Methyldopa

Section: 12. Cardiovascular medicines > 12.3. Antihypertensive medicines

ATC codes: C02AB01

Indication	Gestational hypertension ICD11 code: JA23
INN	Methyldopa
Medicine type	Chemical agent
List type	Core
Additional notes	Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
Formulations	**Oral > Solid:** 250 mg
EML status history	First added in 2003 (TRS 920)
Sex	Female
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Methyldopa
DrugBank	Methyldopa

Summary of evidence and Expert Committee recommendations

Methyldopa was originally added to the EML in 1977 as an antihypertensive medicine. At its meeting in 2002, the Committee recommended that the section 12.3 of the Model List (Antihypertensive medicines) be reviewed in the light of new clinical guidelines for the treatment of hypertension that were being prepared jointly by WHO and the International Society for Hypertension (ISH) (1). The new guidelines update the WHO/ISH clinical guidelines for the treatment of hypertension published in 1999 (2). At the present meeting, the Committee was informed by the Department of Cardiovascular Diseases that WHO plans to incorporate the updated WHO/ISH guidelines into a set of guidelines for cardiovascular risk assessment and management, so as to bring about a paradigm shift from single risk factor management to comprehensive cardiovascular risk management. It was envisaged that this work would not be completed until the end of 2003. As an interim measure, it had been agreed that a draft statement on the management of hypertension would be prepared by the group of experts assigned to update the 1999 WHO/ISH guidelines that reflected their evidence-based work. The Committee assessed all seven antihypertensive medicines currently included in section 12.3 of the Model List in the light of the draft statement on the management of hypertension. According to the draft statement, current evidence indicates that thiazide diuretics, beta-blockers or ACE inhibitors should be used as first-line drug treatment for hypertension. The role of calcium-channel blockers is less certain; they should be used as first-line treatment only in selected populations, for example, in the elderly (where trials have indicated potential benefits in terms of stroke (3)) or in African Americans (4). The Committee noted that the role of the older medicines for the treatment of essential

hypertension (i.e. reserpine, hydralazine and methyldopa) is now considered to be questionable. Systematic reviews of trials of each of these three medicines have been carried out and have been submitted for publication, in the Cochrane database (5, 6). On the basis of these reviews, it would appear that: — there are few large randomized trials that report clinical outcomes (e.g. mortality, stroke, acute myocardial infarction) for these medicines (2, 3); — there are no large comparative clinical trials that report comparative efficacy and safety; — all of these medicines are associated with significant side effects. The Committee's attention was also drawn to the findings of a recently published study, the Anti-Hypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (the ALLHAT trial), which have also brought into question the role of alpha-blockers in the treatment of hypertension (7). In that study, patients treated with the alpha-blocker, doxazosin, had higher mortality rates than those in other treatment groups (i.e. patients treated with chlorthalidone, amlodipine and lisinopril) and the doxazosin arm of the study was suspended early. There was no significant difference between the chlorthalidone, amlodipine and lisinopril treatment groups in terms of the primary outcome of the study, namely, the development of coronary heart disease. The Committee also noted that hydralazine, reserpine and methyldopa are all off-patent and therefore usually relatively inexpensive. However, this alone is no justification to keep these medicines on the Model List as some of the ACE inhibitors and calcium-channel blockers are now also off-patent, and are probably safer and more effective. On the basis of the evidence before it, the Committee recommended that reserpine and hydralazine be deleted from the Model List for the treatment of essential hypertension on the grounds of the lack of evidence of long-term effects on mortality and morbidity and the availability of better and safer alternatives. Subsequent to the meeting Committee Members agreed that hydralazine should remain on the list for the acute treatment of severe pregnancy-induced hypertension pending a further evidence review. The Committee also recommended that prazosin be deleted as a complementary list medicine, because of the lack of evidence as to its additional benefit and given that the adverse effects of doxazosin on mortality and morbidity may be a class effect. In addition, the Committee recommended that captopril (an ACE inhibitor) be replaced by enalapril as the listed example of the therapeutic group, on the basis of its simpler dosage schedule. With respect to the use of calcium-channel blockers, preliminary evidence was presented to the Committee suggesting that dihydropyridine calcium-channel blockers as a class should not be used as first-line drug treatment for hypertension, because of the potential increased risk of adverse outcomes. The Committee thus recommended that there should be a thorough and critical review of the evidence supporting the use of dihydropyridine calcium-channel blockers as first-line drug treatment for hypertension before its next meeting, at which time a decision about their retention or deletion from the Model List would be made. The Committee considered the question of the appropriate treatment of pregnancy-induced hypertension (PIH), something that is not specifically addressed in the draft statement. Two Cochrane reviews have been published on the topic, one on mild-to-moderate PIH, last updated in 2000 (8) and one on severe PIH, updated in 2002 (9). The former concluded that data were insufficient to determine whether or not drug treatment was worthwhile at all; the second review concluded that treatment should be with a medicine with which the physician was familiar. Subsequent studies have suggested that, in terms of effects on the child, methyldopa is the medicine of choice, as it appears to have least impact on long-term development (10). The Committee therefore recommended that methyldopa be retained on the Model List (as a core list medicine) but with the addition of the following note: "Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of further evidence of the efficacy and safety of other medicines." The Committee acknowledged that there is only limited evidence for its recommendation regarding the use of methyldopa in pregnancy, but that methyldopa seems to be the safest alternative for the fetus. The Committee recommended that more research be conducted on the treatment of hypertension in pregnancy, especially with regard to long-term outcomes and effects on child development. References: 1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2002 (including the 12th Model List of Essential Medicines). Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 914) (http://www.who.int/medicines/organization/par/edl/trs/trs914.shtml,accessed 3 October 2003). 2. WHO/ISH guidelines for the management of hypertension. Geneva, World Health Organization, 1999 (withdrawn). 3. Probstfield JL. Prevention of stroke by antihypertensive treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). Journal of the American Medical Association, 1991, 265:3255–3264. 4. Cushman WC et al. Regional and racial differences in response to antihypertensive medication use in a randomised controlled trial of men with hypertension in the

United States. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Archives of Internal Medicine, 2000, 160:825–831. 5. Manyeba J et al. Reserpine for hypertension (Protocol for a Cochrane Review). In: The Cochrane Library [online database and CD-ROM], Issue 3. Oxford, Update Software, 2003. 6. Pillay A, O'Reagan L. Methyldopa in the management of essential hypertension (Protocol for a Cochrane Review). In: The Cochrane Library [online database and CD-ROM], Issue 3. Oxford, Update Software, 2003. 7. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomised to angiotensin-converting enzyme inhibitor or calcium channel blocker or vs diuretic: The Anti-Hypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial. Journal of the American Medical Association, 2002, 288:2981–2997. 8. Abólos E et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy (Cochrane Review). In: The Cochrane Library [CD-ROM], Issue 3. Oxford, Update Software, 2003:AB002252. 9. Duley L, Henderson-Smart DJ. Drugs for the treatment of very high blood pressure during pregnancy [abstract]. In: The Cochrane Library [online database and CD-ROM], Issue 3. Oxford, Update Software, 2003:AB001449 (http://www.update-software.com/abstracts/ab002252.htm). 10. Elhassan EM et al. Methyldopa versus no drug treatment in the management of mild pre-eclampsia. East African Medical Journal, 2002,79:172–175.

