns in both hospital and primary care settings have usually shown delays in translating the evidence from clinical drug trials into routine practice. Patients are thereby denied the benefit of drug therapies proven to improve

Dilated cardiomyopathy (DCM) of unknown cause vies with rheumatic heart disease and hypertension as one of the leading causes of heart failure in Africa.

Under-prescribing and under-dosing of ACE-inhibitors and beta-blockers – both drugs that reduce mortality in patients with heart failure – is a major problem worldwide.

well-being and to prolong life. Less than 50% of patients with heart failure are actually on ACE-inhibitors and even in the highly supervised environment of contemporary heart failure trials, beta-blocker use ranges from 35% to 55%. It is therefore important not to lose sight of our primary goal: the use of ACE-inhibitors and beta-blockers in all patients with heart failure.

Practical recommendations for the use of ACE-inhibitors, beta-blockers, aldosterone antagonists and angiotensin-receptor blockers (ARBs) in heart failure have been published recently.

The current available and recommended types of pharmacological management are outlined in Table II.

Practical recommendations

After establishing the clinical diagnosis of heart failure and possible introduction of a diuretic to treat symptoms and signs of sodium and water retention the first goal should be to assess left ventricular function using echocardiography, radionuclide ventriculography and radiological left ventricular angiography. This first diagnostic step is regarded as representing the minimum standard of care.

The next step requires the initiation of first-line therapy, which, for all patients with heart failure due to left ventricular dysfunction, consists of both an ACE-inhibitor and a beta-blocker, unless there are contraindications.

Recent trials have suggested that a beta-blocker-first strategy is safe and potentially beneficial. A study of black DCM patients from Soweto, Johannesburg, evaluated the therapeutic value of initiating a beta blocker (carvedilol) before an ACE inhibitor in the treatment of heart failure. The carvedilol-first group reached a greater total carvedilol

dose, and had a better improvement of ejection fraction and symptoms. The recently published Cardiac Insufficiency Bisoprolol Study (CIBIS III) trial proved both the safety and efficacy of a beta-blocker-first therapy in heart failure. However, it is important to understand that the greatest benefit for our patients is realised when both agents are used.

Step 3 requires the prescription of additional therapy for patients with persistent signs and symptoms of heart failure. Guidelines recommend the addition of spironolactone in patients with severe symptoms (NYHA FC III - IV). There is also new evidence that ARBs should be added in patients with persistent symptoms (NYHA FC III - IV). It is important to note that there is insufficient evidence as to whether both an ARB and spironolactone should be used in addition to an ACE-inhibitor.

The main role of cardiac glycosides (e.g. digoxin) in heart failure is for patients presenting with atrial fibrillation when rapid control of ventricular rate is needed (which cannot be achieved with cautious introduction and up-titration of a beta-blocker).

Table II. **Pharmacological approach to chronic left ventricular systolic dysfunction**

| | Asymptomatic LV dysfunction (NYHA I) | Symptomatic heart failure (NYHA II) | Worsening heart failure (NYHA III - IV) | End-stage heart failure (NYHA IV) |
|------------------------------|---|---|--|--|
| ACE-inhibitor | Indicated | Indicated | Indicated | Indicated |
| Angiotensin receptor blocker | Only indicated if ACE-inhibitor intolerant | Indicated with or without ACE-inhibitor | Indicated with or without ACE-inhibitor | Indicated with or without ACE-inhibitor |
| Diuretic | Not indicated | Indicated in presence of fluid retention | Indicated, combination of diuretics | Indicated, combination of diuretics |
| Beta-blocker | Post MI | Indicated | Indicated (under specialist care) | Indicated (under specialist care) |
| Aldosterone antagonists | Recent MI | Recent MI | Indicated | Indicated |
| Cardiac glycosides | Atrial fibrillation | Atrial fibrillation or when in sinus rhythm and improved from more severe heart failure | Indicated | Indicated |

In the recent African-American Heart Failure Trial (A-Heft), the combination of hydralazine (initiated at a dose of 37.5 mg and titrated to a target dose of 75 mg tds) and isosorbide dinitrate (initiated at a dose of 20 mg and titrated to a dose of 40 mg tds) improved survival and additional outcomes when added to ACE-inhibitors, spironolactone and beta-blockers in African-Americans with NYHA FC III - IV heart failure.

Pacemakers and implantable cardioverter defibrilators (European Society of Cardiology Guidelines)

Pacemakers have been used in patients with heart failure to treat bradycardia when conventional indications exist. Pacing of the right ventricle only in patients with systolic dysfunction will induce ventricular dys-synchrony and may increase symptoms.

Resynchronisation therapy using bi-ventricular pacemakers can be considered in patients with reduced left ventricular ejection fraction, ventricular dys-synchrony (QRS width > 120 ms) and in those who remain symptomatic (NYHA FC III - IV) despite optimal medical therapy to improve symptoms. Recent publications have shown that, in addition to improving symptoms and exercise capacity, bi-ventricular pacing has a significant beneficial effect on mortality.

An implantable cardioverter defibrillator (ICD) in combination with bi-ventricular pacing can be considered in patients who remain symptomatic with severe heart failure (NYHA FC III - IV) with a left ventricular ejection fraction $\leq 35\%$ and QRS duration of ≥ 120 ms to improve mortality and morbidity.

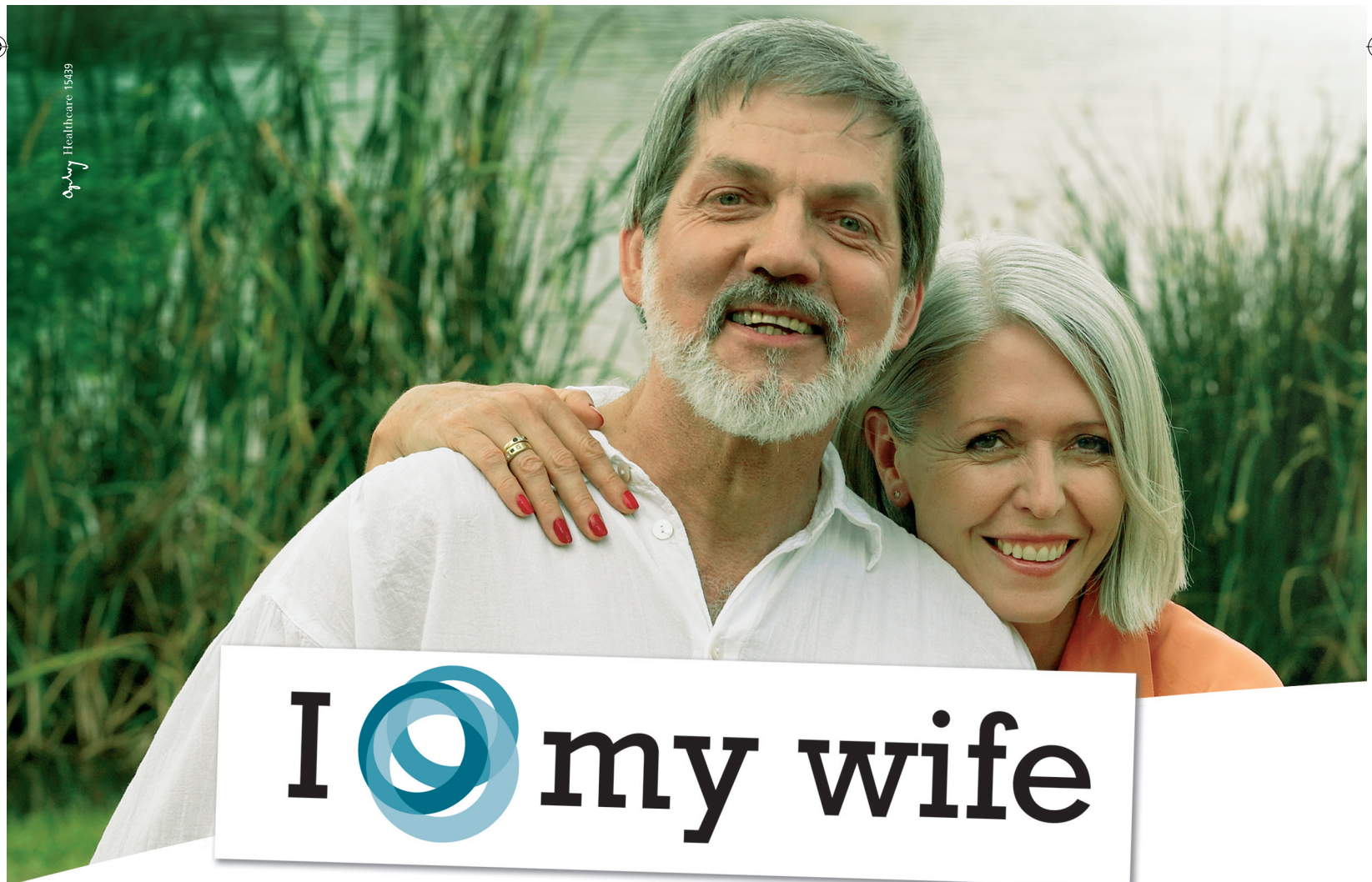
CONCLUSIONS

Under-prescribing and under-dosing of ACE-inhibitors and beta-blockers – both drugs that reduce mortality in patients with heart failure – is a major problem worldwide. The objective is to treat all patients with both an ACE-inhibitor and a beta-blocker, ideally at the target doses used in large randomised trials. There is now good evidence that this goal can be achieved if a concerted effort is made in hospitals, outpatient clinics and the community.

Further reading

Chetty S, Miha AS. Arrhythmias in idiopathic dilated cardiomyopathy. A preliminary study. *S Afr Med J* 1990; **77**: 190-193.

Codd MB, Sugrue DD, Gersh BJ, Melton J. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975 - 1984. *Circulation* 1989; **80**: 564-572.



Pfizer Healthcare 15439



Freers J, Hakim J, Myanja-Kizza H, Parry E. The heart. In: Parry E, Godfrey R, Mabey D, Gill G, eds. *Principles of Medicine in Africa*. 3rd ed. Cambridge, UK: Cambridge University Press, 2004: 837-886.

Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). *Eur Heart J* 2005; **11**:15-1140.

McMurray J, Cohen-Solal A, Dietz R, Eichhorn E, Erhardt L, Hobbs FD, et al. Practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists and angiotension receptor blockers in heart failure:

Putting guidelines into practice. *Eur J Heart Fail* 2005; **7**: 710-721.

Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation* 1998; **97**: 596-601.

Sliwa K, Norton GR, Kone N, Candy G, Kachope J, Woodiwiss AJ, et al. Impact of initiating carvedilol before angiotensin-converting enzyme inhibitor therapy on cardiac function in newly diagnosed heart failure. *J Am Coll Cardiol* 2004; **44**: 1825-1830.

Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krim H, et al. on behalf

of the CIBIS III Investigators: Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared to the opposites sequence: results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III trial. *Circulation* 2005; **112**: 2426-2435.

Working Group on Cardiac Rehabilitation and Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. Recommendation for exercise training in chronic heart failure patients. *Eur Heart J* 2001; **22**: 37-45.

IN A NUTSHELL

Prevention of heart failure is of the utmost importance in patients at risk.

Heart failure should never be the only diagnosis.

All patients with symptoms of heart failure should be investigated for the presence of left ventricular dysfunction.

Patients should be advised to monitor weight gain.

Patients with severe heart failure often develop malnutrition that is called cardiac cachexia, an important predictor of reduced survival.

In acute heart failure physical rest or bed rest is recommended.

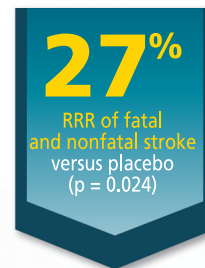
Stable patients should be encouraged to and advised on how to carry out daily physical activities that do not induce symptoms.

All patients with heart failure should be treated with both an ACE-inhibitor and a beta-blocker up-titrated to recommended doses if tolerated.

An implantable cardioverter defibrillator (ICD) in combination with bi-ventricular pacing can be considered in patients who survived cardiac arrest or who have sustained ventricular tachycardia which is associated with severe heart failure (NYHA FC III - IV) with a left ventricular ejection fraction \leq 35% and QRS duration of \geq 120 ms to improve mortality and morbidity.

ASCOT*

Lipitor 10 mg, through its lipid-lowering action, significantly reduced cardiovascular events in hypertensive patients with multiple risks for CHD ⁽¹⁾



* 10 305 hypertensive patients with at least 3 other CV risk factors and TC \leq 6.5 mmol/L were randomly assigned Lipitor 10 mg or placebo. Treatment was stopped after a median of 3.3 years.
** Primary endpoint was a composite of nonfatal MI and fatal CHD

HELPING YOUR PATIENTS DO WHAT THEY LOVE
IS THE HEART OF CV SUCCESS

LIPITOR
atorvastatin 10, 20, 40, 80 mg
Power. Evidence. Confidence.

Reference: 1. Sever PS, Björn-Dahlöf, Poulter NR, et al for the ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361**(9364):1149-1158.

54 Lipitor 10, Lipitor 20, Lipitor 40, Lipitor 80 Tablets. Each Lipitor 10, 20, 40 and 80 tablets contains atorvastatin calcium trihydrate, equivalent to 10 mg, 20 mg, 40 mg and 80 mg atorvastatin respectively. Reg. No.: Lipitor 10: 317/5/0357, Lipitor 20: 317/5/0358, Lipitor 40: 317/5/0359, Lipitor 80: 317/5/0210. **Pharmacological Classification:** A: 7.5 Serum-cholesterol reducers. **Indications:** Lipitor is indicated as an adjunct to diet for reduction of elevated total-cholesterol, LDL-cholesterol, apolipoprotein-B, and triglyceride levels in patients with primary hypercholesterolaemia; mixed dyslipidaemia; and heterozygous familial hypercholesterolaemia. **Contra-indications:** Hypersensitivity to any component of this medication. Active liver disease or unexplained persistent elevations of serum transaminases. Lipitor is contra-indicated in pregnancy, in breast feeding mothers and in women of childbearing potential not using adequate contraceptive measures. An interval of one month should be allowed from stopping Lipitor treatment to conception in the event of planning a pregnancy. Safety and efficacy have not yet been established in children. **Warnings:** **Liver Effects:** Persistent elevations (> 3 times the upper limit of normal (ULN) occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. Active liver disease or unexplained persistent transaminase elevations are contra-indications to the use of Lipitor (see **Contra-Indications**). **Skeletal Muscle:** Rhabdomyolysis with or without renal impairment has been reported with the use of HMG-CoA reductase inhibitors. Myalgia has been reported in patients treated with Lipitor (see **Adverse Reactions**). The patient should be placed on a standard cholesterol-lowering diet before receiving Lipitor and should continue on this diet during treatment with Lipitor. The usual starting dose is 10 mg once a day. Doses should be individualised according to the baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dosage should only be made after an interval of 4 weeks or more. The maximum recommended dose is 40 mg once a day. The maximum dose for treating patients with homozygous FH is 80 mg. Doses may be given at any time of day with or without food. **Side-Effects and Special Precautions:** The most frequent adverse effects associated with Lipitor therapy, in patients participating in controlled clinical studies were: diarrhoea, constipation, flatulence, dyspepsia, abdominal pain, headache, nausea, myalgia, arthralgia, asthenia, insomnia and rash. The following side-effects have also been reported in clinical trials: muscle cramps, myositis, myopathy, paraesthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, impotence, hyperglycaemia and hypoglycaemia. Allergic reactions have been reported rarely. Lipitor may cause elevation of creatine phosphokinase and dose-related increases in transaminase levels may occur (see **Warnings**). **Licence Holder:** Pfizer Laboratories (Pty) Ltd, Reg No 1954/000781/07, 102 Rivonia Road, Sandton, 2196. Tel (011) 320 6000. Please refer to detailed package insert for full prescribing information. PI REF 06/1997
116/LIP/10/2005/JA