(1) Does the application adequately address the issue of the public health need for the medicine?
   Yes.
   Hypertension is increasing in LMICs and in many of these countries where resources are limited there is a need to balance the comparative efficacy of the medicines with cost/cost efficacy. Betablockers have been used in hypertension for 40 years all over the world and atenolol is still used widely.

(2) Have all important studies that you are aware of been included in the application?
   Yes.
   All key trials related to hypertension treatment were included.

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?
   Yes.
   The INVEST trial in 2003 (reference No. 6 in the review) with verapamil (add on trandolapril) versus atenolol (add on hydrochlorothiazide) were equi-effective in controlling blood pressure. All clinical outcomes including non fatal stroke were equal in both arms after 24 months of therapy.

(4) Is there evidence of efficacy in diverse settings and/or populations?
   Yes.
   Atenolol is found to be more efficacious in hypertensive patients with coexisting angina, supraventricular arrhythmia, post myocardial infarction, migraine and anxiety with somatic symptoms. Atenolol is preferred in younger patients (<60 years) with uncomplicated hypertension.

   Atenolol has been used in many populations and in diverse settings. As this is an old drug the number of studies done with this is also more.

(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?
   Yes.
Atenolol is contraindicated in patients with bronchial asthma and grade 2 and 3 atrioventricular block. Relative contraindications include glucose intolerance and metabolic syndrome. Specific adverse effects of atenolol have not been mentioned in the application as they are well known. Insomnia, fatigue, erectile dysfunction are some of the adverse effects that are common.

The LIFE trial in 2002 showed a greater incidence of stroke in patients receiving atenolol compared to losartan. However, there was a conflict of interest of the authors that was not declared. Lindholm et al did a meta-analysis of 13 RCTs using betablockers for hypertension in 2005. The conclusion was that effect of betablockers were less than optimum with an increased risk of stroke.

### ADDITIONAL CONSIDERATIONS:

6. Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?  
No.

7. Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)  
No.

8. Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?  
No - not by name but as a class yes

9. Please comment briefly on issues regarding cost and affordability of this medicine.  
Compared to other beta blockers, generic formulations of atenolol are cheaper and cost effective. Atenolol has long half life and thus once daily dosing is sufficient. This reduces the cost of the treatment and also increases the adherence.

In India, atenolol costs less than two cents per tablet. In the teaching hospital where I work the monthly consumption of atenolol is 185,000 tablets. This is widely used in India as it is cost effective, easily available and is effective.

10. Any additional comments?  
Beta blockers are included in the 18th essential medicines list of WHO for treatment of hypertension, angina, arrhythmia and heart failure. Bisoprolol is
the beta blocker included in the list with metoprolol and carvedilol as alternatives.

The accepted norm in treating hypertension is that blood pressure had to be reduced and this \textit{per se} provided cardiovascular benefit. Hence the class of primary agents chosen did not matter.

Two other studies (ref. 12 and 13) showed no difference in outcomes for betablocker, diuretics, ACEI or CCB at two years and no excess increase in stroke (ref. 13) The 2009 meta-analysis of 46 trials also showed betablockers in a positive light preventing recurrent coronary events in those with recent history of coronary heart disease.

The studies with bisoprolol and carvedilol (which are on the EML at the moment) are not long-term and there are no studies which describe cardiovascular outcomes.

(11) \textbf{Please summarise the action you propose the Expert Committee takes.}
I would suggest that the expert committee should include atenolol in the EML list for
(a) treatment of uncomplicated hypertension below 60 years of age without LVH
(b) young hypertensives with co-existing angina, post myocardial infarction, supraventricular arrhythmias, migraine and anxiety with somatic symptoms.

Bisoprolol, carvedilol and metoprolol should be used in chronic cardiac failure.