

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Most guidelines define ‘hypertension’ as an office blood pressure greater than or equal to 140/90 mmHg. When using 24-h ambulatory blood pressure or home blood pressure averages to define hypertension, the diagnostic thresholds are lower than those used with office measurement. Isolated diastolic hypertension (systolic blood pressure (SBP) <140mmHg, diastolic blood pressure (DBP) >90mmHg) is more common in younger people, and isolated systolic hypertension (SBP>140mmHg, DBP<90mmHg) is the most common form of hypertension in older people¹. Essential hypertension usually clusters with other cardiovascular risk factors such as ageing, being overweight, insulin resistance, diabetes, and hyperlipidaemia. Subtle target organ damage such as left-ventricular hypertrophy, microalbuminuria, and cognitive dysfunction takes place early in the course of hypertensive cardiovascular disease, although catastrophic events such as stroke, heart attack, renal failure, and dementia usually happen after long periods of uncontrolled hypertension only². Worldwide, raised blood pressure is estimated to cause 7.5 million deaths, about 12.8% of the total of all deaths. This accounts for 57 million disability adjusted life years (DALYS) or 3.7% of total DALYS. Globally, the overall prevalence of raised blood pressure in adults aged 25 and over was around 40% in 2008. Across the WHO regions, the prevalence of raised blood pressure was highest in Africa, where it was 46% for both sexes combined. Both men and women have high rates of raised blood pressure in the Africa region, with prevalence rates over 40%. The lowest prevalence of raised blood pressure was in the WHO Region of the Americas at 35% for both sexes. Men in this region had higher prevalence than women (39% for men and 32% for women). In all WHO regions, men have slightly higher prevalence of raised blood pressure than women. This difference was only statistically significant in the Americas and Europe.

Angina is chest pain or discomfort that is caused when heart muscle does not get enough blood. Angina results from the demands of the myocardium being unable to be met by blood supply. This usually implies narrowing of one or more coronary arteries and it tends to occur at times when the heart has to do more work, eg exercise or emotional stress. Angina can much less often be caused by valve disease, especially aortic stenosis, hypertrophic obstructive cardiomyopathy, hypertensive heart disease, arrhythmias, arteritis and anaemia. Stable angina is when the pain is precipitated by predictable factors - usually exercise. Unstable angina: angina occurs at any time and should be considered and managed as a form of acute coronary syndrome.³ Epidemiology: 8% of men and 3% of women aged 55-64 years have, or have had, angina.⁴ Angina is the commonest symptom of CHD, with a prevalence of 2-4% in the UK adult population. It is essentially a set of symptoms resulting from cardiac ischaemia, the most common of which is intense but diffuse, crushing retrosternal pain, normally precipitated by exercise. It can also be brought on by eating a large meal, going out in the cold or emotional responses.⁵ 14% of men and 8% of women aged 65-74 years have, or have had, angina. People of South Asian origin in the UK have an increased risk of ischaemic heart disease but black Caribbean people have a reduced risk compared with the overall UK population rate. In both men and women the rate is significantly higher in lower socio-economic groups. Risk factors for cardiovascular disease include family history, smoking, diabetes mellitus, metabolic syndrome, hyperlipidaemia, hypertension, obesity and lack of exercise. Cardiac abnormalities, especially outflow obstruction such as aortic stenosis or hypertrophic obstructive cardiomyopathy.⁶ Recommendations for pharmacological therapy to improve prognosis in patients with stable angina: Aspirin 75 mg daily in all patients without specific contraindications (ie active GI bleeding, aspirin allergy or previous aspirin intolerance). Consider Clopidogrel as an alternative antiplatelet agent in patients with stable angina who cannot take aspirin eg Aspirin allergic.

¹ Oxford Textbook of Medicine (5 ed.). Chapter: Essential hypertension—definition, epidemiology, and pathophysiology, Author(s): Bryan Williams. Source : <http://oxfordmedicine.com/view/10.1093/med/9780199204854.001.1/med-9780199204854-chapter-161701>

In case of beta-blocker intolerance or poor efficacy attempt monotherapy with a Calcium channel blocker, long acting nitrate, nicorandil or ivabradine.

If the effects of beta-blocker monotherapy are insufficient, add a dihydropyridine calcium channel blocker
In case of beta-blocker intolerance substitute ivabradine If CCB monotherapy or combination Therapy

² Franz H Messerli, Bryan Williams, Eberhard Ritz. Essential hypertension The Lancet, Volume 370, Issue 9587, Pages 591 - 603, 18 August 2007.

³ <http://www.patient.co.uk/doctor/stable-angina-pro#ref-1>

⁴ Stable angina, NICE Clinical Guideline (July 2011)

⁵ http://www.gmccsn.nhs.uk/files/9313/5246/5647/Primary_Care_Guidelines_for_the_Treatment_of_Chronic_Stable_Angina_Pectoris.pdf

⁶ <http://www.patient.co.uk/doctor/stable-angina-pro#ref-1>

(CCB with beta-blocker) is unsuccessful, substitute the CCB with a long-acting nitrate or nicorandil. Be careful to avoid nitrate tolerance.

In 1959 Prinzmetal et al (1) described 32 cases of angina occurring at rest, reporting that the clinical characteristics of these patients differed to those with Heberden's classical angina of effort since:

1. The angina did not occur with exertion and exercise - stress tests were typically negative
2. During pain, ST segment elevation rather than depression occurred
3. The angina episodes often recurred at the same time, frequently awaking the patient from sleep
4. The episodes may be associated with arrhythmias or progress on to myocardial infarction

Considering these differences, Prinzmetal coined the term "variant angina" and speculated that the condition was due to an "increased coronary tonus" or vasospasm. Epidemiology: Coronary artery spasm affects approximately 4 out of 100,000 people. Few UK patients with angina have coronary artery spasm - possibly because of the widespread use of calcium-channel blockers for other indications.⁷ The prevalence of coronary spasm is higher in Japan and Korea. Series in Japan have identified spasm in 40% of patients with angina pain undergoing angiography.⁸ Risk factors: Age, smoking, high-sensitivity C-reactive protein (hs-CRP), and remnant lipoproteins are a significant risk factor for coronary spasm.⁹

The management of Prinzmetal angina focuses on:

- Avoiding predisposing factors such as smoking and preventing coronary spasm by the use of vasodilator therapies.
- Short-acting nitrates are utilised for acute episodes whereas the long-acting nitrates are used to prevent vasospastic episodes.
- The addition of calcium channel blockers to background nitrate therapy has been shown to reduce cardiac events in patients with variant angina.

The potassium channel opener, nicorandil, and the rho kinase inhibitor, fasudil, have both been shown to be effective in preventing coronary spasm episodes and are useful therapies for this condition

VI.2.2 Summary of treatment benefits

Amlodipin Aurovitas 5 mg tablets and 10 mg tablets are indicated for the treatment of hypertension, chronic stable angina pectoris and vasospastic (Prinzmetal's) angina.

No additional studies were conducted as Amlodipin Aurovitas is a generic medicine that is given by oral and contains the same active substance as the reference medicine, Istin ®

Because Amlodipin Aurovitas is a generic, its beneficial treatment effects are taken as being the same as the reference medicines

⁷ <http://www.patient.co.uk/doctor/Prinzmetal-Angina.htm>

⁸ Yasue H, Nakagawa H, Itoh T, et al; Coronary artery spasm--clinical features, diagnosis, pathogenesis, and treatment. J Cardiol. 2008 Feb;51(1):2-17. Epub 2008 Feb 1.

⁹ <http://www.patient.co.uk/doctor/Prinzmetal-Angina.htm#ref-2>

VI.2.3 Unknowns relating to treatment benefits

There are no unknowns relating to treatment benefits that the MAH is aware of.

VI.2.4 Summary of safety

concerns Important identified

risks

Risk	What is known	Preventability
Pulmonary oedema	Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.	Amlodipine must be discontinued. Immediately and appropriate medical therapy instituted. Physician supervision and care.

<p>Use in patients with impaired hepatic function</p>	<p>The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.</p> <p>Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.</p>	<p>Dose titration and careful monitoring</p> <p>Physician supervision and care</p>
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Risk	What is known	Preventability
<p>Risk of cardiovascular events</p>	<p>Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.</p> <p>Myocardial infarction, bradycardia and hypotension have been reported with amlodipine. In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene.</p> <p>Gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia</p>	<p>Amlodipine must not be prescribed to patients with conditions such as low blood pressure, serious circulation problems in arms and legs, very slow heartbeat and certain other heart rhythm problems, and recently experienced heart failure.</p> <p>Patients should inform physician about any unusual heart symptoms.</p> <p>Physician supervision and care</p>

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use in elderly patients	<p>Amlodipin Aurovitas used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care.</p> <p>Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half life in elderly patients. Increases in AUC and elimination half life in patients with congestive heart failure were as expected for the patient age group studied.</p> <p>A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).</p> <p>The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction.</p>

Risk	What is known (Including reason why it is considered a potential risk)
Effect on male fertility	<p>Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.</p> <p>In an rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.</p>

Missing information

Risk	What is known
Use in Pregnancy and lactation	<p>The safety of amlodipine in human pregnancy has not been established. Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.</p> <p>Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.</p> <p>It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.</p>
Use in Children under 6 years old	No data is available in children under 6 years age old for Amlodipin aurovitas.
Use in hypertensive crisis	The safety and efficacy of amlodipine in hypertensive crisis has not been established.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures. This medicine has no additional risk minimisation measures. This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan

Not applicable

Studies which are a condition of the marketing authorization

None

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
NA	NA	NA	NA