7 October 2011
EMA/876851/2011
Patient Health Protection

Assessment report pursuant to Article 30 of Directive 2001/83/EC, as amended

Norvasc and associated names

INN of the active substance: Amlodipine

Marketing authorisation holder: Pfizer group of companies

Procedure no: EMEA/H/A-30/1288

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 2 February 2011, Pfizer Limited presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, as amended, in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products:

Norvasc and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the February 2011 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Dr Catherine Moraiti as rapporteur and Dr Alar Irs as co-rapporteur.

Norvasc medicinal products are registered in the following EU Members States: Austria, Belgium, Bulgaria, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden and United Kingdom and also in Iceland and Norway.

Norvasc medicinal products are currently not registered in the Czech Republic.

2. Scientific discussion

2.1. Introduction

Norvasc (amlodipine) is a calcium ion antagonist of the dihydropyridine group, and acts by inhibiting the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of action of amlodipine as an antihypertensive is due to a direct effect on vascular smooth muscle. Amlodipine reduces myocardial ischemia through the dilation of the main coronary arteries, improving oxygen delivery to the heart, and through the reduction of peripheral resistance (afterload), decreasing myocardial oxygen consumption.

Norvasc received first regulatory approval on 08 March 1989 in Belgium and as of 01 August 2010, it was approved in 140 countries and marketed in 135 countries, including all member states in the EU. Amlodipine has not been withdrawn or suspended due to safety concerns in any country.

Amlodipine besylate 5 mg and 10 mg is registered nationally in all EU countries as tablets except in Belgium, Cyprus, Greece, France and Luxembourg where capsules only are registered. Initial licence applications dating from 1988 were based on identical dossiers, supplemented with additional data in some countries during national assessments. Licences were granted in the majority of countries by the mid-1990s.

Since initial registration, extensions of the marketing authorisations for amlodipine capsules 5 mg and 10 mg were completed in Romania and Lithuania. Duplicate marketing authorisations for amlodipine besylate tablets 5 mg and 10 mg are held in the Spain, Denmark and Italy; duplicate MA applications are ongoing in Germany and Ireland.

Due to the divergent national decisions taken by Member States concerning the authorization of the above-mentioned product, Pfizer Limited (on behalf of the national marketing authorisation holders) notified the EMA of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised SmPCs for the above-mentioned product and thus to harmonise the SmPCs across the EU.

2.2. Quality aspects

2.2.1. Introduction

Pfizer took the opportunity to harmonise the Quality dossier for Norvasc and associated names as part of the Article 30 referral procedure.

The harmonised dossier was provided for the active substance (amlodipine besylate) and for products containing this substance: Norvasc 5 mg and 10 mg tablets, Norvasc 5 mg and 10 mg capsules.

2.2.2. Active Substance

Sufficient information was provided on the active substance – amlodipine besylate.

Pfizer obtained a Certificate of Suitability with requirements of European Pharmacopoeia (CEP) for amlodipine besylate (R1-CEP 2001-342-Rev 01). The detailed information on characterisation and control of the substance, reference materials and container closure system was provided to the EDQM and assessed before granting the CEP.

Amlodipine besylate is described in the European Pharmacopoeia and its manufacturer has confirmed that the substance complies with these requirements. A copy of the CEP has been provided. The CEP includes test for residual solvent used during the synthesis. A retest period and storing conditions of the active substance are confirmed in the CEP.

Pfizer also provided, as part of the harmonised dossier, an evaluation of the potential genotoxic impurities - alkyl benzenesulfonate esters. This evaluation was presented to EDQM as part of the CEP renewal for amlodipine besylate. The formation of alkyl besylate esters and related compounds in amlodipine besylate was considered to be unlikely and no safety risk had been identified.

Harmonisation of the dossier for the active substance was achieved by introduction of the CEP. The CEP certified amlodipine besylate will be the only source of the active substance that will be used for manufacturing of tablets and capsules.

Other manufacturers of the active substance are no longer active and were excluded from the harmonized dossier.

2.2.3. Finished Medicinal Product

Tablets

The provided dossier describes sufficiently the composition, manufacture and control of tablets.

Harmonisation of the data for tablets included, among others, harmonisation of the description for the appearance (5 mg and 10 mg) and scoring (5 mg). Also other specification parameters such as dissolution testing, related substances and analytical methods used to control the quality of the product were harmonised.

Although in the SmPC it is explained that doses of 2.5 mg can not be delivered with this product as the score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses, the CHMP was of the opinion that it should be possible to deliver all doses mentioned in the SmPC. Therefore the CHMP recommended future development: the MAH should either adapt the score line of the 5 mg tablets in order to make it possible to divide them into equal parts or to introduce an additional strength of 2.5 mg for tablets.

The shelf-life of tablets is supported by the stability data given. The storage precaution “Do not store above 25°C” is included in the product information.

Capsules

The provided dossier describes sufficiently the composition, manufacture and control of capsules.

Information about the process and manufacturers involved in the manufacturing process of capsules was updated and harmonised. The latest TSE CEPs for gelatine were also provided and included in the harmonised dossier.

Furthermore, specifications for capsules were harmonised, this included harmonisation of requirements for appearance, disintegration, microorganism count tests and dissolution testing.

In addition Pfizer has provided more current stability data for capsules in support of the proposed shelf-life and storage conditions for the capsules. The shelf-life of tablets is supported by the stability data given. The storage precaution “Do not store above 30°C” is included in the product information.

2.2.4. Discussion and Conclusions on quality

Sufficient information was provided on the active substance (amlodipine besylate) via CEP. Information on development, manufacture and control of tablets and capsules has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that these products should have a satisfactory and uniform performance in the clinic.

The MAH has agreed to address all quality issues in the ongoing development of the medicinal product and to implement them via variations, where necessary. The CHMP recommended that the MAH either adapt the score line of the 5 mg tablets in order to make it possible to divide them into equal parts or to introduce an additional strength of 2.5 mg for tablets (Annex 3.10; letter of undertaking).

2.3. Clinical aspects

2.3.1. Introduction

The main ongoing regulatory activities concerning clinical data are as follows:

- MA Renewal applications: Austria, Bulgaria, Greece, France, Ireland, Italy, Romania, Sweden, Slovenia
- Duplicate licence application for amlodipine tablets: Germany, Ireland
- PSUR Worksharing procedure DK/H/PSUR/0007/001 completed 18 May 2009. Core Safety Profile (CSP) implementation via variations were approved in all EU member states except Belgium, Czech Republic, Cyprus, Greece, France, Ireland, Portugal, Romania, Slovenia, Sweden, United Kingdom where procedures remain ongoing.
- Article 45 Paediatric use procedure NL/W/0002/pdWS/001 completed 21 October 2009. The outcome of this worksharing procedure provides information on use in children in the SmPC sections 4.2, 5.1 and 5.2. The implementation of the outcome of the Article 45 was approved via national variations in all EU member states except Austria, Belgium, Czech Republic, Germany, Spain, Ireland, Italy, Poland, Portugal, Romania, Slovenia and Sweden where procedures remain ongoing.

- SmPC update of Section 4.5 grapefruit interaction statement approved in all EU except Belgium, Greece, France, Ireland, Netherlands, Poland, Portugal, Romania, Slovenia and Sweden where procedures remain ongoing.

2.3.2. Critical Evaluation

Section 4.1 – Therapeutic Indications

Hypertension

The primary indication of hypertension is approved in all EU member states. The wording of the indication is presented with slight differences in some national SmPCs i.e: "essential hypertension", "arterial hypertension" or more expanded wording: "Norvasc is indicated for the first line treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients."

Efficacy in mild to moderate hypertension was originally evaluated in 18 placebo/active comparator controlled studies. The results of the placebo controlled studies demonstrated that once daily amlodipine is an effective treatment in mild to moderate hypertension, allowing 24 hour control. Other studies indicated that amlodipine reduces blood pressure to the same extent as standard comparative agents, is effective in combination with other agents, and that long-term tolerance does not occur. The data from the relevant clinical studies support this indication.

Chronic stable angina pectoris

The primary indication of angina is approved in all EU member states.

Fourteen studies provided data on the efficacy of amlodipine as a treatment of exertional angina. Amlodipine treatment resulted in decreased angina, compared to placebo in all placebo-controlled studies but one study. In some studies, but not all, there were statistically significant differences in treatment related changes in exercise times, in favour of amlodipine.

Vasospastic (Prinzmetal's) angina

The specific indication for vasospastic (Prinzmetal's) angina is approved in all EU member states except Denmark and Sweden and also in Iceland and Norway.

A summary of the data from Study 160 has been provided. This was a 4-week multicenter, randomized, double-blind, placebo controlled study to assess the safety and efficacy of amlodipine 10 mg (once daily) in patients with vasospastic angina pectoris.

The study consisted of a 3- to 14-day single-blind run-in phase followed by a 4-week double-blind treatment phase. All patients were required to have a history of recurrent attacks of angina at rest and one of the following: angina at rest associated with reversible ST segment elevation; spontaneous or ergonovine-induced coronary artery spasm during coronary angiography associated with either ischemic chest pain or ST segment shifts; or ergonovine-induced reversible perfusion defects documented by thallium 201 myocardial scintigraphy. In addition, all patients were required to have had at least 3 or more attacks of angina at rest during the placebo run-in period. Of the 62 patients who entered the single-blind run-in period, 52 patients (24 amlodipine, 28 placebo) entered double-blind treatment.

The primary efficacy endpoint was angina attack rate. Additional endpoints included discontinuation rate due to therapeutic failure, nitroglycerine consumption, investigator global evaluation, and patient self-assessment.

Analysis showed that angina attack frequency was significantly reduced in the amlodipine group compared to placebo ($p<0.01$). A total of 2 (8%) amlodipine patients discontinued from the study due to lack of clinical improvement compared to 7 (25%) placebo patients. This difference approached

statistical significance (p=0.055). Not all of the other endpoint assessments were significantly in favour of amlodipine.

The incidence of adverse effects in patients treated with amlodipine and placebo was similar. No patients discontinued due to adverse effects.

It was concluded that amlodipine 10 mg administered once-daily resulted in a statistically significant reduction of angina attack frequency, and was safe to use in patients with vasospastic angina pectoris.

Coronary Artery Disease (CAD)

The indication for coronary artery disease (CAD) is only approved in 2 member states - Latvia and Romania.

Based on the small number of current registrations, the MAH did not wish to pursue the CAD indication in the EU, and proposes not to include such information in Section 4.1.

CHMP conclusion

The data supporting the proposed indications of hypertension, chronic stable angina pectoris and vasospastic (Prinzmetal's) angina were considered to be acceptable by the CHMP and the following wording proposed by the MAH was agreed:

'*Hypertension*

Chronic stable angina pectoris

Vasospastic (Prinzmetal's) angina'

Section 4.2 - Posology and method of administration

Dosing instructions (including maximum dose) are harmonised in all EU countries. All countries recommend an adult starting dose of 5 mg which may be increased to a maximum of 10 mg.

The MAH proposed dosage recommendation text regarding use in adults is harmonised across all EU national SmPCs. The CHMP was of the view that the text proposed by the MAH is supported by the data submitted with the initial application.

Most but not all countries have dosing recommendations for use in combination with antihypertensive drugs. Only Austria, Cyprus and Greece have a statement on use in combination with antianginal drugs.

Amlodipine in combination with other antihypertensive medicinal products

The use of amlodipine in combination with antihypertensive drugs is mentioned in Section 4.1 in many but not all countries, although similar statements are present also in other SmPC Sections, 4.2 and 4.5.

Clinical study data supporting combination use with thiazide diuretics, beta blockers, and ACE inhibitors were included with the initial application. Specifically the initial application included 3 clinical studies, which demonstrated that the addition of amlodipine therapy to hypertensive patients not adequately controlled on monotherapy with hydrochlorothiazide, atenolol, or captopril, produced a further significant reduction of blood pressure compared to placebo.

Use in combination with alpha blockers was not a part of the initial submission. The MAH added it to the amlodipine Company Core Data Sheet in May 1997, which was subsequently added to many national SmPCs supported by the following publications:

- Brown, MJ and Dickerson JE. Alpha-blockade and calcium antagonism: an effective and well-tolerated combination for the treatment of resistant hypertension, J. Hypertension 1995, 13:701-707. This publication concluded that the combination of alpha-blockade and calcium antagonism should be useful for resistant hypertensive patients who can not tolerate beta-blockers and ACE inhibitors.
- The beneficial effect of combination with alpha blockers was later substantiated in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial in which patients who did not achieve blood pressure target with amlodipine plus perindopril were driven to target achievement by adding Cardura (doxazosin) gastrointestinal therapeutic system (GITS) to their therapy.

The MAH argued that international hypertension treatment guidelines are increasingly emphasizing the importance of combination therapies. Current guidelines suggest that 2 drugs be used for initial therapy even if there is a 20/10 mmHg elevation in blood pressure above goal. In general, combining drugs from complementary classes is approximately 5 times more effective in lowering blood pressure than increasing the dose of 1 drug, and dihydropyridine calcium channel blockers such as amlodipine are recognized to be an important component of the available anti-hypertensive armamentarium. The guidelines suggest the use of combination therapy, because clinical trials have demonstrated that small differences in on-treatment blood pressure can translate into substantial differences in clinical event rates. Available data suggests that at least 75% of hypertensive patients will require combination therapy to achieve blood pressure targets. Thus, it is the MAH's view that it is important to emphasize to physicians that amlodipine has been used to treat hypertension in combination with a variety of agents.

The CHMP agreed that combination therapy using two and recently even three antihypertensive medicinal products is common practice, as it is recommended by hypertension treatment guidelines internationally.

Amlodipine in combination with other antianginal medicinal products

Many but not all EU national SmPCs include the proposed SmPC statement regarding concomitant use with other antianginal agents.

The MAH briefly referred to data from the initial application. There were 2 clinical studies demonstrating safety and efficacy in patients with angina not adequately controlled with beta blockers and/or long-acting nitrates. The results from these studies indicated that addition of amlodipine to background antianginal therapy produced a further significant reduction of anginal symptoms as compared to placebo.

In addition the MAH argues that combination therapy is an important option in the management of angina. The combination of lower doses of 2 agents may be used when 1 agent is not tolerated at a higher dose. Combination therapy may also be used when patients have poorly controlled angina symptoms despite optimal doses of a single agent. Importantly, combination therapy can be more effective than monotherapy [1]. For example, nitrates are more effective when combined with calcium antagonists, and beta blockers and calcium channel antagonists in combination generally produce greater relief of angina, reduction in ischemic episodes, and improvement in maximal exercise time. Thus, the MAH was of the view that it is important to emphasize to physicians that amlodipine has been used effectively and with appropriate safety in combination with other antianginal drugs.

The MAH's proposal on combination therapy with other antianginal medicinal products was considered to be acceptable by the CHMP.

Paediatric population

[1] Fihn SD, Williams SV, Daley J, et al. Guidelines for the Management of Patients with Chronic Stable Angina: Treatment. Ann Intern Med. 2001; 135: 616-632

The MAH has adopted the paediatric wording as finalised for the Article 45 Paediatric use procedure NL/W/0002/pdWS/001 completed on 21 October 2009, and as such was accepted by the CHMP.

Currently the MAH does not have a dosage form approved in the EU that delivers 2.5 mg amlodipine for use in the paediatric population. This was commented upon in the final assessment report from the Article 45 Paediatric Use procedure. Since the breakability of the scored 5mg tablet had not been approved or submitted anywhere in the EU at the start of this Art 30 referral procedure, it was therefore considered to be outside the scope of this procedure.

Special populations

Administration in elderly and patients with renal impairment is already aligned in the vast majority of EU member states. Most countries recommend normal adult doses in the elderly without qualification. In Latvia 2.5 mg is initially recommended, and Austria, Slovakia, Sweden, Netherlands, & Greece advise caution with dose escalation. Normal adult doses are proposed for the elderly and also for patients with renal impairment.

Most countries make no dosing recommendation in hepatic impairment and refer to a cautionary statement in section 4.4 of the SmPC. Some countries advise that no dosing recommendations have been established and advise caution with dose escalation. Two countries (Hungary and Latvia) recommend lower doses initially in patients with hepatic impairment.

The safety and pharmacokinetic profile of amlodipine in patients with hepatic impairment was studied in an open-label, single dose study in which amlodipine 5 mg was administered to subjects with chronic, stable hepatic insufficiency and to healthy subjects (Study Report: Protocol 053-369; An Open Study to Assess the Safety and Pharmacokinetic Profile of Oral Amlodipine in Patients with Stable Chronic Hepatic Insufficiency Compared with a Group of Convalescing Subjects Without Hepatic Impairment).

Half-life was longer in patients with hepatic impairment than in healthy patients. Additionally, the area under the curve (AUC) was higher in patients with hepatic impairment than in healthy patients, but the difference was not statistically significant. No meaningful differences in tolerability were noted between groups. Dosing recommendations have not been established and thus the MAH considered it appropriate to recommend caution when administering amlodipine to patients with hepatic impairment.

CHMP conclusion

Taking into account the recommendation of the CHMP, the following wording proposed by the MAH was agreed:

'*Posology*

Adults

For both hypertension and angina the usual initial dose is 5 mg Norvasc once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.

In hypertensive patients, Norvasc has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, Norvasc may be used as monotherapy or in combination with other antianginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.

No dose adjustment of Norvasc is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Special populations

Elderly

Norvasc 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 (see sections 4.4 and 5.2).

Hepatic impairment

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2). The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Renal impairment

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

Paediatric population

Children and adolescents with hypertension from 6 years to 17 years of age

The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients (see sections 5.1 and 5.2).

Doses of amlodipine 2.5 mg are not possible with this medicinal product.

Children under 6 years old

No data are available.

Method of administration

Tablet for oral administration.

Hard capsule for oral administration.'

Section 4.3 - Contra-indications

Some countries maintain additional contraindications that pre-date the PSUR Worksharing procedure including:

- Germany retains the contraindication of "acute myocardial infarction (within the first 4 weeks)" rather than the CSP contraindication in "all patients with haemodynamically unstable heart failure after an acute myocardial infarction"

This divergence was raised and addressed during the PSUR Worksharing Procedure. At that time, the MAH argued that all patients with haemodynamically unstable heart failure post acute myocardial infarction are at greater risk if treated with amlodipine, irrespective of time. It was agreed in this Worksharing procedure to replace the reference to 4 weeks or 28 days post-myocardial infarction in the 4.3 contraindication section *with 'haemodynamically unstable heart failure after acute myocardial infarction.'*

- Austria and Germany also include the contraindication "severe hepatic dysfunction."

Patients with "severe hepatic dysfunction" were not included in amlodipine clinical studies. The SmPC Guideline states that patient populations not studied in the clinical trial programme should be mentioned in section 4.3. Therefore caution regarding amlodipine use in patients with hepatic impairment is included in the Special warnings and precautions section 4.4 of the SmPC and also mentioned in the Posology and method of administration section 4.2.

- Romania includes the contraindication "Children under 6 years."

There are no amlodipine clinical efficacy studies available in children under 6 years of age. In addition, the Article 45 Paediatric Procedure outcome did not require a contraindication in children under 6 years. On the basis of the above and in accordance with the SmPC Guideline, which states that lack of data alone must not lead to a contraindication, the MAH has provided information in section 4.2 of the SmPC that there are no data with amlodipine in children less than 6 years of age.

The Contraindications Sections is in line with the Core Safety Profile (CSP) that was accepted during the PSUR Worksharing procedure DK/H/PSUR/0007/001- completed 18 May 2009. Therefore the CHMP agreed that Section 4.3 can be accepted with the wording proposed by the MAH.

CHMP conclusion

'Amlodipine is contraindicated in patients with:

- *hypersensitivity to dihydropyridine derivatives, amlodipine or to any of the excipients.*
- *severe hypotension.*
- *shock (including cardiogenic shock).*
- *obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).*
- *haemodynamically unstable heart failure after acute myocardial infarction.'*

Section 4.4 - Special warnings and precautions for use

Only minor points of disharmony have been identified by the MAH, since all EU MS have implemented the CSP wording.

The CHMP noted that section 4.4 is in line with the CSP that was accepted during the PSUR Worksharing procedure DK/H/PSUR/0007/001 and completed 18 May 2009. Cautionary statements on patients with heart failure within the first month of myocardial infarction, impaired hepatic function, and renal failure are covered by the PSUR Worksharing CSP final text currently filed in all EU countries and approved in many. In the SmPC proposed by the MAH, the long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) was summarised, where the reported incidence of pulmonary oedema was observed to be higher in the amlodipine treated group than in the placebo group. Additionally the recommendation by the CHMP to include a general cautionary statement that calcium channel blockers may increase the risk of future cardiovascular events and mortality in patients with congestive heart failure was also included.

More detailed information on dosing recommending caution in patients with hepatic impairment was also agreed by the CHMP, and included in this section.

The statement on the use of amlodipine in children in the proposed harmonised SmPC, is based on the outcome of the Article 45 Paediatric Procedure, which has been included in section 4.2, where dosing recommendations for children aged 6 to 17 years are provided. Therefore the statement 'Amlodipine is not indicated in children' that was included in the CSP has been omitted by the MAH, and was considered acceptable by the CHMP.

CHMP conclusion

Taking into account the recommendation of the CHMP, the following wording proposed by the MAH was agreed:

'The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure

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 (see section 5.1). 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.

Use in patients with impaired hepatic function

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.

Use in elderly patients

In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.2).

Use in renal failure

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.'

Section 4.5- Interaction with other medicinal products and other forms of interaction

All countries have implemented the amlodipine PSUR Worksharing CSP *DK/H/PSUR/0007/001* completed on 18 May 2009, with the exception of some divergences identified below:

- Some countries (Spain, Hungary, Ireland, Malta, Romania and the United Kingdom) additionally include information on administration with other drugs not specified in the CSP

The MAH proposed to retain the following opening statement on concomitant treatment, in line with the 4.5 Interaction texts currently approved in a number of EU countries: *'Norvasc has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.'* The MAH referred to clinical data from efficacy/safety studies that support combination use with thiazide diuretics, beta blockers, alpha blockers, ACE inhibitors and long-acting nitrates that were included with the initial application in support of their proposal.

In view of the fact that the potential interaction of amlodipine with antihypertensive agents has already been included in proposed harmonised SmPC, the CHMP considered that the opening statement on concomitant treatment mentioned above was not necessary.

- Germany advises close monitoring in patients receiving amlodipine and beta-blockers; *'Patients receiving amlodipine and beta-blockers concomitantly must be closely monitored, because the antihypertensive effects can be additive. It is known that beta-blockers can exacerbate heart failure. Clinical trials with amlodipine produced no evidence of negative inotropic effects.*

The MAH considered this statement addressing additive effects of antihypertensive agents to be generally covered by the following PSUR Worksharing CSP drug interaction statement, which the MAH has proposed in section 4.5 of the harmonised SmPC: *'The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other antihypertensive agents.'*

The CHMP agreed with the PSUR Worksharing CSP drug interaction statement, which the MAH has proposed in section 4.5.

- Germany and Spain note the possible additive antihypertensive effects of amlodipine and sildenafil.

The sildenafil statements included in the two national SmPCs do not provide important new safety information. The potential for additive effects of drugs that lower blood pressure is covered by the SmPC proposed statement by the MAH; '*The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other antihypertensive agents.'*

The CHMP agreed with the MAH's proposal since the issue is already covered by the wording of the CSP that is reflected in the proposed harmonised SmPC.

The MAH also proposed to include the concomitant use of non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs with amlodipine, and referred to clinical trials from published data, where such use was well tolerated, to support their argument.

However the CHMP was of the view that these data are not sufficient to support the claim for lack of interactions with these specific classes of medicines, since they are not extracted from specifically designed Pharmacokinetic/interaction studies. Therefore CHMP was of the view that this information should also be deleted from Section 4.5.

CHMP conclusion

Taking into account the comments of the CHMP, the following wording proposed by the MAH was agreed:

'*<u>Effects of other medicinal products on amlodipine</u>*

CYP3A4 inhibitors: 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.

CYP3A4 inducers: 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.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.'

Section 4.6 – Fertility, pregnancy and lactation

No disharmony is observed between MS. All countries have approved or are implementing the EU Workshare CSP 4.6 text adopted in the proposed SmPC.

However the CHMP recommended some amendments to the sections on pregnancy and fertility. As there have been a number of publications concerning sperm anomalies in human and animal studies, the MAH agreed to update the section on fertility stating that although clinical data are insufficient regarding the potential effect of amlodipine on fertility, adverse effects on male fertility have been found in one rat study.

A brief statement on reproductive toxicity in animal studies was also added by the MAH under the section pregnancy (and cross references to section 5.3) in response to the CHMP recommendation.

CHMP conclusion

Taking into account the recommendation of the CHMP, the following wording proposed by the MAH was agreed:

'Pregnancy

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

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.

Breast-feeding

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.

Fertility

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 (see section 5.3).'

Section 4.7 - Effects on ability to drive and use machines

No major differences are observed between the MS. All countries except Germany and Austria have approved or are implementing the EU Worksharing CSP 4.7 adopted text. The text included in the German and Austrian product information texts recommends caution especially at the beginning of treatment, during adjustment of dosage, switching of therapy and in case of concomitant alcohol consumption. However the MAH believes the CSP text adopted in the proposed harmonised SmPC adequately covers this point, and is supported by the CHMP.

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:

'Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.'

Section 4.8 - Undesirable effects

All countries except Germany have approved or are implementing the EU Worksharing CSP text for section 4.8. This text is included in the proposed harmonised SmPC section 4.8.

However an isolated difference was highlighted by the MAH, where tachycardia was included in the initial German SmPC based on the clinical trial data. Ventricular tachycardia has been included in the proposed SmPC, even though it is known that tachycardia is not a commonly (≥1% and <10%) reported adverse event in amlodipine controlled or open clinical trials, and a causal relationship between amlodipine and tachycardia is uncertain.

The CHMP accepted the wording proposed by the MAH for Section 4.8, which is in line with the Core Safety Profile that was accepted during the PSUR Worksharing procedure DK/H/PSUR/0007/001 and completed 18 May 2009.

In addition the necessity of including extrapyramidal syndrome (EPS) as an undesirable effect was discussed since exceptional cases of EPS have been reported, and evidence for an association of EPS with calcium channel blockers (CCBs) exists. EPS has also been discussed in the PSUR WS procedure that was concluded on May 2009, and a further review will take place during the assessment of the second PSUR WS (scheduled for May 2011). Therefore the CHMP recommended that this information is included in the product information and that appropriate revisions are made if necessary, as indicated by the medical and scientific evidence, following further review during the second PSUR assessment. The MAH agreed to the inclusion of EPS as recommended by the CHMP.

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:
'*Summary of the safety profile*

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	*Very rare*	*Leukocytopenia, thrombocytopenia*
Immune system disorders	*Very rare*	*Allergic reactions*
Metabolism and nutrition disorders	*Very rare*	*Hyperglycaemia*
Psychiatric disorders	*Uncommon*	*Insomnia, mood changes (including anxiety), depression*
	Rare	*Confusion*
Nervous system disorders	*Common*	*Somnolence, dizziness, headache (especially at the beginning of the treatment)*
	Uncommon	*Tremor, dysgeusia, syncope, hypoesthesia, paresthesia*
	Very rare	*Hypertonia, peripheral neuropathy*
Eye disorders	*Uncommon*	*Visual disturbance (including diplopia)*
Ear and labyrinth disorders	*Uncommon*	*Tinnitus*
Cardiac disorders	*Common*	*Palpitations*
	Very rare	*Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)*
Vascular disorders	*Common*	*Flushing*
	Uncommon	*Hypotension*
	Very rare	*Vasculitis*
Respiratory, thoracic and mediastinal disorders	*Uncommon*	*Dyspnoea, rhinitis*
	Very rare	*Cough*
Gastrointestinal disorders	*Common*	*Abdominal pain, nausea*
	Uncommon	*Vomiting, dyspepsia, altered bowel habits (including diarrohea and constipation), dry mouth*
	Very rare	*Pancreatitis, gastritis, gingival hyperplasia*
Hepatobiliary disorders	*Very rare*	*Hepatitis, jaundice, hepatic enzymes increased**
Skin and subcutaneous tissue disorders	*Uncommon*	*Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema*
	Very rare	*Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity*
Musculoskeletal and	*Common*	*Ankle swelling*

connective tissue disorders	*Uncommon*	*Arthralgia, myalgia, muscle cramps, back pain*
Renal and urinary disorders	*Uncommon*	*Micturition disorder, nocturia, increased urinary frequency*
Reproductive system and breast disorders	*Uncommon*	*Impotence, gynecomastia*
General disorders and administration site conditions	*Common*	*Oedema, fatigue*
	Uncommon	*Chest pain, asthenia, pain, malaise*
Investigations	*Uncommon*	*Weight increase, weight decrease*

**mostly consistent with cholestasis*

Exceptional cases of extrapyramidal syndrome have been reported.'

Section 4.9 – Overdose

All countries follow the exact EU Worksharing CSP section 4.9 text or similar text. The CHMP accepted the wording proposed by the MAH for section 4.9, which is in line with the CSP that was accepted during the PSUR Worksharing procedure DK/H/PSUR/0007/001 and completed 18 May 2009.

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:

'In humans experience with intentional overdose is limited.

Symptoms

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.'

PHARMACOLOGICAL PROPERTIES

Section 5.1 - Pharmacodynamic properties

The information on the pharmacology and the mode of action is broadly consistent across the EU Member States in the description of amlodipine as a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) that inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The basic texts describing the

pharmacodynamic properties in the Norvasc EU national SmPCs are similar or identical to the proposed harmonised text, and these texts are supported by the data submitted with the initial marketing authorisation application.

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:

'Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01.

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. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

1) 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.

2) The mechanism of action of amlodipine 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. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm 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.'

Use in patients with coronary artery disease (CAD)

The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) and/or Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) studies were submitted in some (Austria, Bulgaria, Estonia, Lithuania, Latvia, and Romania) but not all EU countries (Cyprus, Germany, Greece, Spain, Finland, Ireland, Netherlands, Italy, Norway, and the United Kingdom).

Only the PREVENT study description is included in Belgium, Denmark, Hungary, Iceland, Lithuania, Poland, Portugal, Slovak Republic, Slovenia, and Sweden, and only the CAMELOT study is described in France.

PREVENT was an angiographic trial and CAMELOT was subsequently conducted with the cardiac events endpoint as the primary endpoint.

The primary outcome in the PREVENT study was the average 36-month angiographic change in mean minimal diameters of segments with a baseline diameter stenosis of 30%. The placebo and amlodipine groups had nearly identical average 36-month reductions in the minimal diameter: 0.084 versus 0.095 mm, respectively (P=0.38) and thus the primary hypothesis was not met.

A secondary hypothesis was whether amlodipine would reduce the rate of atherosclerosis in the carotid arteries as assessed with B-mode ultrasonography, which measured intimal-medial thicknesses (IMT). Amlodipine had an effect in slowing the 36-month progression of carotid artery atherosclerosis: the placebo group experienced a 0.033-mm increase in IMT, whereas there was a 0.0126-mm decrease in the amlodipine group (P=0.007).

The rates of clinical events were also monitored, rather being of relevance for safety at the time. There was no treatment difference in the rates of all-cause mortality or major cardiovascular events, although amlodipine use was associated with fewer cases of unstable angina and coronary revascularization. All secondary and tertiary analyses may have been confounded by the negative result of the primary and by multiplicity.

The CAMELOT study had a primary outcome of the incidence of adverse cardiovascular events in patients treated with amlodipine compared with placebo. Events included in the end point were cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack (TIA), and any new diagnosis of peripheral vascular disease.

Although the MAH did not intend to pursue the indication of coronary artery disease in the EU, the results of the data from PREVENT and CAMELOT studies were considered to be clinically relevant to the approved indication of chronic stable angina. It was proposed to be included as valuable information in section 5.1 of the SmPC, because it was argued that the studies CAMELOT and PREVENT together demonstrate that amlodipine safely reduces the risk for coronary revascularization procedures and hospitalization due to angina in patients with coronary artery disease.

However the CHMP was of the view that the PREVENT study had been over-interpreted and that the MAH's proposal to include a summary of the PREVENT study was not acceptable. The MAH agreed to delete the summary based on the PREVENT study results in the Section 5.1 and only to include the results of the CAMELOT study. Regarding the CAMELOT study, the MAH included a revised table with data from the enalapril treatment arm as well as the full set of components of the composite outcome, as suggested by the CHMP. The MAH's proposal was considered to be acceptable by the CHMP.

CHMP conclusion

Taking into account the comments of the CHMP, the following wording proposed by the MAH was agreed:

'*Use in patients with coronary artery disease (CAD)*

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 key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Table 1.Incidence of significant clinical outcomes for CAMELOT

	Cardiovascular event rates, No. (%)			Amlopidine vs. Placebo	
Outcomes	Amlopidine	Placebo	Enalapril	Hazard Ratio (95% CI)	*P* Value

Primary Endpoint					
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54-0.88)	.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-0.98)	.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41-0.82)	.002
Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	.37
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	.27
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50-13.4)	.24

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.'

Use in patients with heart failure

The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) and PRAISE-2 studies are described in all EU countries except France. In Finland, only PRAISE-2 is described.

PRAISE was a long-term, double-blind, placebo-controlled multicenter trial investigating the effects of amlodipine in combination with background therapy (angiotensin converting enzyme inhibitor, digoxin, and diuretics) on the mortality and cardiac morbidity of patients with severe heart failure. The primary endpoint was combined cardiac morbidity and all-cause mortality. Secondary endpoints were all-cause mortality, change in NYHA functional class, Quality of Life scores, and neurohormonal parameters.

In patients with underlying ischemic etiology, amlodipine did not have an adverse effect on either the primary or secondary endpoint. Furthermore, for patients with non-ischemic etiology, treatment with amlodipine resulted in a statistically significant reduction in risk of both the primary endpoint (hazard ratio 0.695; 95% confidence interval 0.494, 0.976; p=0.0358), combined cardiac morbidity and all-cause mortality, and the secondary endpoint (hazard ratio 0.540; 95% confidence interval 0.373, 0.783; p=0.0012), all-cause mortality. The clinically important reduction in primary endpoint and all-cause mortality are especially noteworthy, and these effects occurred in addition to the benefits derived from the combination of angiotensin converting enzyme inhibitor, digoxin and a diuretic.

The overall incidence of reported adverse events was comparable between the two groups. Similarly, there was no difference in the rate of withdrawal from the study between amlodipine-treated and placebo-treated patients. There was a statistically significant greater incidence of both peripheral and pulmonary oedema among those treated with amlodipine.

The purpose of the follow-up PRAISE-2 study was to evaluate the effect of amlodipine compared with placebo on all-cause mortality in patients with moderate to severe heart failure (NYHA III-IV) of non-ischemic etiology. The primary endpoint was all-cause mortality (cardiac and noncardiac). A separate secondary analysis was performed for cardiac mortality.

There was no difference between amlodipine and placebo in all-cause mortality or cardiovascular mortality in this double-blind PRAISE-2 study. However there appeared to be an increased incidence of pulmonary oedema as an adverse event in this patient population.

The MAH's proposed harmonized SmPC 5.1 text on use in patients with heart failure is taken directly from the agreed PSUR Workshare CSP. This SmPC 5.1 text was included in the Workshare CSP because a cautionary statement on patients with cardiac failure was referred to in section 4.4 of the SmPC, and the MAH wished to achieve common texts across the EU product information. Although there was no specific discussion of this harmonised 5.1 text in the final assessment report, it was adopted in the final CSP. This divergence is therefore considered to have been resolved during the PSUR Workshare Procedure.

The MAH's proposal was considered to be acceptable by the CHMP.

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:

'Use in patients with heart failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that Norvasc did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that Norvasc did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of Norvasc in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, Norvasc had no effect on total cardiovascular mortality. In this same population Norvasc was associated with increased reports of pulmonary oedema.'

Prevention of heart attacks

All EU national SmPCs except in 3 countries Cyprus, Italy and Norway, describe results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Two countries (Germany and Austria) describe the ALLHAT text slightly differently from the proposed harmonised SmPC text.

ALLHAT was a large, randomized controlled trial that provided the most extensive mortality and morbidity data for amlodipine in the treatment of hypertension. ALLHAT was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension. It demonstrated that amlodipine had effects comparable to those of diuretics (an established standard), on cardiovascular events across all patient subgroups. The data from this trial demonstrate that Norvasc-based antihypertensive regimens decrease cardiovascular events in patients with hypertension, and the MAH considers that the results from ALLHAT are clinically relevant for the approved indication of hypertension and provide valuable information for prescribers.

The MAH's proposal was considered to be acceptable by the CHMP.

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:

'Treatment to prevent heart attack trial (ALLHAT)

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension."

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). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.'

Use in Children (aged 6 years and older)

The proposed harmonised text regarding use in children in section 5.1 of the SmPC has been agreed in the Article 45 Paediatric Procedure NL/W/0002/pdWS/001 that was completed on 21 October 2009.

The MAH's proposal was considered to be acceptable by the CHMP.

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:

'Use in children (aged 6 years and older)

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

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.'

Section 5.2 - Pharmacokinetic properties

The basic texts on pharmacokinetic properties within the Norvasc EU national SmPCs are supported by the data submitted with the marketing authorisation application, and are similar or identical to the text in the proposed harmonised SmPC.

However the MAH was requested by the CHMP to review all available information about the changes in the pharmacokinetics of amlodipine treated patients with hepatic impairment. In response the MAH provided data from Study protocol 053-369, which was an open study to assess the safety and pharmacokinetic profile of oral amlodipine in patients with stable chronic hepatic insufficiency (n=12) compared with a group of convalescing subjects without hepatic impairment (n=8).

In this study 053-369, oral amlodipine 5 mg was well tolerated by patients with impaired hepatic function. The pharmacokinetic profile of amlodipine compared with the control group of convalescing subjects without hepatic impairment showed that the values for Cmax were essentially similar, although time to attain peak concentration (Tmax) was more rapid in patients with hepatic insufficiency. The data show that the half-life of amlodipine was longer in hepatic patients in comparison with the control group. AUC values were also higher in hepatic patients although these differences were not statistically different.

No clinically relevant cardiovascular changes nor ECG alterations were apparent. Three hepatic patients showed minor drug-induced laboratory changes, but when these values are viewed against background disease-related abnormalities, their clinical significance is unclear.

However the CHMP was of the view that the study report on which the proposal is based was of poor quality and not according to the current guidelines, and therefore did not justify inclusion in the SmPC. The number of subjects in the hepatic impaired group is small (n= 12), the classification of the hepatic function is based on measurement of indocyanine green clearance and not on the Child –Plough classification, the two groups compared do not match in age (mean age hepatic group 53 years, control group 25 years) and no proper statistical analysis was carried out on the pharmacokinetic results. Therefore dosing recommendations in patients with hepatic impairment were not considered possible based on study 053-069 since only a small number of patients were included.

Therefore the MAH agreed to exclude the description of study 053-369, stating only that very limited clinical data are available and that patients with hepatic impairment have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC.

The pharmacokinetics of amlodipine has not been studied in patients with severe hepatic impairment.

The proposed harmonised SmPC 5.2 text regarding use in children is the agreed text from the Article 45 Paediatric Procedure. The use in the elderly text is also similar across the EU national SmPCs for amlodipine, according to CSP.

CHMP conclusion

Taking into account the comments of the CHMP, the following wording proposed by the MAH was agreed:

'*Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.*

The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Use in hepatic impairment

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%.

Use in the elderly

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. 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.

Use in children

A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.'

Section 5.3 - Preclinical safety data

Information in this section is inconsistent across the EU ranging from no data to a description of preclinical studies in carcinogenesis, mutagenesis and impairment of fertility. Effects on reproduction are sometimes described, but in the proposed harmonised SmPC, these effects have been included in 4.6 Pregnancy and lactation.

The proposed harmonised SmPC wording for section 5.3, which included brief summaries of reproductive toxicology, carcinogenesis and mutagenesis was considered to be acceptable by the CHMP.

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:

'*Reproductive toxicology*

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.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times the maximum recommended human dose of 10 mg on a mg/m2 basis). In another 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.*

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.*

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

**Based on patient weight of 50 kg'*

2.4. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.5. Conclusions

The MAH has agreed to address all quality issues in the ongoing development of the medicinal product and implement them via variations, where necessary (Annex 3.10; letter of undertaking). The MAH was recommended to either to adapt the score line of the 5 mg tablets in order to make it possible to divide them into equal parts or to introduce an additional strength of 2.5 mg for tablets.

The data provided by the MAH support the use of Norvasc in the treatment of Hypertension, Chronic stable angina pectoris and Vasospastic (Prinzmetal's) angina. The information in sections 4.4, 4.5, 4.6, 5.1, 5.2 & 5.3 of the SmPC was revised following comments by the CHMP, and was considered to be satisfactory.

The outcome of the Paediatric Article 45 worksharing procedure NL/W/0002/pdWS/001 completed 21 October 2009 has been implemented in sections 4.2, 5.1 and 5.2 of the SmPC.

Based on the published and unpublished updated documentation, as well as the ensuing CHMP discussions, the proposal for the harmonized SmPC including the amendments provided by the MAH was considered to be acceptable by the CHMP.

2.6. Recommendation

The basis for this referral procedure was a harmonisation of the SPC, labelling and package leaflet.

The CHMP having considered:

- the rapporteur and co-rapporteur assessment reports,
- scientific discussion within the Committee,

the CHMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Norvasc and associated names (see Annex I).