19th Expert Committee on The Selection and Use of Essential Medicines

April 8-12 2013

Expert peer review on application for new indication for Spironolactone.

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes
   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   Addition of spironolactone to usual heart failure treatment in large trials of patients\textsuperscript{1,2} with mild to severe heart failure has shown significant reduction (30 – 40%) in all cause mortality, cardiac death and improvement in heart failure class.

   c. Please provide any additional relevant information with reference

   In the RALES study\textsuperscript{1} among 1663 patients with NYHA Class III or IV heart failure, there was a 30\% reduction (HR 0.65 95\% CI 0.60 – 0.82) in all cause mortality, 35\% reduction in hospitalization (HR 0.65, 95\% CI 0.54 – 0.77) and significant improvement in heart failure symptoms with spironolactone (p < 0.001). The number needed to treat (NNT) with spironolactone for 24 months to prevent one death was just 8.8

   Similar results were seen in the JCARE CARD\textsuperscript{2} study of 963 patients. In this study even patients with mild to moderate heart failure (NYHA Class I and II) showed significantly lower all cause mortality and cardiac deaths. Beta blockers were used in 65\% of patients in both arms of the study.

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   A significant increase in the incidence of hyperkalemia, renal failure and gynaecomastia has been reported in patients on spironolactone. The risk can be minimized by ensuring that the baseline serum creatinine is less than 2.5 mg\% and serum potassium less than 5MEq per litre.

   c. Please provide any additional relevant information with reference

3. Assessment of cost and availability
   a. Have all relevant data on cost been provided
      Yes
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   The average international price published by Management Sciences for Health (MSH) in 2010 was 3.7 US cents per 25 mg tablet of spironolactone compared to approximately 1 cent for a 10 mg tablet of Enalapril. In an economic analysis of the RALES study\textsuperscript{1}, spironolactone was found to be cost effective with total savings of $713 per patient treated with spironolactone.
c. Please provide any additional relevant information with reference

There is no cost efficacy data from low and middle income countries.

d. Is the product available in several low and middle income countries?

Yes

4. Assessment of public health need
a. Please provide the public health need for this product (1-2 sentences)

Cardiovascular disease is the leading cause of mortality in the world with 80% of the mortality in LMICs. There is little data on the global prevalence of heart failure but it is a common problem all over the world.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

Spironolactone is already on the EML as a diuretic

European Society of Cardiology

American College of Cardiology

5. Are there special requirements for use or training needed for safe/effective use?

If yes, please provide details in 1-2 sentences

Yes

Hyperkalemia and significant renal function have to be ruled out before initiation. Regular monitoring of serum potassium, creatinine and estimated GFR is required.

6. Is the proposed product registered by a stringent regulatory authority?

Yes

7. Any other comments

8. What is your recommendation to the committee (please provide the rationale)

Spironolactone is already in the EML under the diuretic category

I recommend that the indication be expanded for treatment of heart failure for the following reasons

Use of spironolactone in selected patients with heart failure causes significant reduction in all cause and cardiac mortality and improvement in symptoms.

However, baseline screening for hyperkalemia and renal failure and subsequent monitoring is required.

REFERENCES
