European Medicines Agency

London, 27 April 2004
EMEA/CPMP/540/04

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)
OPINION FOLLOWING AN ARTICLE 29 REFERRAL

Talam

International Non-Proprietary Name (INN): **Amlodipine**

BACKGROUND INFORMATION*

Amlodipine is indicated for use in hypertension and stable angina pectoris.

The applicant submitted an application for mutual recognition of amlodipine maleate on the basis of the marketing authorisation granted by Sweden on 21 February 2003. The Application was submitted to Germany as a Concerned Member State. The dossier was submitted as abridged application according Article 10.1(a) (iii) of Directive 2001/83/EC, as amended, so called "generic application". The Mutual Recognition Procedure started on 18 June 2003.

On 16 September 2003, Germany presented to the EMEA a referral under Article 29 of Directive 2001/83/EC, as amended. The referral by Germany mainly related to the fact that the incompatibility between lactose as an excipient in the chosen formulation and the active substance, as well as impurities in the active substance itself lead to avoidable impurities in the finished product.

The referral procedure started 25 September 2003. The Rapporteur and Co-Rapporteur appointed were: Dr J.L Robert and Dr F. Lekkerkerker , respectively. Written explanations were provided by the Marketing Authorisation Holder by 14 October 2003.

During its January 2004 meeting, the CPMP, in the light of the overall data submitted and the scientific discussion within the Committee, was of the opinion that although, the development of the product and the presence of avoidable impurities have raised important quality concerns, there appears to be no safety concerns arising from the impurity profile in this product, based on the toxicology studies provided by the company. The Benefit/Risk ratio of the product is still favourable and remains unchanged at the end of the arbitration procedure. A positive opinion was adopted on 20 January 2004. At the time of the CPMP opinion a minor quality concern remained, having no impact in the benefit/risk balance of the product. Therefore, the CPMP recommended that this should be dealt with as conditions and should not pose a barrier to a positive opinion. Since the SPC was not a dispute, and no changes were proposed arising from the arbitration process, the latest agreed Summary of Product Characteristics of the Reference Member State remains unchanged.

The list of product names concerned is given in the Annex I. The scientific conclusions are provided in the Annex II, together with the Summary of Product Characteristics in the Annex III.

The final opinion was converted into a Decision by the European Commission on 27 April 2004.

* **Notes**: The information given in this document and Annexes reflect only the CPMP Opinion dated 20 January 2004. The Member States competent authorities will continue to keep the product under regular review.

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ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANT, MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES.

Member State	Marketing Authorisation Holder	Applicant	Invented name	Strength	Pharmaceutical Form	Route of administration
Sweden	Laboratoires Delbert 56, Quai A. Le Gallo 92100 Boulogne Billancourt France		Talam	5 mg	Tablet	oral use
Sweden	Laboratoires Delbert 56, Quai A. Le Gallo 92100 Boulogne Billancourt France		Talam	10 mg	Tablet	oral use
Germany		Laboratoires Delbert 56, Quai A. Le Gallo 92100 Boulogne Billancourt France	Talam	5 mg	Tablet	oral use
Germany		Laboratoires Delbert 56, Quai A. Le Gallo 92100 Boulogne Billancourt France	Talam	10 mg	Tablet	oral use

ANNEX II

SCIENTIFIC CONCLUSIONS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF AMLODIPINE MALEATE TABLETS (see Annex I)

The applicant submitted an application for mutual recognition of amlodipine maleate on the basis of the marketing authorisation granted by Sweden. The Application was submitted to Germany as a CMS. The dossier was submitted as abridged application according Article 10.1(a) (iii) of Directive 2001/83/EC, as amended, so called "generic application".

On 16 September 2003, Germany presented to the EMEA a referral under Article 29 of Directive 2001/83/EC, as amended. In their notification, the BfArM considered that the authorisation of these medicinal products may present a risk to public health due to the fact that the incompatibility between lactose as an excipient in the chosen formulation and the active substance, as well as impurities in the active substance itself lead to avoidable impurities in the finished product. The two foreseeable impurities are referred to by the names:

1. amlodipine - maleic acid adduct / Michael type adduct;
2. amlodipine - lactose adduct / Maillard product.

On the basis of the Referral raised by Germany, the issues to be considered may be summarised as follows:

1. Justification of essential similarity

Although this product contains a different salt from the innovator, it has been shown preclinically, that there is no change in the safety profile of the final product, compared with the innovator, that may potentially arise from the use of a different salt or from impurities / degradants. The product can therefore be considered as having the same qualitative and quantitative composition in terms of active principle as the innovator; the same pharmaceutical form as the innovator and is also bioequivalent with the innovator, and in the light of the scientific knowledge the product does not differ significantly from the innovator in terms of efficacy and safety. Therefore, essential similarity has been demonstrated.

2. Suitability of the drug product

The quality of a medicinal product already starts during the pharmaceutical development studies, and one role of pharmaceutical development is to identify those parameters, which can influence the quality (purity) of the product. An adequate pharmaceutical development and the performance of compatibility studies between the active substance and the excipients would have identified at a very early stage the presence of the referred two foreseeable impurities, and therefore another approach could have been taken in order to avoid their presence.

The development and resulting quality of these products has not been optimised in the normal way and is not state of the art. However, the company has specified the level of both foreseeable impurities in the finished product and the specified acceptance criteria have been qualified by the submission of additional toxicological data in compliance with the ICH NfG Guideline on impurities in new drugs.

3. Justification of the drug substance and lactose

The justification that lactose was the only filler that could be used for this formulation / manufacturing process combination is questionable and the use of the maleate salt due to patent reasons is insufficient as a justification alone. The chosen formulation in combination with this manufacturing process are not optimal and nor state of the art could have been improved in order to avoid the presence of the two foreseeable impurities.

4. Justification of long-term use of the drug product

The company has qualified both foreseeable impurities according ICH Q3B Guideline, which is in line with the current regulatory provisions for drug products for long-term use.

The toxicity studies revealed no harmful effects of the impurities and the proposed limits in the shelf life specification of the finished product are considered acceptable

In conclusion:
Although, the development of the product and the presence of avoidable impurities has raised important quality concerns, there appears to be no safety concerns arising from the impurity profile in these products, based on the toxicology studies provided by the company. Therefore, the Benefit/Risk ratio of the product is still favourable and remains unchanged at the end of this arbitration procedure.

Since the objections and the issues related entirely to pharmaceutical quality matters without any impact on the SPC, it was not considered necessary to amend the latest SPC as proposed on day 90 of the Mutual recognition Procedure. This "day 90" SPC has therefore been adopted as Annex III of the CPMP Opinion.

The CPMP having considered:

- The MRP assessment report of the RMS
- The issues for arbitration
- The written responses provided
- The Rapporteur/Co-Rapporteur's assessment report on these responses
- Comments from CPMP members
- CPMP/CVMP/QWP Report

concluded that the objections raised by Germany have been resolved by the written responses provided during this arbitration procedure and should not prevent the granting of the marketing Authorisation.

At the time of the CPMP opinion one quality concern remained, having no impact in the benefit/risk balance of the product. Therefore, the CPMP recommended that this should be dealt with as conditions and should not pose a barrier to a positive opinion.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was Annexed to the Commission Decision on this Article 29 referral for amlodipine maleate containing medicinal products. The text was valid at that time.

After the CD, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

1 NAME OF THE MEDICINAL PRODUCT

Talam 5 mg tablets
Talam 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Talam 5 mg tablet: Each tablet contains 5 mg of amlodipine (as amlodipine maleate).
Talam 10 mg tablet: Each tablet contains 10 mg of amlodipine (as amlodipine maleate).

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet

Talam 5 mg tablets are white, round and biconvex, diameter approx. 9 mm and height approx. 4.4 mm.
Talam 10 mg tablets are white, round and biconvex, scored on both sides, diameter approx. 9 mm and height approx. 4.4 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Arterial hypertension.
Stable angina pectoris.

4.2 Posology and method of administration

For oral use. Tablets should be taken with a glass of liquid before or between the meals.

Hypertension and angina pectoris: The treatment should be individualised. The starting dose and usual maintenance dose is 5 mg once daily. If the desired therapeutic effect cannot be achieved within 2-4 weeks the dose can be increased to a maximum of 10 mg daily, given as a single dose. If a satisfactory clinical response has not been achieved within at least 4 weeks, supplementary or alternative therapy should be considered. It may be necessary to modify the administered dose if different antihypertensive agents are administered concomitantly.

Elderly patients
No dose adjustment is required in elderly patients, however, increase of the dosage should take place with care.

Paediatric patients
Talam tablets should not be given to children due to insufficient clinical experience.

Hepatic impairment
In patients with hepatic impairment a reduced dose should be used. See 4.4 Special warning and precautions for use and 5.2 Pharmacokinetic properties.

Renal impairment
Normal dosage is recommended.

4.3 Contraindications

Talam tablets are contraindicated in

- patients with known hypersensitivity to amlodipine, other dihydropyridines or any of the excipients
- severe hypotension
- shock
- heart failure after acute myocardial infarction (during the first 28 days)
- obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis)
- instable angina pectoris

4.4 Special warning and precautions for use

Untreated heart failure.
Low cardiac reserve.Should not be given to children due to insufficient clinical experience.
Hepatic impairment (see 5.2 Pharmacokinetic properties).

Amlodipine should be used with caution in patients with severe renal insufficiency undergoing dialysis due to limited experience.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Amlodipine may potentiate the effect of other antihypertensive drugs as beta-adrenoreceptor blocking agents, ACE-inhibitors, alpha-1-blockers and diuretics. In patients with increased risk (for example after myocardial infarction) the combination of a calcium channel blocker with a beta-adrenoreceptor blocking agent may lead to heart failure, to hypotension and to a (new) myocardial infarction.

A study of elderly patients has shown that diltiazem inhibits metabolism of amlodipine, probably via CYP3A4, since plasma concentration increases by approx. 50% and the effect of amlodipine is increased. It cannot be excluded that stronger inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) increase the plasma concentration of amlodipine to a greater extent than diltiazem. Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors.

There is no information available on the effect of CYP3A4 inducers (i.e. rifampicin, St. John's wort) on amlodipine. Co-administration may lead to reduced plasma concentration of amlodipine. Caution should be exercised in combination of amlodipine and CYP3A4 inducers.

Concomitant administration of 240 ml of grapefruit juice with 10 mg amlodipine did not show a significant effect on the pharmacokinetic properties of amlodipine.

4.6 Pregnancy and lactation

There are no adequate data from the use of amlodipine in pregnant women. Animal studies have shown reproductive toxicity at high doses (see 5.3). The potential risk for humans is unknown. Amlodipine should not be used during pregnancy unless the therapeutic benefit clearly outweighs the potential risks of treatment.

It is not known whether amlodipine is excreted in breast milk. Similar calcium channel blockers of the dihydropyridine type are excreted in breast milk. There is no experience of the risk this may pose to the newborn, therefore, as a precaution, breast-feeding should not occur during treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

Very common:	>1/10
Common:	>1/100 and <1/10
Uncommon:	>1/1000 and <1/100
Rare:	>1/10 000 and <1/1000
Very rare:	<1/10 000 including isolated cases

Blood and lymphatic system disorders

Uncommon: Leukocytopenia, thrombocytopenia

Endocrine disorders

Uncommon: Gynaecomastia

Metabolism and nutrition disorders

Very rare: Hyperglycaemia

Nervous system disorders
Common: Headache (especially in the beginning of the treatment), fatigue, dizziness, asthenia.
Uncommon: Malaise, peripheral neuropathy, dry mouth, paraesthesia, increased sweating.
Very rare: Tremor.

Eye disorders

Uncommon: Visual disturbances

Psychiatric disorders

Uncommon: Sleep disorder, irritability, depression

Rare: Confusion, mood changes including anxiety

Cardiac disorders
Common: Palpitations
Uncommon: Syncope, tachycardia, chest pain.

At the beginning of treatment aggravation of angina pectoris may happen.

Isolated cases of myocardial infarction and arrhythmias (including extrasystole, tachycardia and atrial arrhythmias) and chest pain have been reported in patients with coronary artery disease, but a clear association with amlodipine has not been established

Vascular disorders

Uncommon: Hypotension, vasculitis

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea
Uncommon: Cough

Gastrointestinal disorders
Common: Nausea, dyspepsia, abdominal pain

Uncommon: Vomiting, diarrhoea, constipation, gingival hyperplasia
Very rare: Gastritis

Hepato-biliary system
Uncommon: Pancreatitis
Rare: Elevated liver enzymes, jaundice, hepatitis

Skin and subcutaneous tissue

Very common: Ankle swelling

Common: Facial flushing with heat sensation, especially at the beginning of the treatment

Uncommon: Exanthema, pruritus, urticaria, alopecia

Very rare: Angiooedema

Isolated cases of allergic reactions including including pruritus, rash, angioedema and erythema exsudativum multiforme, exfoliative dermatitis and Stevens Johnson syndrome, Quincke oedema have been reported.

Musculoskeletal, connective tissue and bone disorders

Common: Muscle cramps

Uncommon: Back pain, myalgia and arthralgia

Renal and urinary disorders

Uncommon: Increased micturition frequency

Reproductive system and breast disorders
Uncommon: Impotence.

General disorders and administration site conditions

Uncommon: Increase or decrease of weight

4.9 Overdose

Experience of overdose with amlodipine is limited. Excessive doses of amlodipine can be expected to cause peripheral vasodilation with marked hypotension. Circulatory support may be required. Cardiac and respiratoryactivity should be monitored carefully. In hypotension due to cardiogenic shock and arterial vasodilation, intravenous calcium glubionate may be helpful. As amlodipine is highly bound to plasma proteins, dialysis is not expected to be of value.

Gastric lavage or administration of activated charcoal may be worthwhile in some cases.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Dihydropyridine derivates, ATC-code: C08C A01

5.1 Pharmacodynamic properties

The active substance in Talam tablets, the dihydropyridine derivative amlodipine, is a chiral substance, composed of a racemate. Amlodipine is a calcium antagonist that inhibits the transmembranal influx of Ca ions through the potential dependent L-type channels into the heart and smooth muscle. Amlodipine acts on hypertension through a direct relaxant effect on arterial smooth muscle. Animal

studies have demonstrated that amlodipine is relatively vessel-selective with significantly less effect on cardiac muscle than on vascular smooth muscle. Amlodipine does not impair AV conduction and does not have a negative inotropic effect. Amlodipine reduces renal vascular resistance and increases renal plasma flow.
Amlodipine can be given to patients with co-existing compensated heart failure. Controlled studies of haemodynamic effects and exercise tolerance in patients with heart failure class II-IV have demonstrated that amlodipine does not lead to clinical deterioration regarding exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

No metabolic effects, e.g. on plasma lipids or glucose metabolism, have been seen during treatment with amlodipine.

Antihypertensive effect: Amlodipine has an effect on hypertension by a directly relaxing effect on the smooth muscle in the arterial blood vessels. Dosing once daily produces a decrease in blood pressure lasting for 24 hours. The antihypertensive effect follows the normal diurnal variations in blood pressure with very small changes over the 24-hour period. At least 4 weeks' treatment is required to produce maximum effect. Amlodipine is effective in the supine, sitting and standing positions and during exercise.

As the pharmacological effect of amlodipine is of slow onset it does not cause acute hypotension or reflex tachycardia. Treatment with amlodipine produces regression left ventricular hypertrophy. The haemodynamic effects of amlodipine remain unchanged during long term treatment. No long term studies with regard to mortality or morbidity are available.

Talam tablets can be used in combination with beta-blockers, saluretics, ACE inhibitors, or as monotherapy.

Antianginal effects: Amlodipine dilates peripheral arterioles, reducing the total peripheral resistance (afterload). As the heart rate is not affected, reduction of heart load leads to reduction of myocardial oxygen requirements and energy consumption.

Amlodipine probably dilates the coronary vessels, both in ischaemic and normally oxygenated areas. This dilation increases the myocardial oxygen supply in patients with coronary vessel spasm (Prinzmetal's or variant angina).

In patients with stable angina pectoris, amlodipine once daily increases total exercise tolerance, time to angina and time to a 1 mm ST segment depression. In addition, frequency of anginal attacks and use of nitroglycerine are reduced.

The efficacy duration in angina pectoris is at least 24 hours.

Talam tablets can be used in combination with beta-blockers, nitrates or as monotherapy in angina pectoris.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure patients receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or a combined risk of mortality and morbidity with heart failure.
In a follow-up study (PRAISE 2) showed that amlodipine did not have an affect on the total or cardiovascular mortality of heart failure class III-IV patients without ischaemic origin. In this study treatment with amlodipine was associated with an increase in pulmonary oedema, although this could not be related to an increase in symptoms.

5.2 Pharmacokinetic properties

Absorption and distribution

The bioavailability is 64-80%. The bioavailability is not influenced by concomitant intake of food. Peak plasma concentrations are reached, using recommended doses, within 6-12 hours. The volume of distribution is approx. 21 l/kg. Plasma protein binding is high (98%).

Biotransformation and elimination
The plasma half-life varies between 35 and 50 hours and steady-state concentration is reached after 7-8 days. Only minor variations between peak and trough values in plasma concentrations are seen. Plasma clearance is 7 ml/min/kg. Amlodipine is metabolised almost completely in the liver, to exclusively inactive metabolites, of which 60% are excreted in the urine. Approx. 10% of the parent compound is excreted in an unmetabolised form in the urine.

Patients with hepatic impairment:
The half-life of amlodipine is prolonged in patients with impaired hepatic function. See 4.4 Special warnings and special precautions for use.

Patients with renal impairment and elderly patients:
Changes in plasma concentration of amlodipine are not related to the degree of renal impairment. Amlodipine is not expected to be dialysable due to the high degree of plasma protein binding. Elderly patients may receive the normal dosage, even though clearance of amlodipine is slightly lower in the elderly. The half-life and the AUC in patients with heart failure were, as expected, increased in the age group investigated.

5.3 Preclinical safety data

Toxicological animal studies reveal no special hazards for humans regarding safety pharmacology, genotoxicity, carcinogenicity and studies with repeated dosing. Harmful effects have been seen in reproductive toxicological animal studies. Effects in rats (prolonged duration of pregnancy and difficult labour) revealed no evidence of a direct teratogenic effect, but indicate secondary consequences of the pharmacodynamic effects.The significance of these effects for humans is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone k 30
Povidone k 90
Microcrystalline cellulose
Crospovidone

6.2 Sodium stearyl fumarate.Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and content of container

5 mg tablets: Blister packs, aluminium/aluminium 10, 20, 28, 30, 50, 56, 98, 100, 300 tablets,

50 x 1 tablets (unit dose), 100 x 1 tablets (unit dose).

10 mg tablets: Blister packs, aluminium/aluminium 10, 20, 28, 30, 50, 56, 98, 100, 300 tablets, 50 x 1 tablets (unit dose), 100 x 1 tablets (unit dose).

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoires DELBERT
56, quai Alphonse Le Gallo
92100 Boulogne Billancourt
France

8 MARKETING AUTHORISATION NUMBER(S)

5 mg: 18046
10 mg: 18047

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2003-02-21

10 DATE OF REVISION OF THE TEXT

