Reviewer No. 2 checklist for review of: Hydrochlorothiazide in the WHO Essential Medicines List

(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?

The review proposes that the listing of Hydrochlorothiazide in subsection 12.4 (Medicines used in heart failure) of the EML be retained, but that the following dosage forms be listed:

- tablets 25, 50, 100 mg;
- capsules 12.5 mg;
- oral suspension 50 mg/5 ml

Although an extensive listing of products worldwide (Annex A) is provided, this does not indicate which strengths are available in each country.

Although the specific brief of this review was to consider the need for a thiazide diuretic in the management of heart failure (and accordingly, evidence was provided of the need for higher doses in the treatment of acute oedema of congestive heart failure), the major use of this group of agents is in the treatment of hypertension (for which it is also listed in section 12.3, but which may be considered to contribute to the prevention of heart failure). In the management of hypertension, there is evidence to support the use of low-dose (12.5mg) hydrochlorothiazide as a means to limit metabolic adverse
effects (hyperuricaemia, hyperglycaemia, hyperlipidaemia). It is thus recommended that the inscription in both sections 12.3 and 12.4 be consistent, and as follows:

<table>
<thead>
<tr>
<th>hydrochlorothiazide</th>
<th>Oral solid dosage form (scored): 12.5mg; 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral liquid:</td>
<td>50mg/5ml</td>
</tr>
</tbody>
</table>

(9) Additional comment, if any.

Although an oral liquid dosage form is to be included, the following statement from the review (in the form of proposed language for the Formulary) is important: “Safety and efficacy of hydrochlorothiazide and the other thiazides diuretics have not been studied in paediatric patients.”

One report of a small RCT of a thiazide in hypertension was found. This was a double-blind, randomised trial of bisoprolol/hydrochlorothiazide (n=62) compared with placebo (n=32). The combination (B/HT) induced significant reductions compared with placebo for average sitting systolic blood pressure (SiSBP) (9.3 vs. 4.9 mmHg, P<0.05) and sitting diastolic blood pressure (SiDBP) (7.2 vs. 2.7 mmHg, P<0.05). The placebo-subtracted BP reductions were greater in younger children and those with more-severe baseline hypertension. The percentage of subjects with BP less than the 90th percentile at study completion was 45% for B/HT and 34% for placebo (P=NS). Although the study demonstrated that B/HT reduced BP safely compared with placebo, the large placebo effect and failure of most subjects to achieve target BP control make it uncertain whether B/HT is appropriate first-line therapy for pediatric hypertension, particularly in adolescents with mild-to-moderate BP elevation.”

A small case series was also reported, in 10 patients with secondary hypertension (4 with renal parenchymal disease, 2 with renal artery stenosis and 4 with renal transplant rejection). The abstract states that “Captopril combined with hydrochlorothiazide produced a satisfactory therapeutic response in five patients; in four others, additional antihypertensive drugs were required”.

The only other evidence that could be found was an abstract from a very small randomised, crossover study in 9 children with nephrotic oedema. The participants were given furosemide (2 mg/kg per dose) and then either metolazone (dose varied according to weight) or chlorothiazide (10 mg/kg per dose) was added. The abstract stated that: “An additive natriuretic and diuretic effect was observed after both metolazone and thiazide were combined with furosemide. The use of both types of diuretic combination was associated with marked kaliuresis. These combinations of diuretics seem equally effective in inducing natriuresis and diuresis in edematous nephrotic patients.”

The recommendation in the review would thus seem justified, even though off-label use of thiazide diuretics in children is likely to occur, using the oral liquid dosage form in some cases.
References

