Reviewer No. 1 checklist for:

An application to recommend that the representative of the beta-blocker class be switched to bisoprolol from atenolol in all indications for beta-blockade (section 12.1-12.4) in the WHO Model List of Essential Medicines

(1) Have all important studies that you are aware of been included?  
Yes ☒ No ☐

(2) Is there adequate evidence of efficacy for the proposed use?  
Yes ☒ No ☐

(3) Is there evidence of efficacy in diverse settings and/or populations?  
Yes ☒ No ☐

(4) Are there adverse effects of concern?  
Yes ☐ No ☒

(5) Are there special requirements or training needed for safe/effective use?  
Yes ☐ No ☒

(6) Is this product needed to meet the majority health needs of the population?  
Yes ☒ No ☐

(7) Is the proposed dosage form registered by a stringent regulatory authority?  
Yes ☒ No ☐

(8) What action do you propose for the Committee to take?  
I propose to switch from atenolol to bisoprolol as a representative of beta1-selective beta-blocker, due to its better profile of safety in comparison to atenolol.

(9) Additional comment, if any.

Beta-blockade is effective in: the prevention of heart failure in the post-myocardial infarct period; the prevention of recurrence of crises in chronic stable angina pectoris; the protection of ischemic myocardial; the control of ventricular fibrillation, and the treatment of young/middle-aged hypertension.
Atenolol, the representative listed in the 2010 updated WHO Model List of Essential Medicines, was found to be less effective in reducing major cardiovascular outcomes including stroke, myocardial infarction, and death, at least in older hypertensive patients, when compared to other classes of cardiovascular medicines. Concerning safety, a meta-analysis\(^1\) showed a significantly higher mortality with atenolol treatment than with other active treatment, in the five studies comprising 17671 patients who were followed up for a mean of 4.6 years. Moreover, cardiovascular mortality also tended to be higher with atenolol treatment than with other antihypertensive treatment. Stroke was also more frequent with atenolol treatment.

The choice of a beta-blocker is important as benefit or adverse effects do not seem to be a class-effect. For all indications the choice is among bisoprolol, metoprolol succinate and carvedilol for optimal efficacy. Adverse reactions are associated, mainly, with beta-2 blockade and alpha-blockade. Thus the preference is for beta-1 selective agents (metoprolol, bisoprolol), since carvedilol, a non-selective beta-blocker with an alpha-blocking activity, is associated with dizziness and postural hypotension. Metoprolol appear in high concentrations in human brain tissue and are associated with side-effects such as insomnia, dreams and nightmares.\(^2\)

Since carvedilol is a non-selective beta-blocker, the comparisons about efficacy and safety should be done between metoprolol succinate and bisoprolol, both of them selective beta-1-adrenoceptor antagonists. Unfortunately the comparisons head to head between the two medicines are scarce.

As antiarrhythmic medicines, beta-blockers demonstrate the lesser arrhythmogenic effect and efficacy in the control of arrhythmias associated to sympathetic activity. Beta-blockers are useful for rate control in patients with chronic atrial fibrillation but do not help restore sinus rhythm or have antifibrillatory effects in the atria. Bisoprolol has shown efficacy for suppression of diurnal paroxysmal atrial fibrillation, improving subjective symptoms and QOL and eliminating P-AF episodes in ECGs.\(^3\) However, in CIBIS II, despite the heart rate slowing down, morbidity and mortality rates of patients with atrial fibrillation and heart failure were similar in placebo and bisoprolol groups.\(^4\)

As antianginal medicines, beta-blockers demonstrate to prevent new crises of pain, without difference of efficacy among different agents. Beta-blockers provide symptomatic relief in patients with chronic stable angina but do not reduce the risk of myocardial infarction. However, beta 1- selective representatives are better tolerated.
Also they could be administrated in the post-myocardial infarction period, especially in patients with recurrent ischemic pain or with tachyarrhythmia in the beginning of the infarction. In the management of these patients beta-blockers remain a cornerstone. In the randomised COMMIT trial (n= 45,852) metoprolol reduced the recurrence of infarction and ventricular fibrillation, but without benefit on mortality. More cardiogenic shock episodes were seen in metoprolol group. Bisoprolol was associated with a significant reduction of 30-day cardiac death and nonfatal MI in 533 intermediate-risk patients undergoing noncardiovascular surgery.

The available current evidence does not support the use of beta-blockers as first-line drugs in the treatment of hypertension. Despite lowering blood pressure, beta-blockers have never shown to reduce morbidity and mortality in uncomplicated hypertension. Beta-blockers weakly reduce stroke and show absence of effect on coronary heart disease when compared to placebo or no treatment. They present worse outcomes in comparison with calcium-channel blockers, renin-angiotensin system inhibitors, and thiazide diuretics in the treatment of hypertension. Most of the evidence for these conclusions comes from trials where atenolol was the beta-blocker used.

One new Cochrane review evidenced that first-line low-dose thiazides reduce all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust. First-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides.

An old indirect comparison between metoprolol and atenolol demonstrated the superiority of metoprolol in patients with hypertension.

In blood pressure responses (intermediate outcome), bisoprolol, hydrochlorothiazide, amlodipine and losartan in monotherapy act similarly. Finally, the variable effects induced by different beta-blocker agents in hypertensive patients may be consequence of individual properties of these agents, or response to different pathophysiological mechanisms of hypertension according to patient age, or dependence on genetic variation of beta1- and beta2-adrenergic receptor polymorphisms.

The efficacy in heart failure is discussed in an individual review. Beta-blockers remain a cornerstone for patients with heart failure.

In conclusion, the scarce powerful evidence and the frequent incoherence about their cardiovascular benefit for all situations do not allow the selection of one beta 1-representative based on efficacy regarding hard clinical outcomes. Focusing in this, in my point of view, metoprolol and bisoprolol
seem quite interchangeable relating to efficacy. So, the choice of bisoprolol is based on its relative safety in patients with co-morbid chronic obstructive pulmonary disease (COPD). Otherwise, it is important to notice that bisoprolol is not recommended for children and pregnant women what is, at least, a disadvantage for the treatment of hypertension in these patient groups. Once-daily dosing, favouring adherence, and the ability for using in renal and hepatic insufficiencies without needed correction of dosage seem to be bisoprolol advantages.

References: