7.2 Part VI.2 Elements for a Public Summary

7.2.1 Part VI.2.1 Overview of disease epidemiology

Overall, approximately 20% of the world's adults are estimated to have hypertension, when hypertension is defined as BP in excess of 140/90 mm Hg. The prevalence dramatically increases in patients older than 60 years: In many countries, 50% of individuals in this age group have hypertension. Worldwide, approximately 1 billion people have hypertension, contributing to more than 7.1 million deaths per year. National health surveys in various countries have shown a high prevalence of poor control of hypertension. These studies have reported that prevalence of hypertension is 22% in Canada, of which 16% is controlled; it is 26.3% in Egypt, of which 8% is controlled; and it is 13.6% in China, of which 3% is controlled. A progressive rise in BP with increasing age is observed. Age-related hypertension appears to be predominantly systolic rather than diastolic. The SBP rises into the eighth or ninth decade, whereas the DBP remains constant or declines after age 40 years. The third NHANES survey reported that the prevalence of hypertension grows significantly with increasing age in all sex and race groups. The age-specific prevalence was 3.3% in white men (aged 18-29 y); this rate increased to 13.2% in the group aged 30-39 years. The prevalence further increased to 22% in the group aged 40-49 years, to 37.5% in the group aged 50-59 years, and to 51% in the group aged 60-74 years. In another study, the incidence of hypertension appeared to increase approximately 5% for each 10-year interval of age. According to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII), in individuals older than 50 years, SBP of greater than 140 mm Hg is a more important cardiovascular disease risk factor than DBP. Beginning at a BP of 115/75 mm Hg, the cardiovascular disease risk doubles for each increment of 20/10 mm Hg. Individuals who are normotensive (SBP < 120 mm Hg; DBP < 80 mm Hg) at 55 years will have a 90% lifetime risk of developing hypertension. However, the age-related BP rise for women exceeds that of men. The prevalence of hypertension was reported at 50% for white men and 55% for white women aged 70 years or older. (1)

The prevalence of angina increases sharply with age in both sexes from 0,1-1% in women aged 45-54 to 10-15% in women aged 65-74 and from 2-5% in men aged 45-54 to 10-20% in men aged 65-74. Therefore, it can be estimated that the most European countries, 20 000 – 40 000 individuals of the population per million suffer from angina. (2)

7.2.2 Part VI.2.2 Summary of treatment benefits

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements. The mechanism also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina). In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-center, randomized, double- blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

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%). The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001).

The diagnostic threshold for hypertension in the elderly is highly variable and hypertension is frequently untreated or inadequately controlled in the elderly population, despite the well-documented benefits of treatment. Controlling hypertension in older patients appears to yield as much, if not more, clinical benefit as it does in younger patients. The combined results of six studies in patients aged 60-96 years demonstrate that treatment of either diastolic or isolated systolic hypertension reduces the incidence of all cardiovascular complications by approximately 30%, fatal coronary events by 26% and fatal stroke by 33%. Similar benefits were seen in two other studies of elderly patients with isolated systolic hypertension (3).

7.2.3 Part VI.2.3 Unknowns relating to treatment benefits

None

7.2.4 Part VI.2.4 Summary of safety concerns

Table 7-5 Important identified risks

Risk	What is known	Preventability
Arrhythmia	A risk of arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) as a very rear adverse event is suspected.	Patients should be carefully monitored for arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation).
Pulmonary oedema in patients with severe heart failure	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.	Patients with heart failure should be treated with caution. 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.
In patients with severe hepatic impairment	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.

Table 7-6 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Drug interaction with CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem)	Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.
Drug interaction with CYP3A4 inducers (e.g., rifampicin, hypericum perforatum)	There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Table 7-7 Important missing information

Risk	What is known (Including reason why it is considered a potential risk)
Use in pregnancy and breast feeding	The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses. Use in pregnancy is only

Risk	What is known (Including reason why it is considered a potential risk)
	recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus. 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.
Use in children under 6 years of age	No data are available on children under 6 years old. The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established

7.2.5 Part VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a 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.

7.2.6 Part VI.2.6 Planned post authorisation development plan

None

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

None